# CHAPTER ONE

## INTRODUCTION

### 1.1     General

Oral drug delivery is the most widely utilized among all the routes of administration that have been explored for the systemic delivery of drugs using various dosage forms. The reason that the oral route has achieved such popularity may be attributed to its ease of administration as well as the traditional belief that by oral administration, the drug is well absorbed (Davis and Freely, 1988; Rubinstein, 2005). Medicaments that are administered orally can be presented as solids or liquids. Currently, over 74% of all pharmaceutical products are offered as solid dosage forms (Sinko, 2011). Solid preparations include powders, granules, tablets and capsules. The most commonly used oral preparations are capsules and tablets (Rubinstein, 2005). Tablets are prepared primarily by compression and the basic components of tablets can be divided into the active and inactive constituents, the latter usually referred to as excipients (Rubinstein, 2005). A wide variety of tablet forms are available, and the science and technology of tablet compression has advanced substantially (Adetunji *et al*, 2012). Pharmaceutical tablets must be able to withstand the rigours of handling in their manufacture, packaging, transportation, dispensing and even administration in the hands of users. In addition to their mechanical strength, tablets should be able to release their drug content where necessary (such as in the gastrointestinal tract) for absorption to take place (Odeku and Itiola, 1998).

Attempts to meet the drug delivery challenges and improve drug therapy of existing conventional drug delivery systems have culminated, among other formulation strategies, in the upsurge of advanced drug delivery systems (Sinko, 2011). The search for competitive alternatives to the expensive excipients incorporated during the formulation development of new drug entities or modification of already existing ones has led to the

exploitation of naturally existing substances as excipients in modified drug delivery systems because they are less expensive, biocompatible and biodegradable (Hillery, 2011). Efforts to develop some local gums sourced from various tropical African plants as pharmaceutical excipients in tablet formulations have been reported (Kalu *et al*, 2007; Odeniyi and Jaiyeoba, 2009; Adeleye *et* al, 2010; Bamiro *et al*, 2010).

## 1.2    Justification of the Study

Mucoadhesive drug delivery systems are designed to prolong drug retention, thus offering advantages over conventional dosages through reduced dosage regimen and improved patient compliance. Mucoadhesive polymers have been utilized in many different dosage forms such as tablets, films, patches, semisolids and powders (Bhaskara-Jasti *et al*, 2003). Carrier systems that release drugs based on zero order kinetics for an extended period of time are usually considered optimal (Porter and Bruno, 1990). The model membranes used for quantitation of mucoadhesion vary from mouse peritoneal membranes to cellulosic paper disks impregnated with mucous gelatin (Ahuja *et al*, 1997), while the use of polymers as binders has attracted a lot of attention (Krishnaiah *et al*, 2002)

*Entandophragma angolense* gum (Family: Meliaceae) obtained from the early morning exudates of the incised trunk of the tree is widely available throughout the whole year in tropical Africa. The gum is used in traditional medicine as a febrifuge (Burkhill, 1997), but its excipient properties are yet to be fully exploited. *Entandophragma angolense* gum was demonstrated to exhibit good potentials as a suspending agent when compared with *Acacia* gum and gelatin (Adetunji *et al,* 2011b). On contact with water, the gum swells to form a viscous gel when left standing for about 30 min. Thus, *Entandophragma angolense* gum was investigated as a binder and mucoadhesive component in oral tablets, using chlorpheniramine maleate and ibuprofen as model drugs.

## 1.3    Rationale for Choice of Model Drugs

Chlorpheniramine maleate and ibuprofen powders cannot be tabletted on their own, and thus require, among other things, a binder to form compact tablets. Also, the solubilities of the drugs in aqueous and lipophilic media differ; while chlorpheniramine

maleate (a weakly basic drug with a pKa of 9.2±0.01) is freely soluble in water and slightly soluble in ether, ibuprofen (a weak acid with a pKa of 4.3±0.01) is practically insoluble in water, but freely soluble in ether (British Pharmacopoeia, 1998). These properties thus provide a platform for comparing the effects of *Entandophragma angolense* gum on the drug models.

## 1.4  Objectives of the Study

### 1.4.1  General Objectives

A lot of attention has been given to hydrophilic polymers in the design of oral drug delivery systems due to their flexibility, cost-effectiveness, and broad regulatory acceptance. Among the hydrophilic polymers, cellulose derivatives such as methylcellulose, hydroxypropyl methylcellulose, and sodium carboxymethylcellulose are generally considered to be stable and safe as excipients in the development of oral controlled release dosage forms, and their use as binders.  These synthetic polymers are quite expensive when compared with natural polymers such as guar gum and alginates, while the natural polymers are also non toxic and easily available (Krishnaiah *et al*, 2002).The present study was designed to evaluate the natural gum obtained as an exudate from the plant *Entandophragma angolense* (family: Meliaceae synonym; *Swietenia angolensis*), for its tablet binding and mucoadhesive properties in comparison with gelatin and hydroxypropylcellulose, using direct compression and wet granulation techniques. Matrix tablets containing different compositions of *Entandophragma angolense* gum (or gelatin and hydroxypropylcellulose) and the model drugs (chlorpheniramine maleate and ibuprofen) were also prepared to evaluate the controlled release potentials of the polymers.

*Entandophragma angolense* gum obtained from the incised trunk of *Entandophragma angolense* tree, which is indigenous to Tropical Africa, has been administered by traditional medical practitioners to counter stomach pains (Burkhill, 1997), thus, it is expected that this natural gum will not exhibit the gastro intestinal side effects usually associated with the use of synthetic mucoadhesive polymers (Hassan and Galo, 1990; Ahuja *et al*, 1997).

**1.4.2      Specific Objectives**

The specific objectives of the present work were:

i. To study the physicochemical, morphological and compressional properties of *Entandophragma angolense* gum.

ii. To evaluate the mechanical and release properties of *Entandophragma angolense* gum in comparison with gelatin and hydroxypropylcellulose using chlorpheniramine maleate (water soluble) and ibuprofen (water insoluble) tablets formulated by wet granulation and direct compression techniques.

iii. To evaluate the matrix properties of *Entandophragma angolense* gum in comparison with gelatin and hydroxypropylcellulose.

iv. To evaluate the mucoadhesive properties of *Entandophragma angolense* gum in comparison with gelatin and hydroxypropylcellulose in 0.1M Hydrochloric acid (pH 1.2) and phosphate buffer (pH 7.4) media, representing the gastric environment and the small intestine respectively.

v. To evaluate the quantitative individual and interaction effects of nature and concentration of binder, relative density, and tabletting technique, on disintegration time, tensile strength, brittle fracture index and mucoadhesion using factorial experiments.

## CHAPTER TWO
## LITERATURE REVIEW

### 2.1    General

The vast array of effective medicinal agents available today represents one of Man's greatest achievements. It would be frightening to perceive our civilization devoid of these remarkable and beneficial agents that are presented in different delivery systems (Sinko, 2011). Among all oral drug delivery systems, the compressed tablet is the most frequently employed drug form throughout most areas of the world, accounting for over 70% of all the ethical pharmaceutical preparations produced (Rubinstein,1988). When properly formulated and prepared, the tablet offers a stable, highly concentrated and convenient dosage form, which contributes towards accurate dosage and rapid dispensing, and encourages good patient compliance. The technology related to the development and production of compressed tablets has grown as well, thus further emphasizing the convenience of administering this dosage form, as well as ensuring good patient compliance (The Pharmaceutical Codex, 1994).

Tablets have been defined as solid preparations, each containing a unit dose of one or more medicaments that are prepared by compressing uniform particulate volumes of the medicament or mixture of medicaments usually with added substances (The Pharmaceutical Codex, 1994).

### 2.2    Desirable Properties of Compressed Tablets

The way that a tablet is made requires careful study of the physical and chemical properties of its component in order to achieve a stable, efficacious product. These properties, such as dissolution, solid-state stability and drug-additive interaction, can have profound effects on the physiological availability and on the physical and chemical stability of the drug. It is important, therefore, to achieve a balance between those factors

that affect the biological activity of the drug. Thus, there are two competing sets of desirable properties of tablets, and they are:

    i.   Physical properties.

   ii.   Therapeutic properties.

### 2.2.1   Physical Properties of Compressed Tablets

Modern medicines require that tablets are acceptable to the patients. Unfortunately, many medicaments are unpalatable and unattractive in their natural state. It is therefore necessary to formulate the medicaments into tablets in such a way that is acceptable to the patient to promote compliance. The ideal physical properties of tablets are enumerated thus:

    i.   A tablet should be an elegant product having its own identity while being free of defects such as chips, cracks, contamination, and discolouration.

   ii.   A tablet must possess adequate strength to withstand the rigours of mechanical shocks encountered in its production, packaging, shipping and dispensing.

  iii.   A tablet must be able to maintain its physical attributes over time by having adequate chemical and physical stability. (Banker and Anderson, 1986)

### 2.2.2   Therapeutic Properties of Compressed Tablets

The goal of a well formulated tablet is to achieve the expected therapeutic effect. Thus, apart from the aforementioned physical properties, the following therapeutic properties are of important consideration when formulating compressed tablets:

    i.   A tablet must be able to release the medical agent it contains into the body in a predictable and reproducible manner.

   ii.   A tablet must possess suitable chemical stability so as not to allow degradation of the medicinal agent over time.

The design of tablets thus involves a series of compromise between the aforementioned physical and therapeutic objectives.

**2.3    Types of Compressed Tablets**

Tablets are classified based on their methods of preparation, mechanism of action and their sites of action (Rubinstein, 1988).

**2.3.1    Lozenges**

These are tablets that are intended for slow dissolution in the mouth (perhaps 10 to 15 minutes) and as such do not disintegrate readily because they contain no disintegrants. They produce local action in the throat and often release antibacterial or anaesthetic agent.

**2.3.2    Chewable Tablets**

These are meant to be chewed in the mouth and in this case mastication ensures thorough break up of the mass, thus speeding up the processes of disintegration and dissolution of tablets. Chewable tablets present an alternative for patients who have difficulty in swallowing tablets whole or for children who have not yet learned to wash tablets down with water. Mannitol is usually the diluent of choice, due to its negative heat of solution, which produces a cooling sensation in the mouth and acts as an effective mask for unpleasant tastes.

**2.3.3    Soluble Tablets**

These are meant to be dissolved in water for oral administration, topical (external) application or parenteral administration. All ingredients must therefore be soluble in water.

**2.3.4    Dispersible Tablets**

These disintegrate rapidly in cold water to produce a suspension suitable for ingestion. Although there is no need for all the ingredients to be totally water soluble, the need for a disintegrant which is effective in cold water, is paramount.

**2.3.5    Effervescent Tablets**

These are a special type of soluble tablets formulated to hasten dissolution of the active drug and to enhance palatability. Such tablets are dissolved to produce a clear sparkling solution in a specified quantity of water and are administered orally.

### 2.3.6   Buccal Tablets

These are placed in the buccal pouch of the cheek where they dissolve slowly for eventual absorption without passing into the alimentary canal.

### 2.3.7   Sublingual Tablets

These are placed beneath the tongue where they dissolve quickly and are absorbed directly through the oral mucosa.

### 2.3.8   Implants

Implants consist of small pellets of compressed drug, normally about 2-3 mm in diameter and are aseptically prepared without excipients. They are designed for insertion in the body tissues by surgical procedures, where, as a result of their hardness and low solubility, are slowly absorbed into the body over a period of months to exert their necessary action. They are used for the administration of hormones.

### 2.3.9   Boluses

They are tablets weighing 5 g or more and used in veterinary medicine (The Pharmaceutical Codex, 1994). Boluses consist of a larger dose of the active ingredient (hence the large weight) and are administered at the beginning of a treatment programme to raise the blood concentration rapidly to a therapeutic level.

### 2.3.10  Multi layer and Compression Coated Tablets

These are tablet dosage forms developed to overcome particular problems of stability. A multilayer tablet consists of several granulations that are compressed, on top of each other, to form a single tablet composed of two or more layers. Such tablets are mainly used for incompatible substances.

### 2.4   Advantages and Disadvantages of Compressed Tablets
### 2.4.1   Advantages of Compressed Tablets

The advantages of compressed tablets as a dosage form include the following (Banker and Anderson, 1986):

i. Convenience and ease of administration and transportation.

ii. The precision with which their drug content can be controlled thus enabling administration of an accurate dose of the medicament.

iii. They are generally stable towards physical and chemical degradation thus ensuring high durability.

iv. They are cost effective in production because they can be mass produced simply and quickly.

v. Unpleasant tasting medicaments can have such effects masked by sugar, film or press coating, thus improving palatability and attractiveness.

vi. Compressed tablets are the lightest and most compact of all oral dosage forms. This affords easy portability and durability.

vii. Compressed tablet is an essentially tamper-proof dosage form unlike liquid dosage forms (e.g. solutions, suspensions, emulsions) which are easy to adulterate.

viii. They have the best combined properties of chemical, mechanical and microbiological stability.

ix. Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.

## 2.4.2 Disadvantages of Compressed Tablets

The disadvantages of compressed tablets include:

i. Not all compressed tablets can be swallowed and still provide the desired pharmacological effects.

ii. Only very few materials can be tabletted on their own. Problems such as capping, lamination, chipping, sticking, picking and variation in weight may occur.

iii. Drugs which have bitter taste, objectionable odour or high sensitivity to atmospheric moisture or oxygen are better presented as coated tablets thus increasing cost, but encapsulation may be a more cost effective approach.

iv. Some drugs resist compression into dense compact owing to their amorphous nature or flocculent low-density character and thus cannot be made into tablet form.

v.    Drugs with poor wetting, slow dissolution properties or those that require intermediate to large dosages or a combination of these features may be difficult to formulate as tablets that will still provide adequate bioavailability.

## 2.5    Formulation Additives

In nearly all cases, medicaments cannot be tabletted on their own. Therefore, a tablet does not only contain the active ingredient(s) but also includes other substances, known as excipients, which have specific functions. These excipients include diluents, binders, lubricants, disintegrants and other optional components like colours, flavours and sweeteners (Rubinstein, 1988).

It is extremely rare to find a drug system that does not incorporate excipients. The addition of these non-active components is required to produce satisfactory drug release, to achieve acceptable physical and mechanical properties and to facilitate the manufacture of tablets (Itiola, 2009).

Classification of additives is usually based on some primary functions they perform in the tablet. Many of the additives have secondary effects, which may be beneficial or deleterious. For instance, most effective lubricants are water-repellant in nature and this may retard tablet disintegration and dissolution.

Palin (1982) showed that "inert ingredients" could significantly affect the properties of the final dosage form. He concluded that the proper choice of excipients is critical when formulating water-insoluble drugs unlike their water-soluble counterparts. Thus, a thorough understanding of these additives is essential especially when the concentration of the drug is so small such that the disintegration, dissolution and eventual release characteristics of the final tablet will be immensely affected.

Based on their primary functions, formulation additives are classified into two categories as follows (Shangraw, 1992).

a.    Those which principally affect the compressional characteristics of the tablets:

  i.    Diluents (Fillers)

 ii.    Binders (adhesives)

iii.    Lubricants, Glidants, Anti-Adherents.

b.      Those which principally affect the bio-pharmaceutics, chemical and physical stability:

  i.      Disintegrants.

 ii.      Flavours and sweeteners

iii.      Colourants

iv.      Miscellaneous components such as adsorbents

## 2.5.1   Diluents

Diluents (otherwise referred to as bulking agent(s) are 'inert' substances, which are added to the active ingredient in sufficient quantity to make a reasonable sized tablets, especially in cases where the dose of the active ingredient is low. Secondarily, diluents may be added for the following reasons:

a.  To provide better tablet properties such as improved cohesion.

b.  To enhance tablet characteristics such as dissolution rate.

c.  To permit the use of direct compression thus eradicating problems associated with disintegration when a single component is compressed.

d.  To promote powder flow during manufacturing.

A comparative study involving the effect of diluents on the physical properties of diazepam tablets was carried out by Soyeux *et al* (1998). Lactose, starch, mannitol and microcrystalline cellulose were the diluents employed in the study. It was observed that starch produced the weakest tablets with highest friability and lowest crushing strength values while microcrystalline cellulose gave the strongest tablets.

## 2.5.2   Adsorbents

Adsorbents are substances included in a formulation that is capable of holding quantities of fluids in an apparently dry state. Oil-soluble drugs, fluid extracts or oils can be mixed with adsorbents and then granulated and compressed into tablets. Adsorbents promote disintegration and tend to decrease tablet strength and relative density because of adsorben's ability to swell.

Examples are fumed silica, microcrystalline cellulose, magnesium carbonate, Kaolin and bentonite.

### 2.5.3 Disintegrants

Disintegrants are agents added to tablets to promote breakup of the tablets when placed in an aqueous environment (Singh *et al*, 2006). The objective of a disintegrant is to cause the tablet to disintegrant rapidly so as to increase the surface area of the tablet fragments and so promotes rapid release of the drug. This implies opposing the efficiency of the tablet binder and the physical forces that act under compression to form the mechanical body of the tablet; therefore, the stronger the effect of the binder, the more efficient must be the action of the disintegrating agent.

Wagner (1966) proposed a scheme which related breakup to drug dissolution and absorption. Release rate of the drug is greater from disintegrated particles than from the intact tablet or fragmented tablet. Thus, a good disintegrant will quickly break up a tablet into primary particles and ensure that the drug is assimilated at a fast rate.

Materials used as disintegrants include (Singh *et al*, 2006):

i. Starch derivates such as maize and potato starches.
ii. Alginic acid and alginates; 10-15% being usually required.
iii. Cellulose derivatives such as methyl cellulose and sodium carboxymethylcellulose.
iv. Clays such as Bentonite and veegum.
v. Gums (both natural and synthetic).
vi. Effervescent mixtures.

Three types of disintegrants are however in common use:

i. Substances that swell up on contact with moisture e.g. starches, which are the most widely used and best established disintegrants.
ii. Substances that melt at body temperature e.g. cocoa butter.
iii. Substances that react with effervescence on contact with moisture e.g. citric acid or tartaric acid with a chemical equivalent of sodium bicarbonate in a small quantity.

Disintegrants may be incorporated using the following methods (Singh *et al*, 2006):

a. **External addition**: When the disintegrant is added to the granulation prior to compression.

b. **Internal addition**: When the disintegrant is incorporated within the granule by mixing with other powdered materials before wetting.

c. **Ratio addition**: a third approach utilizes both methods by dividing the total amount of the disintegrating agent into two equal halves, so that one portion is added to the powdered components before the wet granulation process and the remaining portion is added to the finished granulation just prior to compression. The proposal for this approach is based on the fact that a disintegrant is required between the granules as well as within them so that the disintegrating action will not only force the tablets apart into the original granules, but will also break down the granules themselves.

### 2.5.4 Lubricants

Lubricants are agents that act between surfaces in relative motion to prevent friction and wear. They are required to prevent adherence of the granules to the punch faces and dies, and also to ensure smooth ejection of the tablet from the die. Many lubricants also enhance the flow properties of the granules. Examples of lubricants are magnesium stearate, stearic acid, talc and liquid paraffin. Rees and Lewis (1994) also found that lubricants generally decrease tablet strength.

Magnesium stearate is the most popular lubricant used and is normally effective on its own as both a die and a punch lubricant. Talc and stearic acid appear to be more effective as punch lubricant and die lubricant respectively (Kushret, 2004).

Higuchi *et al* (1953) reported that the efficacy of magnesium stearate and other fatty acid salts is thought to be due to their polar nature. Factors affecting efficiency of lubricants include mixing time of the tablet mass with lubricant, which was found to have direct effect on tablet properties. Selection and concentration of lubricants are also important factors, as poor selection and excessive amount of lubricant have resulted in poor tablet disintegration and dissolution of the drug substances (Wagner, 1966).

### 2.5.5 Glidants

These are materials that improve the flow characteristics of granules. They function by reducing interparticulate friction thereby eliminating the problems associated with the flow of materials from larger through smaller apertures in tablet presses, and have been found very useful in automated high speed processes. The most commonly used and effective glidant is fumed colloidal silica; others include talc and corn starch (Kemp, 2004).

### 2.5.6 Antiadherents

They function to prevent tablet granulations or materials from sticking to the faces of the punches and the die walls. Sticking obliterates the idenfication marks on monogrammed punch faces. An example of an antidherent is colloidal silica. Some lubricants also posses antiadherent properties such as corn starch, talc and magnesium stearate (Rubinstein, 1988).

### 2.5.7 Flavours and Sweeteners

They are used to render palatable a product that contains a drug with a particular unpleasant taste. Flavours can be obtained from natural sources (such as fruit juices including blackcurrant, rasp berry and cherry; aromatic oils including peppermint and lemon oils, herbs and spices) or from synthetic sources, which are cheaper, more readily available (as alcoholics or powders), more stable and less variable in chemical composition, than the natural ones. Sweeteners are to enhance the degree of sweetness and to enhance a pleasant taste of the drug. The use of flavours and sweeteners is limited to chewable tablets and paediatric preparations to improve compliance. They are seldom found in standard compressed tablets.

### 2.5.8 Colourants

Colourants are added to tablet formulations for the following reasons: to increase patient acceptability, to disguise off-colour drugs, product identification and for the production of more elegant tablets. Colourants can be classified into three groups (Rubinstein, 1988):

i. Synthetic organic dyes and their respective lakes: Dyes are water soluble, while the lakes of the respective dyes are insoluble and are formed by the precipitation of dyes in solution on an inert base. Lakes are commonly used in tablets and tablet coatings because of their greater stability to light when compared with water soluble dyes.

ii. Inorganic pigments: These are used mainly in formulations intended for external use such as creams, lotions, and ointments. Examples include iron oxide, calcium carbonate and talc.

iii. Natural colourants: These are extracted from vegetable and animal sources, and include chlorophyll, carotenoids, riboflavin, carmine and anthocyanins. The relative instability in the presence of non-ionic surfactants as well as batch to batch colour variation has limited the use of natural colourants.


### 2.5.9       Binders

In order to produce tablets of desired crushing strength, it is often necessary to incorporate binding agents into the formulation to add to the cohesive strength already available in the bulking agent (Esezobo and Pilpel, 1976; Adetunji *et al,* 2006).

Binders thus act as adhesives to bind powders together as well as to improve the free flowing qualities of the granules by formation of granules of desired size and crushing strength in order to maintain the integrity of the final tablet (Wells and Walker, 1983; Kushret, 2004). Binders are normally included with the granulating agent in solution. Many materials are employed for this purpose, but the most common ones are starch mucilage,
sugars, cellulose, silicates, gums and polymers such as polyvinylpyrrolidone  (PVP), hydr o-xypropylcellulose (HPC), hydroxypropylmethylcellulose   (HPMC).   According   to Rubinstein (1988), the desirable qualities of a good binder are that:

i. It should be physiologically inert, non-toxic and free from unacceptable microbial load.

ii. The viscosity should be as low as possible with high cohesive tendency.

iii. It should blend easily with other ingredients.

iv. It should be as non-hygroscopic as possible.

v.  It should be as soluble as possible in the cold so that it can be made with a minimum amount of solvent.

Binding agents can be added in two ways depending on the method of granulation.

a.  As a powder in the formulation as in "slugging" or in dry granulation method. There are not many examples in this group since most substances require some moisture to make them adhesive.

b.  As a solution to the mixed powders as in wet granulation.

Kushret (2004) showed that the physical characteristics of tablets such as chipping, disintegration time and crushing strength were influenced by the method of binder incorporation. Joneja *et al*, (1999) also carried out a study to determine the effect of binder toughness on crushing strength, friability and capping using hydroxypropylcellulose (HPC), methylcellulose (MC) and polyvinylpyrrolidone (PVP) as binders. The binder properties were determined using a diametral compression test. The tablets containing HPC as binder showed the highest toughness while those containing other binders tended to fail by capping and random cracking in the middle. Rubinstein and Rhughani (1988), using four binders in a tablet formulation, showed how the choice of binder affects dissolution rate. They observed values between 3.62 minutes with PVP to 117 minutes with starch mucilage. This implies that the rate of dissolution was faster with tablets formulated using PVP than with those formulated using starch mucilage.

Generally, increasing the binder concentration has the following effects on the final granulation:

a.  Increased average granule size.

b.  Decreased granule friability.

c.  Increased interparticulate porosity.

d.  Decreased granule flowability.

Table 2.1 shows a list of some binders in common use (Talman, 1977).

**Table 2.1:** List of Some Commonly Used Binders

| Binder | Concentration in granulating fluid (%w/v) | Concentration in dried granules (%w/v) | Comments |
|---|---|---|---|
| Acacia | 5-15 | 1-5 | High quality gum that yields very hard granules. |
| Gelatin | 5-20 | 1-3 | Forms gel in cold, therefore warm solutions should be used. It is a strong adhesive used in lozenge granules. |
| Glucose | 10-30 | 5-20 | Tablets soften under humid conditions. |
| Methyl cellulose | 2-10 | 0.5-3 | Low viscosity grade may be used. May prolong disintegration time. |
| Polyvinyl pyrrolidone (PVP) | 2-10 | 0.5-3 | Soluble in water and in some organic solvents, therefore can be used for anhydrous granulation |
| Sodium alginate | 2-10 | 0.5-3 | May prolong disintegration time, hence low viscosity grade should be used. |

## 2.6       Preparation of Components for Compression

Compression refers to a reduction in the bulk volume of the material as a result of displacement of the gaseous phase (Keith, 1986). Because of the poor flowability and poor compaction characteristics exhibited by powders, they are usually formulated as granules in order to enhance tablet properties. Granulation is thus a preliminary step in the preparation of tablets. The reasons why granulation is often necessary are as follows:

i.      To prevent segregation of the constituents in the powder mix.
ii.     To improve the flow properties of the mix.
iii.    To improve the compression characteristics of the mix.
iv.    To overcome the problem of dustiness.

Until recently, the techniques for preparing compacts and tablets remained largely empirical. High-speed tablet machines had been developed, but very little was known about the mechanisms involved in compression. Since then, three broad lines of investigation have been undertaken.

i.      Studies on distribution of forces at die and punch walls and within compacts during compression using instrumented single and multiple punch machines.
ii.     Analysis of the relationship between applied pressure and the resulting density of the compact.
iii.    Analysis of the relationship between the density of the compact and the resulting strength of the interparticulate bonding.

From these studies, it is now known that the sequence of events during compression of pharmaceutical materials, as the applied force is increased, may be said to involve four stages.

i.      The initial repacking of the particles.
ii.     Elastic deformation of the particles until the elastic limit (yield point) is reached.
iii.    Plastic deformation and/or brittle fracture then dominate until all voids are virtually eliminated.
iv.    Compression of the solid crystal lattice then occurs.

Thus, the preparation of powdered pharmaceutical materials for compression may follow one or a combination of these established methods: Direct compression, compression granulation or wet granulation.

## 2.6.1          Direct Compression

Direct compression is a dry method of compression and it is usually preferable to those methods employing liquids, since dry processes do not require the equipment and handling expenses required in wetting and drying procedures, and can avoid hydrolysis of water-sensitive drugs. This method consists of compressing tablets directly from powdered materials without modifying the nature of the material itself. The method is particularly useful for materials which possess free flowing properties that enable them to be compressed directly in a tabletting machine without need for prior processing (Banker and Anderson, 1986).

Some drugs, for example aspirin, can be tabletted without further treatment, but the vast majority of drugs require the addition of a direct compression vehicle to aid compression. Materials currently available as direct compression diluents may be divided into three groups according to their disintegration properties and their flow characteristics as follows:

i.   Disintegration agents with poor flow characteristics e.g. microcrystalline cellulose, cellulose, microfine cellulose and directly compressible starch.
ii.  Free flowing materials which do not disintegrate e.g. dibasic calcium phosphate.
iii. Free-flowing powders, which disintegrate by dissolution e.g. dextrose, sucrose, spray-dried lactose, anhydrous lactose, mannitol and amylase.

Direct compression vehicles should be free flowing, physiologically inert, tasteless, colourless, have a good mouth feel and should also improve the compressibility of poorly compressible drugs, be relatively inexpensive and be capable of being reworked with no loss of flow or compressibility. Direct compression diluents should also promote rapid disintegration, be white in colour, and be able to produce tablets containing a high proportion of non – compressible material.

The advantages of direct compression process include reduction in appliance and handling costs because it involves very few stages. Furthermore, the absence of an adhesive granulating agent would imply good availability of drug from the dosage form, while the elimination of the drying and moistening stages would eradicate many of the stability problems associated with the wet granulation process (Talman, 1977). Limitations of this method are stratification in handling and variation in drug content of

the resultant tablets as a result of differences in particle size and bulk densities between the diluents and the active ingredient. Static charges may also develop on the drug during mixing which may prevent uniform distribution and therefore inadequate mixing may result. In some cases, the direct compression diluents may interact with the drug as observed in maillard reaction, which is a yellow colouration resulting from the reaction between amine compounds and spray dried lactose (The British Pharmaceutical Codex, 1994).

### 2.6.2        Compression Granulation

This method is adopted when the tablet ingredients are sensitive to heat and/ or moisture. The blend of powders is forced into dies of a large heavy – duty tabletting press and compacted. The compacted masses are called *slugs*; hence this method is sometimes referred to as dry granulation or slugging. The method is adopted for materials which are hydrolabile, thermolabile or yield granules with poor flow or compression properties when processed by the wet granulation technique (Banker and Anderson, 1986)

An alternative method is to squeeze the powder blend into a solid cake between rollers: this is known as roller compaction. The slugs or roller compacts are then milled and screened in order to produce a granular form of tabletting material, which flows more uniformly than the original powder mix.

Slugging has the advantage over direct compression in that once the slugs are formed, no segregation of drug and excipients can occur.

### 2.6.3        Wet Granulation

This is the most widely used method for preparing pharmaceutical materials for compression. It enhances the physical characteristics of the material and affords a greater chance of producing granules which satisfy all physical requirements for compression into the desired tablets. This method is however not readily suitable for hydrolysable and/or thermolabile drugs such as antibiotics.

In a conventional massing and screening wet granulation process, the following steps are involved (Armstrong and Morton, 1979):

i.    Blending of solid ingredients.

ii.     Wetting.

iii.    Granulation

iv.     Drying

v.      Sizing

vi.     Second blending

## i.    Blending of solid ingredients

This is an initial blending of solid ingredients and in this stage, the drug substance is mixed, if needed, with the diluent or filler. Tablets weighing much less than 50 mg are so small as to be difficult to pick up and manipulate with the fingers, yet many drug substances are active in far lower doses. Accordingly, it is necessary to dilute the drug to make a tablet of reasonable size.

The ideal diluents, which should be inert both chemically and pharmacologically, are blended in a powder mixer with the aim of producing a uniform dispersion of the drug in the filter.

## ii.    Wetting

The mixture of powders is now wetted and the granulating agent, usually in an aqueous solution or dispersion, is introduced at this stage. The choice of the granulating agent is governed often by the intended use of the tablet.

Though size enlargement takes place primarily with the adhesion of particles by a film of granulating agent, a second mechanism is available if the solid particles are soluble in the granulating fluid. Partial dissolution occurs, yielding a supersaturated solution of the solid, and on subsequent drying, re-crystallization occurs and the resultant crystal bridges between the particles can contribute significantly to granule strength.

The wetting stage is usually carried out in the same apparatus in which the dry powders were blended. Sufficient granulating agent is added to form a dump, coherent mass, though over-wetting should be avoided.

## iii.    Granulation

The damp mass is now passed through a coarse sieve (usually of mesh size 1-2 mm) to produce roughly spherical granules. This product is usually achieved by means of

an oscillating granulator, in which a rotor, oscillating about its horizontal axis, passes the damp material through the screen. Alternatively, a comminutor, containing a number of rapidly revolving blades, may be used.

**iv**.     **Drying**

The granules are now dried using either a tray drier or more usually, a fluidized bed drier to produce a coarse, free-flowing solid.

The drying temperature is about 60 $^0$C but may be reduced if thermo labile substances are present. With tray driers, air exchange is essential to prevent saturation of oven temperature with solvent vapour. By spreading the granules as thin layers on the tray and raking the layers from time to time, agglomeration of granules and migration of solutes are minimized while an even drying of granules is promoted. For large batches, granules are dried for up to 24 hours and if drying is prolonged the amount of fines increases. However, oven-dried granules have inferior compressional characteristics. During drying, interparticulate bonds results from fusion of particles and hardening of the binding agents.

In fluidized bed drying, a means of rapid drying is offered and it has advantages enumerated below:

a.     Efficient heat and mass transfer that gives high drying rates.

b.     Individual particles, rather than the entire bed, are dried.

c.     There is absolute control and uniformity of temperature.

d.     The containers can be mobile, making handling simple, and reducing labour costs.

e.     Free movement of individual particles eliminates the risk of soluble materials migrating, as may occur in static-beds.

However, certain disadvantages such as attrition of materials due to turbulence and generation of static electricity charges, including entrainment of fine particles are inherent in fluidized bed drying.

**v.**     **Sizing**

The size of granules at this point will usually be considerably larger than the size required for tabletting where there is need to also ensure that a constant weight flows into

the die of the tablet press. Hence, a communition stage followed by sieving, will normally be needed, the usual granule size for tabletting being 350-700 μm (Ansel, 1981).

**vi.     Second Blending**

A second blending stage incorporates other important additives into the material prior to compression.

### 2.6.3.1 Factors Affecting Wet Granulation

Several factors have been identified to affect the physicochemical properties of granules and tablets resulting from wet granulation. These factors include:

 i.    The nature, volume and concentration of the binder.

 ii.   The particle size distribution of the starting materials.

 iii.  The massing time of granulation; solute migration during drying.

 iv.   The temperature of granulation including the quantity of granulating fluid.

Increase in granule strength has been attributed more to the quantity of granulating fluid used and the concentration of binding agent. For a given material, smaller initial particle sizes usually lead to granules of greater strength presumably due to increased occurrence of interparticulate contacts (Hunter and Ganderton, 1972). These factors are further discussed:

**i.     Effect of binder**

The type and amount of binder added to the powder during the process of granulation affect the overall nature of the granules produced. Too much binder leads to the production of very hard tablets leading to difficulty in disintegration and dissolution of such tablets; while too little amount of binder leads to granules producing tablets that cannot withstand the hazard that tablets undergo before getting to the user.

Wells and Walker (1983) carried out a study on the effect of binder vehicle on granule and tablet properties in a model system, in which polyvinylpyrrolidone was used as a binder with acetylsalicylic acid as the medicinal agent. Using ethanol- water mixtures to produce differing drug solubilities, they found that greater drug solubility was produced by larger granules which were less friable and gave better size uniformity.

Also, Zeiko *et al* (1998) did a study on the evaluation of substrate binder effects on interfacial interactions. They found that increasing the amount of binder in granules improved the adhesive interaction existing between the substrate and the binder. Their results also indicated that the mechanical properties of the tablets produced were basically determined by the physico-chemical interactions of the substrate and the binder agent.

**ii.      Effect of initial particle size of materials**

Increasing the initial particle size of any of the components of a binary mixture leads to an increase in granule strength and generally reduces mean pore size for powders (Opakunle and Spring, 1977).

**iii.     Effect of massing Time**

Massing time can be simply referred to as the length of time used in mixing the binder and blending it into drug powder or the time used in mixing the powders and adhesive in a dry granulation process or the time used in mixing the liquid to wet the powders even if binders are not added. It is usually carried out before screening or sieving of the dry or damp drug mass.

According to Klienebudde and Thies (2000), a study involving the melt pelletisation of a hygroscopic drug in a high shear mixer revealed that massing time is an important variable influencing mean granule size and size distribution.

**iv.     Effect of granulation method**

Different granule characteristics have resulted from the use of different granulation methods in the production of granules from powders.

Soyeux *et al* (1998) compared different granule characteristics such as packing ability, particle size distribution, flow ability, granule strength and porosity, etc, between granules produced using the fluidized bed granulation method and other methods. It was discovered that the fluidized bed granulation method produced the densest packing of granules followed by the kneading method and extrusion method respectively.

**2.6.3.2 Theory and Mechanism of Moist Granulation**

The addition of a granulating liquid to a mass of powder may be characterized in a series of stages described by Newitt and Conway-Jones (1958) as illustrated in Fig 2.1.

When the powder particles are wetted during the initial stage, liquid films will be formed on the surface and may combine to produce discreet liquid bridges at the point of contact. The surface tension and negative capillary pressure in such bridges provide the cohesive force and result in the pendular stage (Fig 2.1a), which has a low mechanical strength. With an increase in the liquid content, several bridges may coalesce giving rise to the funicular stage (Fig 2.1b) with a modest increase in granule strength. Eventually, as more liquid is added and the mass is kneaded to bring the particle into closer proximity, the void spaces within the granules are entirely eliminated. At this point, bonding is effected by interfacial forces at the granule surface and by negative capillary pressure throughout the interior liquid filled spaces, a condition referred to as the capillary stage (Fig 2.1c). Further addition of liquid results in the formation of droplet (Fig 2.1d) in which the particles are now held together by surface tension, however, without intragranular forces; such structures are weaker.

Thus, the capillary stage coincides with the maximum strength of well-formed granules and optimization of many granulating processes is aimed at ensuring that this state has been achieved. The granulating equipment can, for example, be equipped with torque measuring devices which sense the change in agitation power required at the capillary stage.

**2.7     Compression Sequence**

The formation of a coherent tablet is based on the attractive forces that exist between the particles. These forces may be non-specific force (e.g. Vander Waals forces) or specific forces brought about by features of molecular structures of the particles (e.g. hydrogen bonding). However, a significant degree of interparticulate attraction is only obtained when the particles are actually touching each other or are in very close contact. Thus, anything that increases the area of interparticulate contact will favour the formation of coherent tablets.

When extra mechanical forces are applied to a powder mass, there is closer repacking of the powdered particles thus resulting in volume reduction. As the load increases, rearrangement becomes more difficult and further compression involves some type of plastic deformation. If on removal of the load, the deformation is to a large extent spontaneously reversible that is, if it behaves like rubber, then the deformation is said to be elastic. All solids undergo some elastic deformation when subjected to external forces.

In some groups of powdered materials, an elastic limit or yield point is reached and any load above the level results in deformation that is not easily reversible on the removal of the applied force. Bulk volume reduction in these cases results from plastic deformation and/or viscous flow of the particles, which are squeezed into the remaining void spaces, resembling the behaviour of modeling clay. This mechanism predominates in materials in which the shear strength is less than the tensile strength.

Conversely, when the shear strength is greater, particles may be preferentially fractured (fragmentation) and the smaller fragments then help to fill up any adjacent air spaces. This is most likely to occur with hard brittle particles (such as sucrose) and is known as brittle fracture.

The predisposition of a material to behave in a particular manner depends on the lattice structure. Irrespective of the behaviour of large particles of the materials, small particles may undergo microsquashing, by deforming plastically, and the proportion of fine powder in a sample may therefore be significant. Asperities that are sheared off larger, highly irregular particles could also behave in this way, thus particle shape is another important factor (Marshall, 1986)

Basically, the events during compression involve the application of forces, via two punches. The punches are termed the lower punch, the tip of which moves up and down within the die, but never actually leaves it, and the upper punch, which descends to penetrate the die and apply the compressive force, and then withdraws to permit ejection of the tablet. The die and punches are almost invariably made of hardened steel.

Irrespective of the type of tablet press, the process of compression can be divided into four distinct stages (Stenlake, 1981) as shown in Fig 2.2:

  i.    Initial repacking of particles

 ii.    Elastic deformation of the particles until the elastic limit is reached (Yield point)

iii.    Plastic deformation and/or brittle fracture then dominates until all voids are virtually eliminated.

iv.    Compression of the solid crystal lattice then occurs.
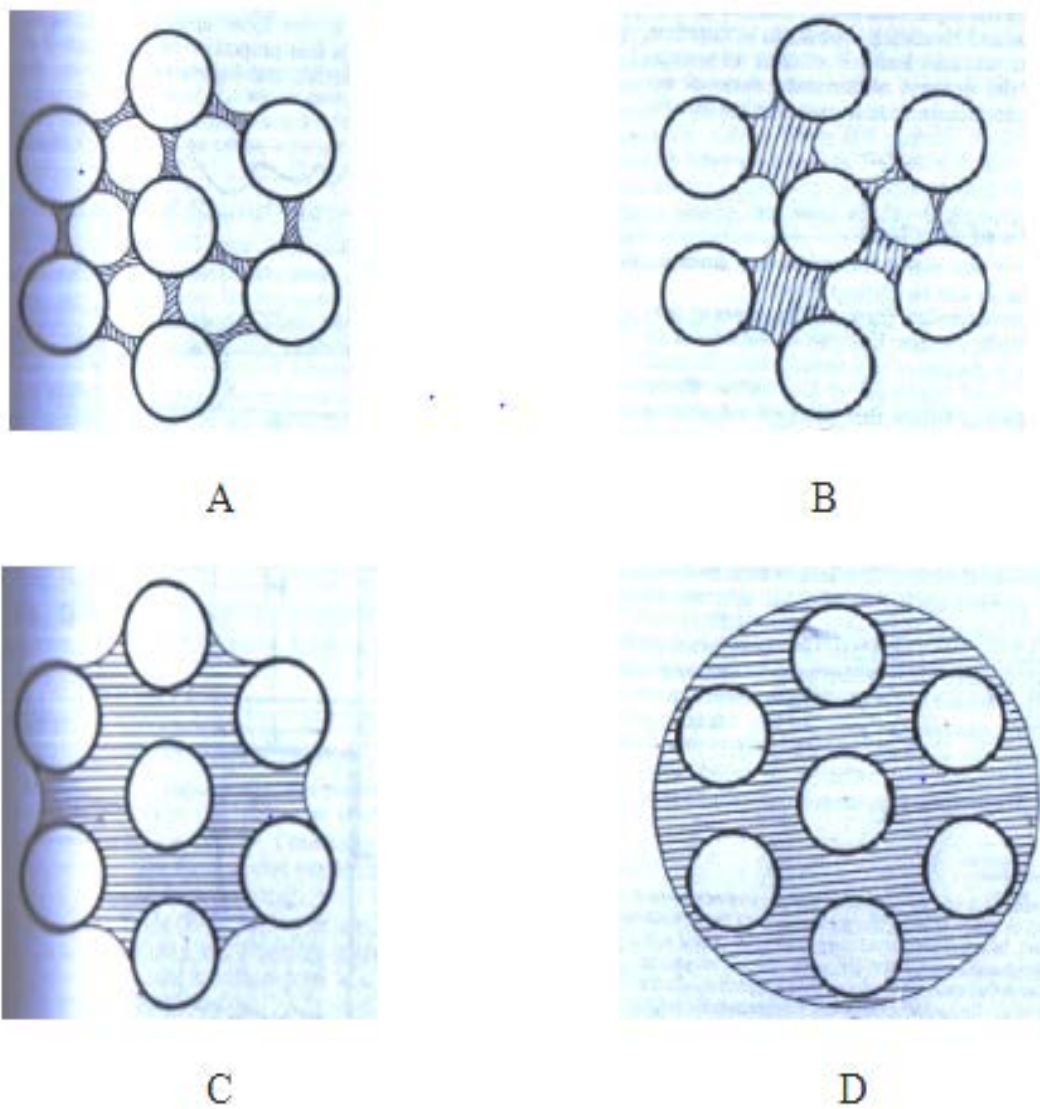
**Fig 2.1:** Stages in the development of moist granules as the proportion of the liquid is increased (A) Pendular (B) Funicular (C) Capillary (D) Droplet
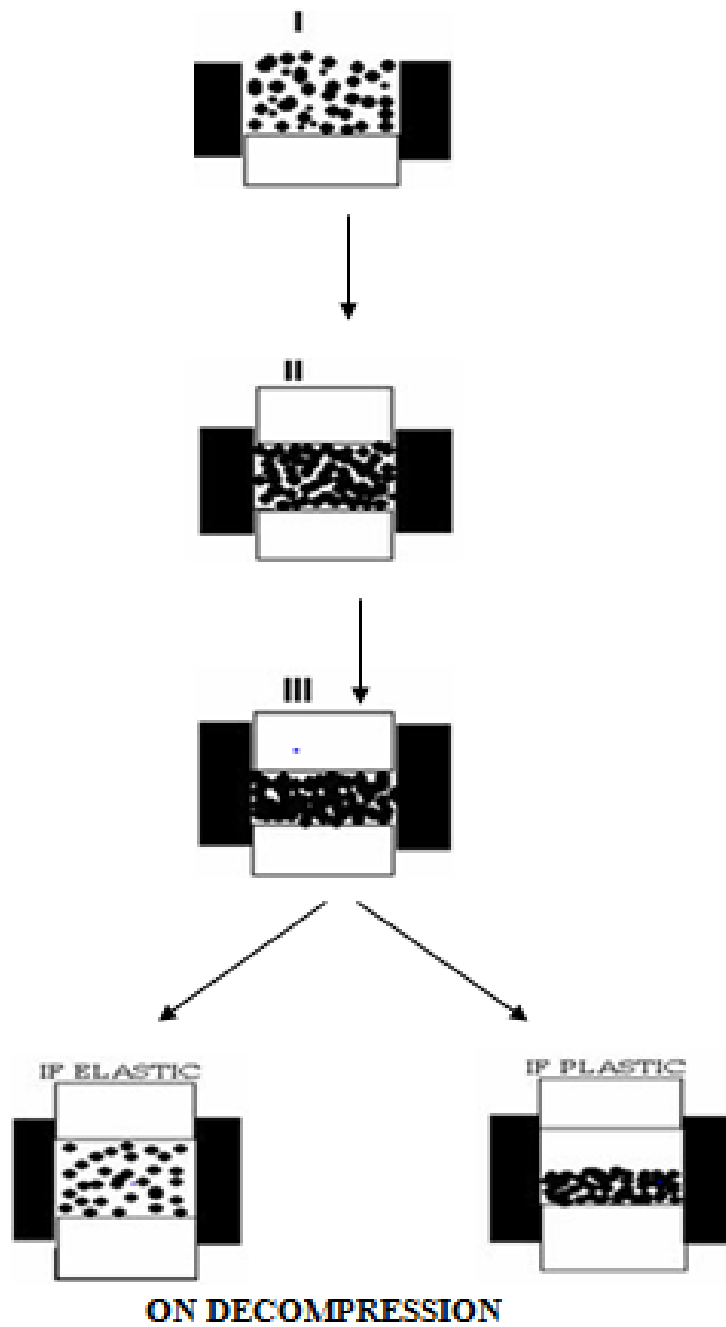
**Fig 2.2:** Stages involved in compression (I-III) and decompression

**2.8    Tablet Compression Machines**

There are two basic types of tablet machines in common use (Armstrong, 1979). They are:

i.    The single stroke or eccentric press.

ii.    The rotary tablet (multiple-station) press.

Another classification was made by King and Schwartz (1985) and included a third class of compression machine; the advanced high speed press.

These machines operate on the same principle but differ in their productivity. The basic operation of these tablet machines involves the compression of tablet granulation within a steel die cavity by the pressure exerted by the movement of the lower and upper punches.

**2.8.1        The Single Stroke or Eccentric Press**

This type possesses one die and one pair of punches. The particular solid, contained in a hopper, is fed into the die by means of a shoe, which moves to and fro over the die. The output of this type of press is 150-200 tablets per minute at a maximum and so its use is limited to relatively small-scale production or research work (Fig 2.3).

The force detected from the lower punch of an eccentric press is less than that applied by the upper punch. However, this reduction in force is not uniform on descent (Ghanam and Kleinebudde, 2011). Significant features are zones of high force at the periphery near the moving punch and much lower on the central axis of the tablet. Conversely, a zone of lower force occurs on the axis just below the top surface. Since tablet strength depends on porosity, which in turn depends on the applied force, it follows that same parts of the tablet will be weaker than others.
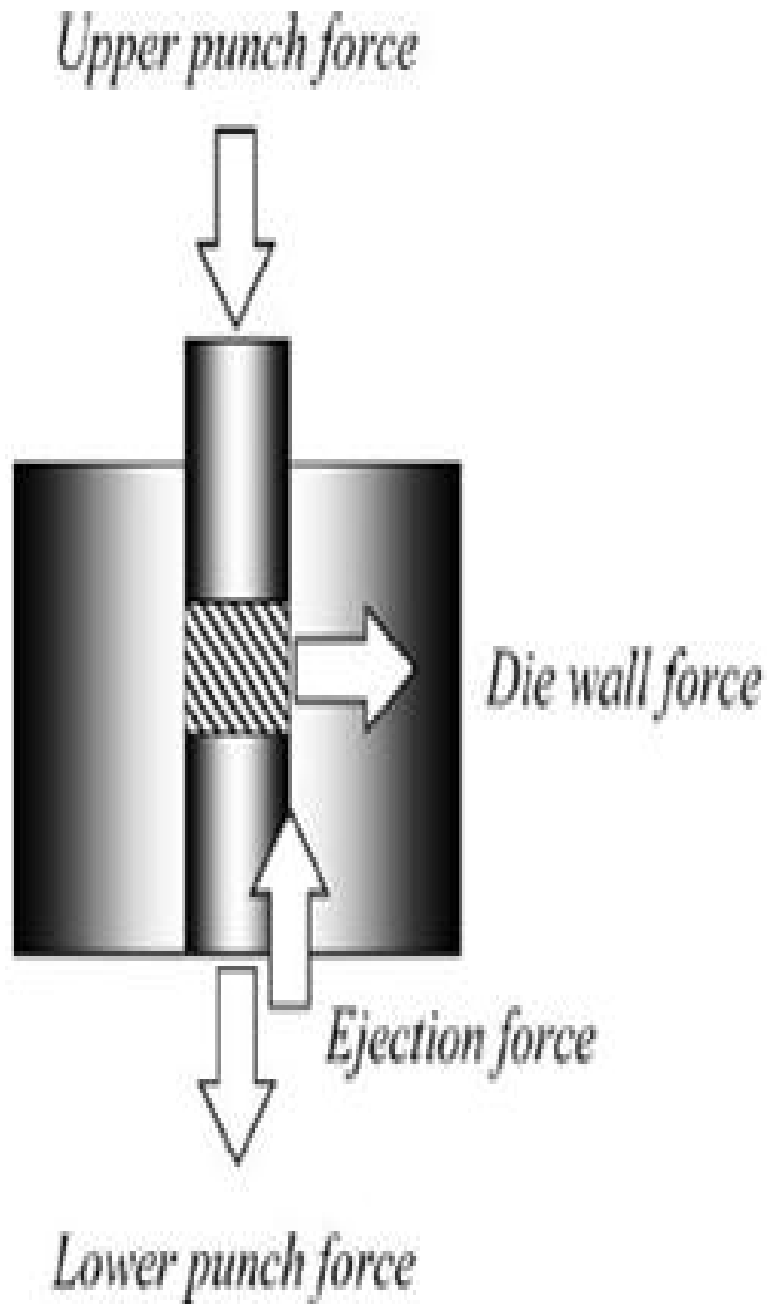
**Fig 2.3:** Diagram of a cross section of a typical single punch and die assembly used for compaction studies (Banker and Anderson, 1986)

If a tablet is to be disrupted, this will occur at its weakest point which is near the top surface; this gives rise to a well known phenomenon of tablet manufacture called *capping*.

For many years, capping was considered to be due to the entrapment of air in the tablet. However, it is now recognized to be fundamentally due to variation in porosity within the tablet structure, and although pores contain entrapped air at elevated pressure, this will only assist disruption of the tablet structure.

### 2.8.2   The Rotary Tablet Press

This consists of a number of dies arranged in a rotating disc or "table", and sets of punches in tracks mounted above and below the table. The table and tracks rotate together, so that one die is always associated with one pair of punches. The vertical position of the lower punch in the die is governed by passage above cams, and the force is applied by the punches passing over and under pressure rolls. This type of press can achieve outputs of over 600,000 tablets per minute, based on the speed of rotation of the table and the number of sets of punches.

Generally, apart from different shapes of the punch faces ranging from circular to non-circular or flat, the punches may be embossed, so that an identification mark, product name or manufacturer's logo appears on the tablets.

### 2.8.3   The Advanced High Speed Press

The development of devices for promoting granule flow, die-filling and the removal of air during compression has permitted the introduction of ultra-high speed presses (Talman, 1977; King and Schwartz, 1985) - the double and triple-rotary machines. Granule flow from the hopper into the feed frame of the conventional tabletting machines is governed by the height of the hopper outlet above the die table (i.e. gravity controlled). This process of die fill is grossly inadequate for the high speed presses which may require the die filling, compression and ejection operations to be completed in a fraction of a second (Armstrong and Palfrey, 1987). In order to provide granule flow that is commensurable with the speed of rotation of the turrets of rotary presses, vibratory

devices are attached to the hopper. However, the flow rate desired for the ultra-high speed presses require more efficient feeding devices (King and Schwartz, 1985).

Another technique that has been employed is the induced feeding of the die cavity. The Manesty rotaflow feeder employs contra-rotating vane rotors in an enclosed feed frame to direct granules into the dies (Talman, 1977). The very short compression cycle operational in the ultra-high speed presses would not permit a complete removal of air from the granule bed under compression. This may inhibit inter-granular bonding that may, in turn, promote capping and lamination of tablets. In order to eliminate this problem, precompression rollers have been designed in some rotary presses to exert a slight compaction on granules prior to the main compression process.

Some additional features designed into the ultra-high speed presses have contributed significantly to the attainment of some standard requirements of Good Manufacturing Practice (GMP). Such features include computerization and programming of production sequence, continuous in-process control and facilities for full data storage (King and Schwartz, 1985).

Examples of ultra-high speed presses include Novapress, Excelpress, Rotapress and Unpress (Manesty Machines, U.K.) and the perfecta series (Wilheim Fette GmbH, Germany). The Fette PT 2080 models are available as 22-,29-,36- and 43- station presses with capacity in excess of 290,000 tablets per hour and facilities for handling tablets with diameters up to 25mm and compression forces up to 80,000N (King and Schwartz, 1985).


## 2.9    Consolidation

Consolidation is an increase in the mechanical strength of the material as a result of particle-particle interaction (Marshal, 1986; Gabriel *et al*, 2003).

Deformation effects may be accompanied by the breaking and formation of new bonds between the particles which gives rise to consolidation as the new surfaces are pressed together, and on the micro scale, when the surfaces of two particles approach each other closely enough (for example at a separation of less than 50 μm), their free surface energies result in a strong attractive force; a process known as *cold welding*.

The nature of the bond so formed is similar to those of the molecular structure of the interior of the particles, but, because of roughness of particle surface, the actual

surface area involved may be small. This hypothesis is favoured as a major reason for the increasing mechanical strength of a bed of powder when subjected to high compressive force. On the macro scale, most particles encountered in practice have an irregular shape so that there are many points of contact in a bed of powders. Any load applied to the bed must be transmitted through these particle contacts. Under appreciable forces, this transmission may result in the generation of considerable frictional heat. If this heat is not dissipated, the local rise in temperature could be sufficient to cause melting of the contact area between particles which will relieve the stress in that particular region. In that case the mesh solidifies giving rise to *fusion bonding*, which in turn results in an increase in the mechanical strength of the mass (Higuchi *et al*, 1953).

In both 'cold' and fusion' welding, the process is influenced by several factors including:

  i.    The chemical nature of the materials.
 ii.    The extent of the available surface.
iii.    The presence of surface contaminants, which tend to reduce surface bonding.

Also, the type and degree of crystallinity in a particular material influence its consolidative behaviour under appreciable applied force. For example, it has been shown that substances which possess the cubic lattice arrangement are tabletted more satisfactory than those with a rhombohedral lattice. The isotropic nature of the cubic lattices would be expected to contribute to better tabletting because no alignment of particular lattice planes is required.

Thus, during normal tabletting operations, consolidation is accentuated in the regions adjacent to the die wall due to the intense shear to which the material is subjected as it is compressed axially and is pushed along the wall surface.

## 2.10   Decompression

A complete tabletting cycle involves compression, decompression and ejection stages. It is now realized that the decompression stage is as important as (but not independent of) the compression stage in determining whether or not a tablet formulation will form satisfactory tablets.

Some deformation processes, such as plastic deformations, are time dependent and occur at various rates during the compaction sequences, so that the tablet mass is never in a state of stress/strain equilibrium during the actual tabletting process. This means that the rate at which load is applied and removed may be a critical factor in materials for which dependence on time is significant. More specifically, if a plastically deforming solid is loaded (or unloaded) too rapidly for this process to take place, the solid may exhibit brittle fracture.

Research and investigations in recent years have shifted to relating capping and lamination tendencies of tablet formulation to its plastic and elastic behaviour during the compression/decompression/ejection cycles (Itiola and Pilpel, 1986; Adolfsson and Nystrom, 1996).

Decompression leads to a new set of stresses within the tablet as a result of elastic recovery, which is augmented by the forces necessary to eject the tablet from the die. Irrespective of the consolidation mechanism, the tablet must be mechanically strong enough to accommodate these new stresses, otherwise structural failure will occur. In particular, the degree and rate of stress relaxation within tablets, immediately after the point of maximum compression, have been shown to be characteristic of a particular system. This phase of the cycle can provide valuable insight into the reasons behind inferior tablet quality and may suggest a remedy.

If the stress relaxation process involves plastic flow, it may continue after all compressional forces have been removed, and the residual pressure will decay with time. The plastic flow can be interpreted in terms of a viscous and elastic parameter in series (Itiola, 1994). This interpretation leads to a relationship of the form:

$$\text{Log } F_t = \text{Log } F_m - K_v \tag{1}$$

where   $F_t$     = Force left in the viscoelastic region at  time t.

   $F_m$     = Total magnitude of force at time $t = 0$

   $K_v$     = Viscoelastic slope and a measure of plastic flow.

Materials with higher $K_v$ values undergo more plastic flow and such materials often from strong tablets at relatively low compaction forces. Alternatively, the changing thickness of the tabletting mass due to the compactional force, and subsequently due to

elastic recovery during unloading, can be used to obtain a measure of plastoelasticity (ER/PC)

where ER = Elastic recovery of the material during compression

PC = Plastic compression of the material under constant load.

PC is a measure of plastic deformation and has been defined by Malamataris *et al* (1984) as:

$$PC = \frac{(H_p - H_t)}{H_t} \times 100 \qquad (2)$$

where $H_p$ = Tablet thickness at maximum pressure

$H_t$ = Tablet thickness after being held at maximum pressure for a specified time

ER has been defined by Krycer *et al* (1982) as:

$$ER = \frac{(H_0 - H_p)}{H_p} \times 100 \qquad (3)$$

where $H_0$ = Tablet thickness after ejection and some specified storage time.

It should be noted that the value of ER/PC will be influenced by a number of experimental variables such as the rate of loading, the magnitude of the applied force, the time for which it is held, the dimensions and state of the punches and die used, and die wall reaction effects.

An inverse relationship has been established between the values of ER/PC of some pharmaceutical materials and the tensile strength of their tablets (Malamataris *et al*, 1984; Itiola and Pilpel, 1986; Itiola, 1994)

## 2.11 Density

The density of a powdered material can be defined as the ratio of mass (M) of the material to its volume (V). Three different densities of powdered solids may be defined mathematical as follows:

i.      True density, $\rho_t = M/V_t$             (4)

ii.     Granular density, $\rho_g = M/V_g$         (5)

iii.    Bulk density, $\rho_b = M/V_b$          (6)

where $V_t$, $V_g$ and $V_b$ are the true volume, granular volume and bulk volume respectively (Marshall, 1986).

Comparing the bulk density, $\rho_b$, of a sample under specific test conditions with the true density, $\rho_t$ (sometimes called the theoretical density) of the material leads to a dimensionless quantity, $\rho_r$, known as the relative density (or packing fraction or solid fraction) where:

$$\rho_r = \rho_b/\rho_t \qquad\qquad (7)$$

Relative density is an inverse measure of the porosity of a tablet and during compressional processes, the relative density increases to a maximum of unity when all air spaces have been eliminated.

### i. True density

True density, $\rho t$, is the density of the solid material when all the void spacies have been excluded. True density, can be measured using x-ray diffraction methods or by the use of helium pycnometer (helium is an inert gas), or a liquid pycnometer with mercury or a solvent of low surface tension such as benzene or xylene as the displacement fluid (a liquid pycnometer can measure only granular volume). True density may influence compressibility, tablet porosity, dissolution and other properties.

### ii. Bulk Density

The bulk density, $\rho_b$, of a powder bed is the weight of the powder comprising it divided by the volume of the bed. Bulk density, the value of which depends largely on the particle shape, changes with the degree of packing of the particles or granules. As particles become more spherical, bulk density increases due to a decrease in bulk volume of the bed. Also, as granule size increases, the bulk density decreases (Itiola, 1991).

**2.12      Heckel and Kawakita Plots**

Many hypotheses have been proposed to describe the behaviour of powders during tabletting in relation to the properties of the resulting tablets. Also, numerous mathematical descriptions of the compression process have been compiled in the literature (Heckel, 1961; Cooper and Eaton, 1962; Kawakita and Ludde, 1970).

**2.12.1 The Heckel Equation**

The Heckel equation is the most widely applied and probably the most useful of the compression equations. The Heckel equation (Heckel, 1961) is widely used for relating the relative density, $\rho_r$, of a powder bed during compression to the applied pressure, P. The equation has been applied to pharmaceutical powders of both single component (Duberg and Nystrom, 1985; Itiola, 1991) and multiple-component systems (Garr and Rubinstein, 1991; Odeku and Itiola, 1998; Ayorinde *et al*, 2005). It determines the process of volume reduction of the materials on application of compaction force (Heckel, 1961; Alderborn, 2002).

From the relationship, as the applied pressure increases, the degree of mass densification is a direct function of the porosity. That is:

$$E = d\rho_r/dP \tag{8}$$

where E is porosity and the relative density, $\rho_r$ is at pressure, P. The porosity can also be defined as:

$$E = (V_p - V) / V_p = 1 - \rho_r \tag{9}$$

where $V_p$ and V are the volume at an applied load and volume at theoretical zero respectively.

Thus, equation (9) can be expressed as:

$$d\rho_r/dP = K (1- \rho_r) \tag{10}$$

and then transformed to the Heckel equation below:

$$\text{In } [1/(1-\rho_r)] = KP + A \tag{11}$$

where K and A are constants.

Plotting the value of In $[1/(1-\rho_r)]$ against applied pressure, P, yields a linear graph having slope, K and intercept, A. The slope of the straight line portion, K, is the reciprocal of a material dependent constant known as the means yield pressure, $P_y$, of the material (Nokhodchi $et\ al$, 1996).

The intercept of the extrapolated linear portion, A, is a function of the original compact volume. The particular value of Heckel plots arises from their ability to identify the predominant form of deformation in a material. They have been used to distinguish between substances which consolidate by fragmentation and those that consolidate by deformation, and also as a means of assessing plasticity.

Materials that are comparatively soft and that readily undergo plastic deformation (e.g. sodium chloride) retain different degrees of porosity depending on the initial packing in the die. This in turn is influenced by the size distribution, shape, etc of the original particle.

From the value of A, the relative Density ($\rho_{rA}$), which represents the total degree of densification (Itiola, 1991; Mitrevej $et\ al$, 1996) can be calculated using the following equation (Humber-Droz $et\ al$, 1983; Roberts and Rowe, 1986):

$$A = \text{In } [1/(1-\rho_{r\,A})] \tag{12}$$

Thus,

$$\rho_{rA} = 1 - e^{-A} \tag{13}$$

The relative density of the powder bed at the point when the applied pressure equals zero, i.e. $\rho_r$o, is used to describe the initial rearrangement phase of densification as a result of die filling and this is obtained from the ratio of the loose density to the particle density (Chowan and Chow, 1981).

The relative Density, $\rho_{rB}$ describes the phase of rearrangement of particles during the initial stage of compression. The extent of the rearrangement phase depends on the theoretical point of densification at which deformation of particles begin.
Thus,

$$\rho_{rB} = \rho_{rA} - \rho_{r0} \qquad\qquad (14)$$

Hersey and Rees (1970) have classified powders into three types (A, B and C) on the basis of the Heckel equation (Fig 2.4)

Type A materials, exemplified by sodium chloride, exhibit a linear relationship at all applied pressures indicating densification only by plastic deformation (Fig 2.4A). This is because they are comparatively soft and readily undergo plastic deformation, retaining different degrees of porosity depending on the initial packing of powder in the die.

Type B materials (e.g. lactose) show an initial curved region followed by a straight line (Fig 2.4B). This indicates that the particles are fragmenting at an early stage of the compaction. This occurs with harder materials with higher yield pressure, and fragmentation takes place first to provide denser packing (Esezobo and Pilpel, 1977).

Type C materials (e.g. lauric, palmic and stearic acid) exhibit an initial steep region which becomes superimposed and flattens out as the applied pressure is increased (Fig 2.4C). This behaviour is due to the absence of a rearrangement stage and densification is due to plastic deformation and asperitic melting (York and Pilpel, 1973).

Type A

$\ln [1/(1-D)]$

Compression pressure

Type B

$\ln [1/(1-D)]$

Compression pressure

Type C

$\ln [1/(1-D)]$

Compression pressure
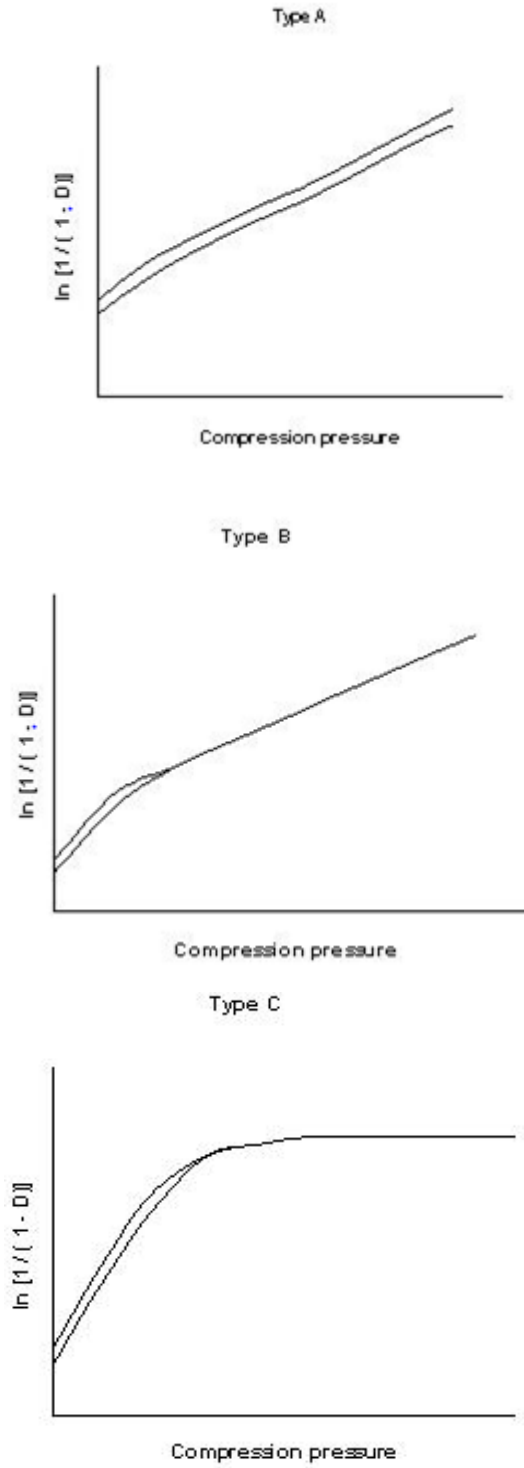
**Fig 2.4:** Shapes of the Heckel plots for types A, B and C materials

Generally, hard brittle materials are more difficult to compress than soft ones because fragmentation with subsequent percolation of fragments is less efficient than void filling by plastic deformation. In fact, as the porosity approaches zero, plastic deformation may be the predominant mechanism for all materials.

The two regions of the Heckel plots in type B are thought to represent the initial repacking stage and the subsequent deformation process, the point of interception corresponding to the lowest force at which a coherent tablet is formed. In addition, the crushing strength of tablets can be correlated with the values of K of the Heckel plots; larger values of K usually indicate harder tablets. Such information can be used as a means of binder selection when developing tablet formulations.

The Heckel equation has proved useful in characterizing the compression charcteristics of some pharmaceutical excipients developed locally in Nigeria. Three different local starches from cassava (*Manihot utilissima*), potato (*Ipomea batatas*) and yam (*Dioscorea dumetorum*) have been shown to deform mainly by plastic flow as has been observed for many official and proprietary starches. The potential advantage of Khaya gum as a promising binding agent over official Gelatin BP in solving lamination and capping problems in oral Griseofulvin tablet formulations has also been established using the heckel equation (Adeyemo and Itiola, 1993).

Heckel plots can be influenced by the overall time of compression, the degree of lubrication and even the size of the die, so that the effects of these variables should also be studied. It is also worth mentioning that Heckel plots have their limitations and are believed to generally exhibit linearity for many materials at high pressures (Celik, 1992).

## 2.12.2 Kawakita Equation

The Kawakita equation was developed to study powder compression using the degree of volume reduction under pressure (Kawakita and Ludde, 1970) and is expressed as:

$$C = (V_0 - V_p)/V_0 = abP/ (1-bP) \qquad (15)$$

The equation in practice can be rearranged as:

$$P/C = (P/a) + (1/ab) \qquad\qquad (16)$$

where  C= Degree of volume reduction

$V_o$ = The powder's initial bulk volume.

$V_p$ = The powder's volume after compression.

The constant "a" is the material's minimum porosity before compression while the constant "b" relates to the material's plasticity. The reciprocal of b defines a pressure term $P_K$, which is the pressure required to reduce the powder bed by 50% (Shivanand and Sprockel, 1992; Lin and Cham, 1995; Alderborn, 2002).

Some limitations in the use of the Kawakita equation have been reported. Celik (1992) observed that the equation would describe the compaction process up to a certain pressure, above which the equation would no longer be linear. However, Odeku and Itiola (1998) successfully demonstrated the application of the Kawakita equation to granular materials.

Thus, while the Kawakita equation usually shows linear relationship at low compression pressures, the Heckel equation generally shows linearity at high pressures. This has prompted the decision in recent times, to employ both equations simultaneously as this combination usually presents a more complete description of compaction behaviour of pharmaceutical powders (Odeku and Itiola, 1998; Alebiowu and Itiola, 2002)

## 2.13    Mechanical Strength of Tablets

The mechanical strength of tablets has been defined by several means such as the crushing strength (Keith, 1986); the axial strength (Jarosz and Parrott, 1982), radial strength (Fell and Newton, 1970; Jarosz and Parrott, 1982), Friability (Odeku and Itiola, 2003), tensile strength and tablet hardness (Rees and Rue, 1978; Adetunji *et al*, 2006). Ideally, tablets should be formulated to release the active ingredients in such a way that the desired effects will be achieved with neither adverse effects nor toxicity. Also, such formulations    will    be    expected    to    have    the    desired    absorption,    distribution,

biotransformation and elimination properties and consequently, offer the expected pharmacodynamic characteristics.   There is however, no such tablet formulation, but the aim of drug development is to approach this ideal situation.

The design of tablets and subsequent monitoring of tablet production quality, quantitative evaluation and assessment of the chemical, physical and bioavailability properties of the tablets must be made. The in-process tests routinely needed to monitor or evaluate tablet production quality include tests for evaluation of mechanical strength (such as crushing strength and friability), evaluation of drug content and release (uniformity of weight and content, disintegration and dissolution times) and various methods of evaluation of elegance (Banker and Anderson, 1986).

### 2.13.1   Crushing Strength and Friability

Tablets are prone to mechanical shocks of handling during the process of their manufacture, packaging and transportation. It is therefore required that tablets should possess a certain amount of strength and a reasonable resistance to friability in order to withstand these mechanical shocks in the hands of the consumer.

### 2.13.1.1 Crushing Strength

Crushing strength has been defined as that compressional force ($F_c$) which when applied diametrically to a tablet, just fractures it (Keith, 1986). Most practical tests involve placing the tablet on or against a fixed anvil and transmitting the force to it by means of a moving plunger, until the tablet just fractures. Since tablets are anisotropic, and test conditions rarely provide well-defined uniform stresses, full and exact interpretation of findings is difficult. With flat-faced anvil and plunger, the failure may be compressive (that is, the tablet is crushed). If one of them is knife-edged, however, then it is more likely to be tensile, with the tablet splitting open across a diameter (Keith, 1986).

Crushing strength of a tablet is a function of the die fill and compression force. At a constant die fill, the crushing strength value increases and thickness decreases as additional compression force is applied. This relationship holds up to a maximum value for crushing strength and a minimum value for thickness beyond which increase in pressure causes the tablet to laminate or cap, thus destroying the integrity of the tablet. In

general, tablets are harder several hours after compression than they are immediately after compression. Larger tablets require a greater force to cause fracture and are therefore harder than small tablets.

Tablet crushing strength has been documented to affect the disintegration time and dissolution rate of the drug. Lubricants in turn affect tablet crushing strength when used in too high a concentration or when mixed for too long a time (Banker and Anderson 1986). Several devices are available for testing crushing strength. These include the Strong-Cobb tester, Erweka tester, Monsanto hardness tester and the Schlewniger tester. Modern tests are mechanically driven and may even come with visual display units or may be interfaced with a computer monitor that would permit the follow up or recording of the stress-strain relationship that precedes tablet failure.

Crushing strength is often imprecisely taken as synonymous to hardness. Hardness, however, defines the resistance of a solid to local permanent deformation (Celik, 1992). Hardness can be determined by either static or dynamic methods. The static indentation method involves the formation of a permanent indentation on the surface of the material being tested and the hardness is determined by means of the load applied and the size of the indentation formed.

In the dynamic indentation test, a pendulum is allowed to strike the material surface from a known distance or an indenter is allowed to fall under gravity onto the surface of the material. The hardness is determined from the rebound height of the pendulum or volume of the resulting indentation.

### 2.13.1.2     Friability

Some formulations tend to 'cap' on attrition when compressed into very hard tablets and as such they tend to lose their crown portions. Thus, another measure of tablet strength is friability i.e. the resistance of a tablet to surface abrasion.

Friability is an assessment of the resistance of a tablet to abrasion and is a measure of tablet weakness (Odeku and Itiola, 2003). Tablet defects such as lamination (capping) and chipping (Fig. 2.5) may be immediately apparent on decompression or concealed in a manner that can be revealed by the friability test.

The Roche friabilator (Fig. 2.6) is an example of a tablet friability tester which subjects a number of tablets to the combined effects of abrasion and shock. It utilizes a

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plastic chamber that revolves at specific revolutions per minute (usually 25 r.p.m.), dropping the tablets at a distance of six inches with each revolution. Tablets that have been preweighed are placed in the friabilator and after 100 revolutions of operation; the tablets are dusted and reweighed. Conventional tablets that lose less than 1% of their weights are generally considered acceptable (British Pharmacopoeia, 1998).

## 2.13.2 Tensile Strength and Brittle Fracture Index

Tensile strength, T, is a measure of interparticulate cohesion of a tablet while the brittle fracture index, BF1, is a measure of a tablet's tendency to cap or laminate. Tensile strength is a way of assessing the mechanical strength of a tablet (Wells and Walker, 1983) and measurement of tensile strength using diametral compression are now widely employed in commercial production for controlling the strength of tablets as it is independent of tablet dimensions.

The tensile strength, $T_1$ can be calculated from the equation.

$$T = 2L / \pi dt \tag{17}$$

where T = Tensile Strength ($Nm^{-2}$).

L = Load causing fracture (N)

d = Tablet diameter (m)

t = Tablet thickness (m)

The tensile strength of tablets has been shown to be due to operation of different types of forces acting between the particles (Kurup and Pilpel, 1979). These forces include;

i.   Interparticulate forces of attraction.

ii.  Electrostatic forces of attraction.

iii. Surface tension and capillary forces.

iv.  Frictional and mechanical forces.

v.   Forces due to formation of solid bonds.
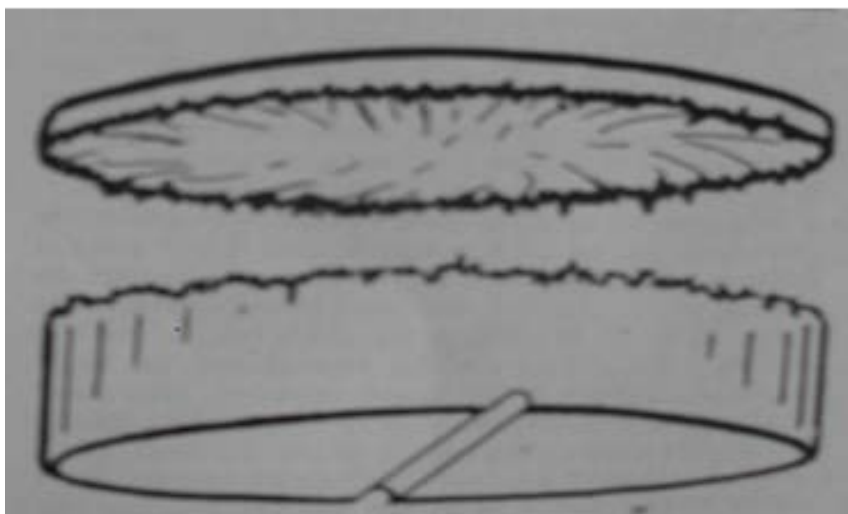
**Capped Tablet**

**Chipped Tablet**

**Fig 2.5**: Representation of Tablet Defects (Leon *et al*, 1986)

287.0 ± 4.0 mm
inside diameter

156.0 ± 2.0 mm
drop
height

80.5 ± 5.0 mm
inside radius

10.0 ± 0.1 mm
diameter

25.0 ± 0.5 mm
diameter

302.5 ± 4.0 mm
diameter

38.0 ± 2.0
mm
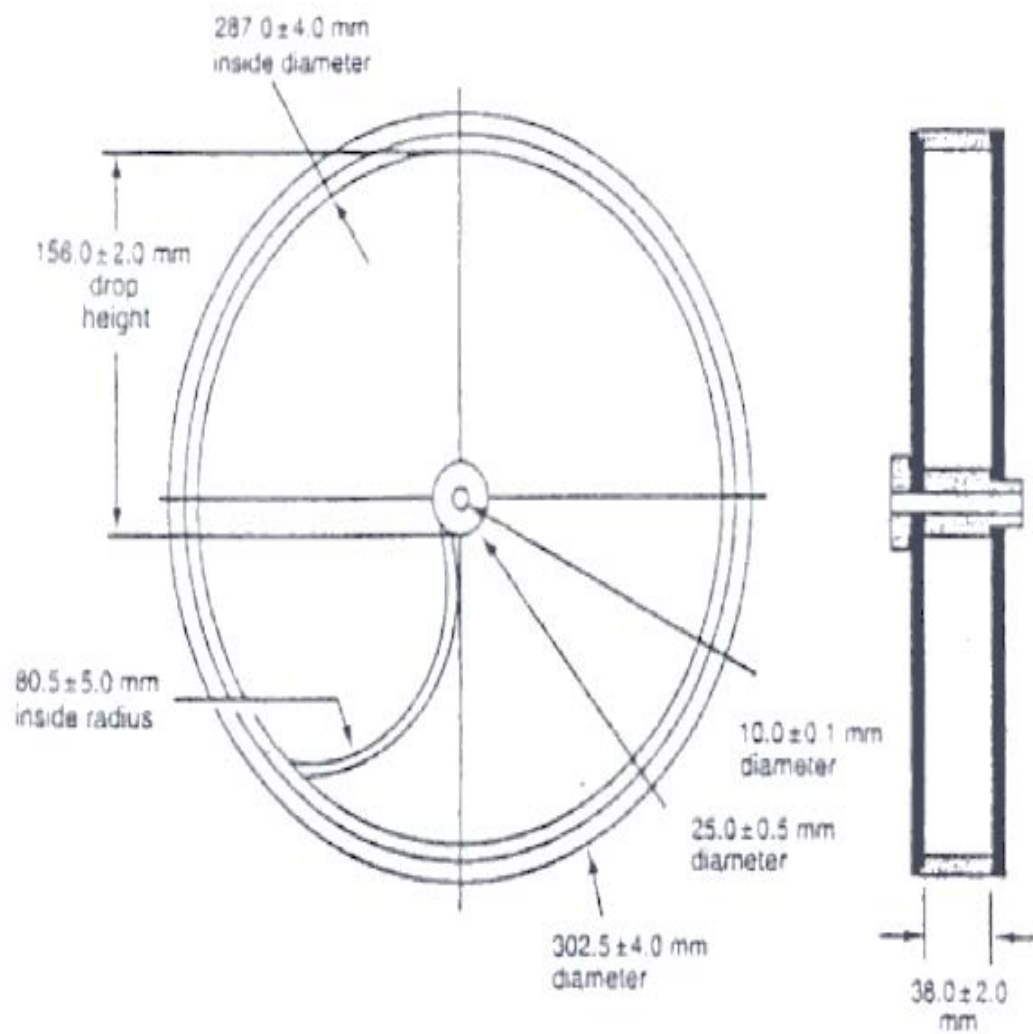
**Fig 2.6**: Schematic representation of a Roche friabilator (WHO Report, 2012)

Although, all the five types of forces operate in tablets, the effects of the solid bonds appear to be predominant over all the others. The solid bonds are formed when the heat produced during compression causes melting of asperities to form strong bonds between the particles.

Some of the factors, which have been shown to affect the tensile strength of compressed tablets, include compression pressure (Adetunji *et al*, 2006), moisture content (Odeniyi and Jaiyeoba, 2009), binder concentration (Adetunji *et al*, 2006), and size and shape of the particles or granules (Alebiowu and Itiola, 2002).

The tabletting performance of pharmaceutical materials is difficult to characterize because several simultaneous mechanisms are involved in the consolidation and bonding of particles. For example, the phenomenon of capping, which was first thought to be due entirely to entrapment of air within the tablet, has proved to be an extremely complex process. It was shown that classical capping was replaced by a tendency to laminate when certain problematic granulations were compressed under partial vacuum. In some cases strongly bonded tablets have been shown to laminate or cap on ejection.

Hiestand *et al* (1977) have devised a test for obtaining what they have termed the brittle fracture index, (BFT), which is obtained by comparing the tensile strength of tablets with a hole at their centre, which acts as a built in 'stress concentrator defect', with the tensile strength of tablets without a hole. The BFI is defined as:

$$BFI = 0.5 \ [(T/T_o)-1] \hspace{4cm} (18)$$
$$(0 \leq BFI \leq 1)$$

where T = Tensile strength of the tablet without a hole.

$T_0$ =   Tensile strength of the tablet with a hole.

(Both at the same relative density)

The BFI is a measure of localized stress relief within the tablet (at the edge of the hole) by plastic deformation.

A low value of the BFI indicates the ability of the material to relieve localized stresses while a value approaching unity indicates a tendency of the material to cap or laminate.

## 2.14    Factors Affecting Mechanical Properties of Tablets

### 2.14.1  Effect of Temperature

During the tabletting of pharmaceutical powders and/or granules, temperatures above ambient occur due to generation of frictional heat at points of contact between the particles (Hanus and King, 1968). Localized melting of the material caused by high pressure may occur (Rankell and Higuchi, 1968; York and Pilpel, 1972). When this pressure is released, welded bonds form and these contribute to the subsequent strength of the tablets. The temperature, at which compression occurs, influences the number of welded bonds formed and hence tensile strength.

The effect of temperature on the tensile strength of fatty acids, lactose and oxytetracycline and paracetamol tablet formulations at temperatures between $-20^0$C and $90^0$C was studied. The tensile strength of the materials tested increased as their temperature was raised; conversely at low temperatures, the tensile strength became very small (Britten and Pilpel, 1978). In agreement with work of previous workers, tablets of chloroquine diphosphate and paracetamol tablet formulations prepared at temperatures between $-10^0$C and $65^0$C were observed to produce an increase in tensile strength at fixed relative density as the compression temperature was raised (Esezobo and Pilpel, 1986)

### 2.14.2 Effect of Binding Agents

Binding agents are often added to tablet formulations to impart structural strength required during processing, handling and packaging of tablets (Itiola, 1986; Soyeux *et al*, 1998).

The heat produced during the compression of tablets causes melting of asperities and of the binding agent, which on cooling solidify to form strong bonds between the particles. Being soft and plasto-elastic, under the high pressure involved in compression, the binding agents also undergo plastic and elastic deformation and are forced into

interparticulate spaces thereby increasing the area of contact between particles and forming more solid bonds (Malmataris *et al*, 1984; Sugimoto *et al*, 2005).

Davies and Gloor (1992) found that increasing binder concentration led to an increase in crushing strength and a decrease in granule size. They also suggested a direct relationship between increase in binder concentration and increase in crushing strength due to heavier coating of the powder particles with binder at higher concentrations. The strength of oxytetracycline tablets was found to depend on the amount of Gelatin binder present in the formulation (Stenlake, 1981). Adetunji *et al* (2006) also reported a similar result in the incorporation of *Dioscorea dumetorum* starch as a binder in chloroquine phosphate tablets.

Inadequate amount of granulating fluid leads to increase in the risk of complications in the tablet compression process, in the form of sticking, capping and weight variation. Hence, insufficient amount of binder solution could lead to the production of more friable tablets (Malamataris *et al*, 1984; Sugimoto *et al*, 2006).

### 2.14.3  Effect of Moisture

The moisture content of the tablet granulation and finished product influences tablet friability. A low but acceptable moisture level frequently acts as binder. Very dry granulations containing only fractional percentage of moisture often produce friable tablets than granulations containing 2-4 % moisture. It was found that the crushing strength of tablets stored at 71 % relative humidity for 28 days was unchanged but the tablets became more friable (Omoyeni, 1997).

Chowhan *et al* (1982) reported that at a fixed crushing strength, friability decreases as the moisture content increases until it reaches its optimum value. Further increase in moisture content resulted in an increase in friability. The report suggested that moisture content of the granulation at the time of compression plays a vital role in the hardness of the resultant tablet on storage. On compression of granules containing moisture above a certain level, solution of the soluble excipient and binder are forced into void spaces. Recrystallization of the dissolved excipient from the binding solution results in the formation of bridges at points of contact (Ando *et al*, 2007).

### 2.14.4  Effect of compression pressure

Podczeck (2012) reported that higher compression forces resulted in less porous tablets with the particles more strongly bonded together leading to increased crushing strength of the tablets.

Joneja *et al* (1999) however, had observed that increase in crushing strength of the tablet with increase in compression force holds up to a maximum value for the crushing strength, beyond which pressure increase causes the tablet to laminate or cap, thus, destroying the integrity of the tablet.

Rebonding of surface formed by fragmentation rather than granule interlocking is an apparently more important factor in determining tablet crushing strength (Podczeck, 2012).

### 2.14.5  Effect of granule size

The manifold physical advantages of a large powder aggregate or granule over the component particles has led to the adoptions of granulation by many industries. Granulation overcomes the problem of dustiness, improves the uniformity of the tablets and ensures that their composition is not significantly altered from that of the original formulation as a result of segregation and demixing of ingredient (Itiola, 2009).

Different tensile strength values have been reported for tablets prepared from different granule size fractions obtained from the same granulation.

Granules have been shown to fragment under high compressional forces employed for tabletting and this depends on the strength of the interparticulate bonds which are in turn affected by the nature and concentration of binding agents employed in wet granulation to impart strength to granules and subsequent tablets (Sakar *et al,* 2011).

It has been shown that in the absence of an added binding agent, the strength of granules made from a variety of materials obey the expression (Rees and Lewis, 1994).

$$L = Kd^2 \hspace{5cm} (19)$$

where L = granule breaking load.

d = diameter

K = different constant for each material

The addition of a binding agent considerably increases the granule breaking load (Peck *et al*, 2000).

Large granules contain less entrapped air than small ones (Krycer *et al*, 1982; Itiola, 2009). In effect, on fragmentation under high compressional force, large granules will exhibit greater ability to fill up the void spaces between particles than small granule size. This promotes the formation of more solid bonds in the compressed tablets, and thus the tensile strength of tablets prepared from large granules are usually higher than might be expected from such granule size (Omoyeni, 1997; Sakar *et al,* 2011).

## 2.15    Tablet Disintegration and Dissolution

## 2.15.1  Disintegration

For a drug to be readily available to the body, it must be in solution. The first step to making the drug effective is the rate at which it dissolves in the gastrointestinal tract (Banker and Anderson, 1986). Basically, disintegration is the process which accomplishes the breakup of tablets into small particles for eventual dissolution and subsequent absorption. The disintegration test determines whether a tablet breaks up within a specified time. The British Pharmacopoeia specifies that uncoated tablets must disintegrate within 15 minutes while up to 2 hours is required for coated tablets (British Pharmacopoeia, 1998)

The time taken for a tablet to disintegrate is measured in a device described in various official books. In most of these tests, attempts are made to simulate in – vivo conditions. The in-vitro tests represent quality control procedures that help to ensure product uniformity from batch to batch.

The essential features common to various tests described in the literature are: an aqueous disintegration medium, agitation of the tablet in the medium to simulate peristalsis and a means of recognizing the end point of complete disintegration. Disintegration time is defined as that state in which no residue of the tablet, except fragments of undissolved coating, remains on the screen of the test apparatus. Disintegration time tests provide rapid efficient screening for formulations and manufacturing processes as they can be used to detect changes in production conditions

and ingredient properties, packaging materials and storage conditions with respect to drug release.

It is accepted that elegance and dosage accuracy will have no meaning if disintegration does not occur in reasonable time since such rate can be crucial in the overall effect of the medicament contained in the tablet. The reasoning is that a fast break up of the tablet into numerous particles can facilitate the release of the active ingredient by virtue of increased surface area.

**2.15.1.1 Mechanism of Disintegration**

The break up of tablets into small particles is by one or more of the following mechanisms:

**(i) Capillary Action**

Liquid uptake is always the first step in disintegration. When a tablet is placed in a medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tabletting conditions. Thus, maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary in disintegration (Banker and Anderson, 1986; Pabari and Rantoola, 2012).

**(ii) Swelling**

Swelling is the most accepted mechanism of tablet disintegration. The grains of the disintegrant swell in the presence of water and exert pressure on the granules to force them apart (Ringard and Guyot-Herman, 1981; Bala *et al*, 2012). Pabari and Ramtoola (2012) reported that tablets of water insoluble drugs disintegrated faster with starches than those of water soluble drugs due to the diminished water absorption capacity of the starches in the latter case.

**(iii) Heat of Wetting**

When a tablet is immersed in water, it produces heat which causes entrapped air in the tablet to expand and this exerts sufficient pressure to cause tablet disintegration (Bala *et al*, 2012)

**(iv) Evolution of Gas**

An effervescent tablet produces gas when it comes in contact with water. Disintegration of such tablets is due to the generation of pressure within the tablets. As the disintegrants in effervescent tablets are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets.

**(v) Porosity of Tablets**

It has been shown that the penetration of water into a tablet is proportional to its mean pore diameter or porosity. As tabletting pressure is increased, the porosity and permeability of the tablet decrease. Decrease in porosity leads to an increase in disintegration time (Shangraw *et al,* 1980). Nogame *et al* (1967) developed an equation to calculate the time for water penetration into a tablet:

$$P_t = (25\eta/\acute{y}) . (d_A .H)/ (d_p \cos \varphi) \qquad\qquad (20)$$

Where $P_t$ is the penetration time, $d_A$ is the diameter of the particles of the drug in the tablet, $d_p$ is the average pore diameter, H is the thickness of the tablet, $\varphi$ is the contact angle between liquid and drug particles, and $\acute{y}$ and $\eta$ are the surface tension and viscosity of the liquid respectively. With this equation, a quantitative correlation was established between penetration times of water and disintegration time.

**2.15.1.2  Factors Affecting Disintegration of Tablets**

In the context of tablet technology, disintegration implies penetration of the tablet by an aqueous liquid, disruption of internal bonds and subsequent breakdown of the tablet into free granules or primary particles. These granules containing the active drug can then dissolve and go into solution for subsequent absorption to take place. This often makes

tablet disintegration a necessary first step to achieving rapid availability of the active ingredients.

Disintegration time of tablet is determined by the complex interactions of a wide variety of factors. The rate at which liquid penetrates a tablet, the nature and method of incorporating lubricants, the degree of compression, and the reduction of inter-particle bond strength in the presence of water, and the quantity and type of diluents are all clearly of major importance in disintegration.

**(i) Effect of Binding Agent**

The extent of the influence of binders on disintegration depends on the nature and concentration employed in the formulation. Kurup and Pilpel (1979) explained that the presence of a binder in a formulation leads to the formation of solid bonds between the particles. This was believed to interfere with the disintegration process depending on the mechanism of disintegration.

Esezobo and Pilpel (1976) found that at a constant moisture level and packing fraction, an increase in gelatin concentration resulted in increased tensile strength, increased disintegration and dissolution times and reduced capping tendencies. Chalmers and Elworthy (1976) also demonstrated that at constant porosity, an increase in binder concentration led to increased disintegration time of oxytetracycline tablets. Sakr *et al* (1973), Khan and Rhodes (1976) and Guyot-Herman (1992) also showed that increasing the gelatin content of tablets caused increase in their disintegration times.

The wettability of the formulation also plays a vital role in the process of disintegration. Itiola and Pilpel (1986) found that incorporating polyvinylpyrrolidone (PVP), gelatin and methylcellulose binding agents in a metronidazole formulation altered the disintegration time of the tablets by reducing their wettability as measured by adhesion tension of water.

**ii. Effect of Compression Force**

Compression force is another factor whose alteration may influence the disintegration time. The porosity and permeability of tablet decrease as the compaction pressure is increased (Adetunji *et al,* 2006). As porosity decreases, particle-to- particle bonds become stronger, resulting in a longer penetrating time for water into the tablet and

eventually increase in the disintegration time. (Alebiowu and Itiola, 2002). Sakar *et al* (2011) also showed that increased compression force leads to tablets with longer disintegration times and demonstrated that disintegration time increased essentially linearly with rise in compressional force.

Adetunji *et al* (2006) showed that disintegration time has pronounced effect on the relationship between compressional pressure and dissolution efficiency. Tablets with insoluble disintegrants, the disintegration time initially showed a dramatic increase after which a further increase in compressional force appears to have no effect on disintegration time. In the case of soluble disintegrants, variation in compressional force had little or no effect on disintegration time (Santl *et al*, 2012).

### iii. Effect of Disintegrants

The presence and nature of disintegrants have an effect on the disintegration time of a tablet (Alebiowu and Itiola, 2003). The methods of incorporating disintegrants have been discussed earlier (section 2.5.3).

Odeku and Alabi (2007) studied the role of starch in the mechanisms of tablet disintegration using millet starch. They found that increasing the content of millet starch in had a profound effect on the porosity of chloroquine phosphate tablets.

Adetunji *et al* (2006) found that the disintegration time of tablets prepared with corn starches were somewhat lower than those of tablets prepared using trifoliate yam starch under almost all conditions of storage.

### iv. Effect of Granule size

The size of the granules in a formulation plays an important role on the disintegration of the tablet (Santl e*t al*, 2012). A decrease in disintegration time with decrease in granule size observed by Adebayo and Itiola (2003), could be attributed to the increased surface area of the smaller granules, which can be more easily dispersed with mild agitation and more easily pass through the sieve of the disintegration apparatus than larger ones.

**v. Effect of Lubricants**

A lubricant is another excipient that has shown significant influence on the disintegration of tablets. Hydrophobic materials such as magnesium stearate and stearic acid have been found to reduce significantly the rate of disintegration of some tablets. These agents appear to decrease the effective drug-solvent interfacial area and disintegration rate. Some medicaments e.g. phenothianine and most die wall lubricants are hydrophobic and impart this property on the pore walls in the tablets. The resultant increase in the contact angle makes the pore to be less readily penetrated by an aqueous liquid and this is reflected in the longer disintegration time which occurs when, for instance, the stearate lubricants are used. Khan and Rhodes (1976) found that talc, mineral oil, stearic acid and calcium lacatate made the surface of starch-lactose tablets water repellant, which resulted in the increased disintegration time observed for the tablets.

**vi. Effect of Surfactants**

Surface active water- soluble lubricants such as sodium lauryl sulphate enhance disintegration by permitting better penetration of solvent into the tablets and granules. Cooper and Bretch (1957) observed that when surfactants were sprayed onto granules of magnesium oxide, magnesium trisilicate and aspirin tablets, the disintegration of the tablets was improved. This effect was reported to be due to hydrophilization, consequent upon lowering of inter-facial tension and decrease in contact angle.

**vii. Effect of Moisture Content and Storage Condition of the Granules**

The moisture content of the granules, the storage condition of the granules, and those of the tablets, as well as the age of the tablets, are other factors affecting disintegration. Chowan and Palagy (1978) suggested that the granule moisture content should be adjusted to an optimal range to obtain desirable compaction properties. This was in recognition of the fact that moisture content of the granules at the time of compression plays an important role in the increased disintegration time of the resultant tablets on storage. Pilpel *et al* (1978) showed the effects produced on disintegration time of chloroquine phosphate tablets by varying the moisture content. They observed that the

disintegration time increased with moisture content of the granules and attained maximum value at about 4-5% w/w moisture.

Mital and Ocran (1968) using calcium carbonate, sodium hydrogen carbonate and lactose tablets prepared with cassava and yam starches as disintegrants observed a two-fold increase in disintegration time when the tablets were stored at 81% relative humidity. They concluded that the increase in tablet disintegration time was probably due to the adhesion of the particles in the presence of moisture.

Nasipuri (1976) observed a slight increase in disintegration time when sulphathiazole and promethazine tablets prepared using cassava starch as binder and disintegrant were stored at room temperature for 8 months. Similarly, sulphadimidine and chlorpheniramine maleate tablets formulated with potato and cocoyam starches as binder and disintegrant showed increase in disintegration time after 8 months especially when stored at higher temperatures (Nasipuri, 1997).

Successful correlations between parameters of drug absorption have been reviewed by Wagner (1966). The few quantitative correlations that have been reported involve only sugar-coated or enteric-coated tablets. Results with uncoated tablets have been disappointing. For example, studies with commercial aspirin tablets showed that their disintegration times have no relation to the rate of absorption of aspirin in human subjects (Remon, 1998). There are also reports that although certain enteric-coated products conform to compendia standards for disintegration, they may in fact be poorly absorbed. Bioavailability studies with a marketed enteric-coated aspirin tablet showed incomplete absorption ranging from 0 to 25 % of the dose in 3 of the 4 subjects. The fourth subject absorbed the entire dose (Zeiko *et al* 1998).

Tablet disintegration time, determined by the United States Pharmacopoeia XVI procedure for enteric-coated tablets of amino salicylic acid met all U.S.P. specifications, including disintegration, but failed to yield detectable blood levels of drug in normal adults (Remon, 1998).

The method and the apparatus used in the determination of disintegration time are known to influence disintegration. There are a considerable number of methods available for the determination of disintegration time in-vitro and the same results are rarely

obtained with different pieces of equipment. Moreover, a particular apparatus may not be suitable for all tablets (Khan and Rhodes, 1973).

The disk used in the disintegration apparatus to prevent the tablets from floating in the assembly has also been shown to aid disintegration. Knoechel *et al.* (1967) reported that the presence of disk caused a high degree of abrasion resulting in rapid tablet disintegration.

### 2.15.2 Dissolution

Prior to research carried out on tablet dissolution, disintegration tests were the only official *in vitro* tests used by most pharmacopoeias throughout the world, and although the disintegration test is indirectly related to drug bioavailability, the dissolution test has been approved since the early 60s when it appeared in the USP, as the official in-vitro test and a much better choice for assessing in-vivo release pre-determined tablet performances. The time required for a given percentage of the tablet per unit time that goes into solution is known as the dissolution time.

The United States pharmacopoeia (USP) has played an important role in the development of dissolution standards for many drug products, and although the approach of the USP and British Pharmacopoeia (BP) to dissolution differs slightly, the common approach is that 70% of the stated amount of the active drug substance must be in solution after 45 minutes. Although these specifications are primarily for the purpose of quality control, they represent a first step in the assurance of bioavailability (Joneja *et al*, 1999).

The earliest reference to dissolution is probably by an article written in 1897 by Noyes and Whitney about the rate of dissolution of solid substances in their own solutions (Banker and Anderson, 1986; Rubinstein, 1988; Hurst *et al*, 2007). It was suggested that tablets could be evaluated by their rate of dissolution, which is determined by the rate of diffusion of a very thin layer of saturated solution that forms instantaneously around the solid particle. The authors developed a mathematical equation (The Noyes- Whitney equation) that correlates the dissolution rate to the solubility gradient of the tablet. This equation is still the most basic formula upon which most modern mathematical treatment of dissolution phenomenon revolves, and it is written as follows:

$$dm/dt = KA (Cs-C) \qquad\qquad (21)$$

where $dm/dt$ = Rate of diffusion

$A$ = Surface area

$Cs$ = Concentration of drug at equilibrium

$C$ = Concentration of drug at bulk phase

$K$ = Dissociation constant

Furthermore, Noyes and Whitney (1897) showed that the rate of dissolution of a solute in a solvent is proportional to the difference between the saturation concentration gradient. Following this theory, various other theories have been propounded.

Wagner's theory (1969) relates the apparent first order kinetics under sink conditions to the reduction of available surface area as dissolution progresses such that $C_b \leq C_s$, where $C_b$ is the concentration of the solute in the bulk solution and $C_s$ is the equilibrium solubility of the solute. Carstensen's theory (1980) considers the dissolution process in the USP basket apparatus as proceeding in three steps – tablet disintegration, particle size reduction and particle dissolution, which are steps that have also been clarified by Pillay and Fassihi (1999). The phases, however, require some complex mathematical calculations, and this is a major limitation in the application of this theory.

Kitazawa *et al* (1975), in their own theory, also suggested that the surface area of the active ingredient available for dissolution from a compressed uncoated tablet might be regarded as a constant sink condition. Basing their investigation on the observation that the rate at which a solid substance dissolves in its own solution is related to the difference between the concentration of the solute and the eventual concentration at saturation, they investigated the dissolution rate constant of uncoated caffeine tablets. The theory of kitazawa *et al* (1975) has been observed to be consistent with that of Wagner (1969). Moreover, various reports have shown its applicability to the analysis of dissolution profiles of various drugs from tablets (Itiola and Pilpel, 1986).

Further studies by Peck *et al* (2000) and Verma *et al* (2004) have confirmed *in vivo* correlation between *in vitro* dissolution rate of tablet and drug bioavailability. Thus, any report on formulation and development of tablets usually starts with dissolution testing.

It has been proposed that dissolution of tablets be studied at more than one pH, and particularly at pH 1 and 7 to simulate the extremes of the gastrointestinal tract (Cohen *et al*, 1990; Verma *et al,* 2004). Others have suggested that small quantities of surface active agents be added to the dissolution medium to simulate the wetting of drugs believed to be a function of bile salts (Langoth *et al*, 2003). However, these suggestions have been discarded because of the complexity of the calculations involved (Langoth *et al*, 2003).

The dissolution of a tablet is a multi step process involving heterogeneous interactions between the solute-solute, solute-solvent and solvent-solvent interphase. The component heterogeneous interactions may be broadly categorized into:

  i.    The rate of solute liberation and transport from across interfacial boundaries.

  ii.    Diffusion or convective transport of the solute from the interface to the bulk phase.

Diffusion is much slower and is therefore the rate limiting step. The process of diffusion may be considered to involve the relocation of the solute molecule from an environment where it is surrounded by other identical molecules, with which it forms intermolecular attractions into a cavity in a liquid where it is surrounded by non identical molecules with which it may interact to a different degree (Rudnic and Schwartz, 1990).

### 2.15.2.1 Theories of Dissolution

Wurster and Taylor (1965), Swarbrick and Ma (1981) and Verma *et al* (2004) have reviewed the factors which can affect the dissolution of tablets and these include the stirring speed, temperature, viscosity, pH, composition of the dissolution medium and presence or absence of wetting agents.

Physical models have been set up to account for the observed dissolution of tablets. There are three models which either alone (Higuchi, 1967) or in combination (Verma *et al*, 2004), can be used to describe the dissolution mechanism. These are:

### (i) The Diffusion Layer Model

This model (Fig 2.7) assumes that a layer of liquid, H cm thick, adjacent to the solid surface remains stagnant as the bulk liquid passes over the surface with a certain velocity. The reaction at the solid/liquid interface is assumed to be instantaneous, forming a saturated solution, Cs, of the solid in the static liquid film. The rate of dissolution is

governed entirely by the diffusion of the solid molecules from the static liquid film to the bulk liquid according to Fick's first law:

$$J = -D_f \, dc/dx \tag{22}$$

where J is the amount of substance passing perpendicularly through a unit surface area per time, $D_f$, is the diffusion coefficient and $dc/dx$, is the concentration gradient.

After a time t, the concentration between the limit of the static liquid layer and the bulk liquid layer becomes $C_t$. Once the solid molecules pass into the bulk liquid, it is assumed that there is rapid mixing and the concentration gradient disappears.

The theory predicts that if the concentration gradient is always constant, that is, $C_s-C_t$ is constant because $C_s \gg C_t$ (''sink'' conditions which usually means $C_s > 10C_t$) then a uniform rate of dissolution is obtained.
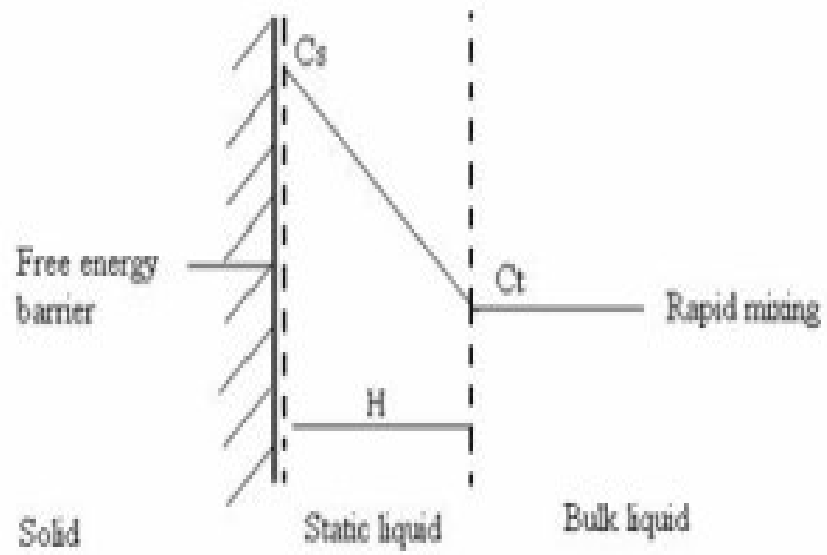
**Fig 2.7:** The Diffusion Layer Model

**(ii)  The Interfacial Barrier Model**

In the interfacial barrier model, it is assumed that the reaction at the solid/liquid interface is not instantaneous due to a high activation free energy barrier which has to be surmounted before the solid can dissolve. Thereafter the dissolution mechanism is essentially the same as in the diffusion layer model, with the concentration at the limit of the static layer becoming $C_t$ after time t.

The rate of diffusion in the static layer is relatively fast in comparison with the surmounting of the energy barrier, which therefore becomes rate limiting in the dissolution process.

**(iii)  The Danckwert's Model**

The Danckwert's model (Fig 2.8) assumes that macroscopic packets of solvent reach the solid/liquid interface by eddy diffusion in some random fashion. At the interface, the packet is able to absorb solute according to the laws of diffusion and is then replaced by a new packet of solvent. This surface renewal process is related to the solute transport rate and hence to the dissolution rate.

The rate laws predicted by the different mechanisms both alone and in combination, have been discussed by Higuchi (1967). However, the earliest equation expressing dissolution rate in a quantitative manner was proposed by Noyes and Whitney (1897) as:

$$dc / dt = k \, (C_s - C_t) \qquad\qquad\qquad (23)$$

where dc / dt is the rate of change in concentration with respect to time, and k is the rate constant.
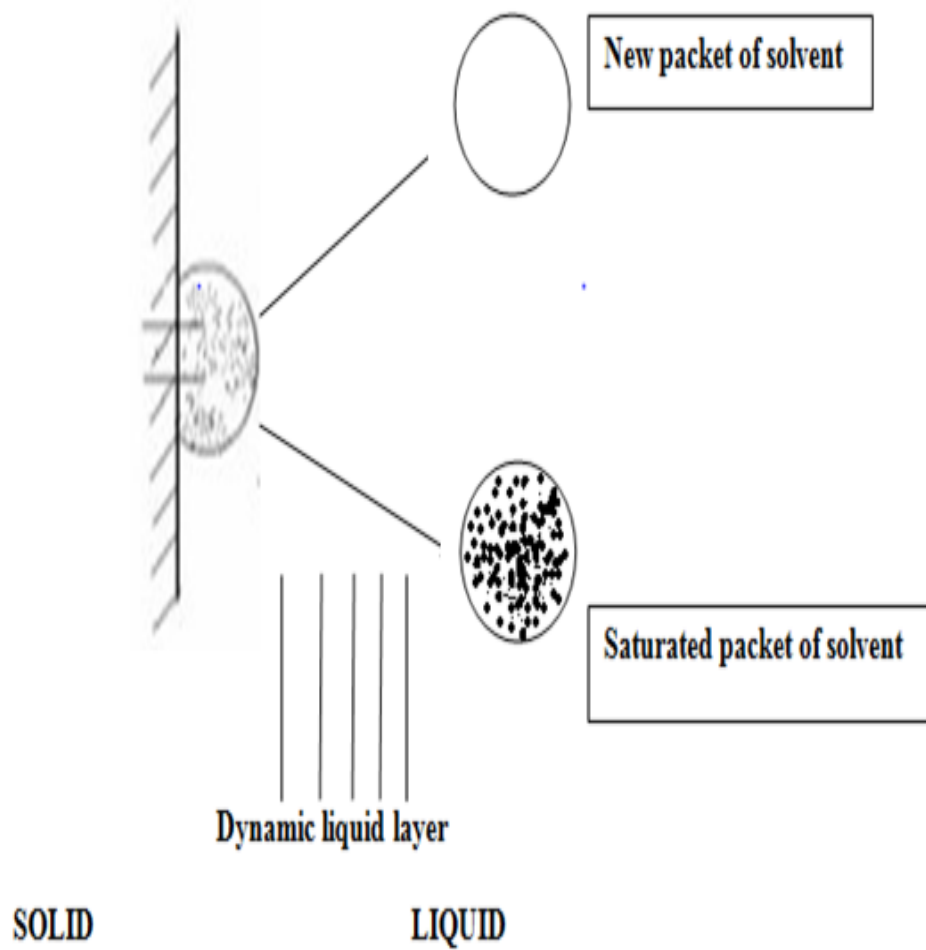
**Fig 2.8:** The Danckwert's Model

The integrated form of the equation is:

$$\ln [C_s / (C_s - C_t)] = kt \qquad (24)$$

The equation in resemblance to the other rate law equations (Higuchi, 1967), predicts a first order dependence on the concentration gradient (i.e. $C_s - C_t$) between the static liquid layer next to the solid surface and the bulk liquid. Noyes and Whitney (1897) explained their dissolution data using a concept similar to that used for the diffusion model (Higuchi, 1967).This consideration relates to conditions in which there is no change in the shape of the solid during the dissolution process (that is, the surface area remains constant). However, for pharmaceutical tablets, disintegration occurs during the dissolution process and the surface area generated therefore varies with time.

Wurster and Taylor (1965) proposed a scheme which holds that dissolution occurs only when the drug is in small particles. Wagner (1969) modified this idea and showed that dissolution occurs from both the intact tablet and the aggregates and/or granules produced after disintegration by using a plot of the percentage of drug dissolved versus time.

A modification of this approach was proposed by Kitazawa *et al* (1975). Employing the integrated form of Noyes and Whitney equation (equation 21), they determined the dissolution rate constant of uncoated caffeine tablets An equation for the time, $t_{100}$ for 100% of the solute to dissolve was also derived:

$$t_{100} = \frac{6.909 + 2.303 \log C_s + t_1 (k_2 - k_1)}{k_2} \qquad (25)$$

The Kitazawa equations have been used to determine the dissolution rates of some pharmaceutical tablet formulations (Odeku and Itiola, 1998; Adetunji *et al*, 2006).

## 2.15.2.2    Mathematical Description of the Dissolution Process

Koch and Liu (1997) gave an overview of the different mathematical models available for describing the dissolution process.

**(i)       Hixson-Crowell/ Cube Root Law**

Hixson-Crowell/ Cube root Law describes the release from systems where there is a change in surface area and diameter of particles or tablets and mainly applies in case of systems which erode over time (Hixson and Crowell, 1931). This is represented by equation:

$$100^{1/3} - M^{1/3} = Kt \qquad\qquad\qquad (26)$$

where M is percentage of undissolved drug at time t

The law is valid for all solids with a defined surface area, i.e. regular geometric solid bodies and bulk of powder. However, the solid can change its characteristic dimension during dissolution in a way that the cube root l.aw in its original form cannot be applied anymore. This is the case when the dosage form consists of materials with different dissolution characteristics.

This expression (Eq. 26) applies to pharmaceutical dosage forms such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form remains constant all the time (Chen *et al*, 2009)

**(ii)      Higuchi Model**

Higuchi (1963) described the release of drugs from insoluble matrix as a square root of the time dependent process based on Fickian diffusion.

$$M = kt^{1/2} \qquad\qquad\qquad (27)$$

The equation indicates that the speed of the diffusion out of the non disintegrating dosage form in the surrounding dissolution medium is directly proportional to the square root of time. This equation was formulated originally for ointment bases containing drugs in suspensions and is valid for up to 60% of the total amount of drug released (Kiortsis *et al*, 2005)

**(iii)  Zero Order Release**

It describes the system in which the drug release rate is independent of its concentration (Najib and Suleiman, 1985). The real dissolution of a drug substance (intrinsic dissolution rate) undergoes a zero order reaction, if its surface is kept temporarily constant. It can be described with the following equation (Wurster and Taylor,1965):

$$M = k_0t \tag{28}$$

where M is the amount of drug released at time t and $k_0$ is the release rate constant.

The zero order model describes release from porous matrices (Gurny *et al*, 1982). This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms as is the case of some transdermal systems, as well as matrix tablets containing low soluble drugs (Reza *et al*, 2003).

**(iv)  Korsemeyer-Peppas Model**

Two factors limit the applicability of Higuchi's equation to matrix systems. One factor is that the model fails to allow for the influence of swelling of the matrix upon hydration, while the second factor has to do with the gradual erosion of the matrix (Reza *et al*, 2003). Hence dissolution data are further fitted to the Korsemeyer-Peppas equation (Korsemeyer and Peppas, 1981) which is used to describe drug release from polymeric systems:

$$M_t/M_\infty = Kt^n \tag{29}$$

where $M_t$ corresponds to the amount of drug released in time t, $M_\infty$ is the total amount of drug released after an infinite time. K is a constant related to the structural and geometric properties of the drug delivery system (tablet) and 'n' is the release exponent related to the mechanism of the release (Korsemeyer and Peppas, 1981).

**(v)    First Order Kinetics**

This describes the drug release from the systems in which the release rate is concentration dependent (Reza *et al*, 2003).

$$\text{Log } M_t = \text{Log } M_0 + kt/2.303 \tag{30}$$

where $M_t$ is the amount of drug released in time t. $M_0$ is the initial amount of drug in the solution and k is the first order release constant. In this case, drug released at each time is proportional to the residual drug inside the dosage form.

If the first order drug release kinetic is obeyed, then a plot of Log $M_t$/ Log $M_0$ versus t will be a straight line with a slope of kt/2.303.

**2.15.2.3  Factors Affecting Dissolution Rate**

The factors affecting the dissolution rate of tablets are:

 i.   Physiochemical properties
 ii.   Formulation and manufacturing methods
 iii.   Environmental factors.

**i. Physiocochemical Properties**

The aqueous solubility of a tablet in the dissolution medium is a very important factor that governs its dissolution time (Guyot-Hernann, 1992; Martinez and Amidon, 2002). This solubility factor is affected by temperature of dissolution medium, nature of dissolution medium and other additives present in the tablet.

An increase in temperature will lead to an increase in the solubility of a tablet with a positive heat of solution, thus indicating a short dissolution time (Carstensen, 1980, Vippagunta *et al,* 2007).

Davies and Gloor (1992) reported that the reduction in aqueous solubility of a drug by its etherification is an example of changes in solubility as a result of chemical structure modification. Hurst *et al* (2007) also gave similar reports.

## ii. Formulation and Manufacturing Methods

The many processing factors involved in tabletting greatly influence the dissolution of the active ingredients in the dosage form. Granule size, method of granulation, amount and type of additives, compression force and speed, and type of tabletting machine are factors that affect the dissolution rate of tablet.

Hurst *et al* (2007) reported that identical tablets manufactured using different tabletting machines, but containing exact proportion of ingredients, exhibited significant differences in their rates of dissolution.

## iii. Environmental Factors

Humidity at the time of tabletting and storage conditions of tablets also influences the rate of dissolution and consequently the dissolution of tablets.

### 2.15.2.4   Measurement of Dissolution Rate

One of the first decisions to be made in the process of determining the dissolution rate of a tablet is the choice of apparatus (Cohen *et al*, 1990; Hurst *et al*, 2007). There are four official or conventional apparatus listed in the United States pharmacopoeia and these are:

### (i)        Apparatus 1(Basket Apparatus)

The assembly (Fig 2.9) consists of the following: a vessel, which may be covered, made of glass or other inert, transparent material; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size or heated by a suitable device such as a heating jacket. The water bath or heating device permits holding the temperature inside the vessel at $37 \pm 0.5\ ^0\text{C}$  during the test and keeps the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. An apparatus that permits observation of the specimen and stirring element during the test is preferable.

The Shaft and basket components of the stirring element are fabricated of stainless steel, type 316, or other inert material, to the specifications shown in. A basket having a gold coating of about 0.0001 inch (2.5 µm) thick may be used. A dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the bottom of the basket is maintained at $25 \pm 2$ mm during the test (British Pharmacopoeia, 1998; United States Pharmacopoeia/National Formulary, 2007).

**(ii)    Apparatus 2 (Paddle Apparatus)**

The assembly is similar to that of Apparatus 1, except that a paddle formed from a blade and a shaft is used as the stirring element (Fig 2.10). The shaft is positioned so that its axis is not more than 2 mm from the vertical axis of the vessel at any point and rotates smoothly without significant wobble that could affect the results. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft.

The paddle blade and shaft may be coated with a suitable coating so as to make them inert. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float.

**(iii)    Apparatus 3 (Reciprocating Cylinder)**

The assembly (Fig 2.11) consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; inert fittings (stainless steel type 316 or other suitable material), and screens that are made of suitable non-absorbing and non-reactive material and that are designed to fit the tops and bottoms of the reciprocating cylinders; and a motor and drive assembly to reciprocate the cylinders vertically inside the vessels and, if desired, index the reciprocating cylinders horizontally to a different row of vessels.

The vessels are partially immersed in a suitable water bath of any convenient size that permits holding the temperature at $37 \pm 0.5\ ^0C$ during the test. A device is used that allows the reciprocation rate to be selected and maintained at the specified dip rate given in the individual monograph within $\pm5\%$. An apparatus that permits observation of the specimens and reciprocating cylinders is preferable. The vessels are provided with an

evaporation cap that remains in place for the duration of the test (British Pharmacopoeia, 1998; United States Pharmacopoeia/National Formulary, 2007).

**(iv)    Apparatus 4 (Flow-Through Cell)**

Apparatus 4 (Fig 2.12) consists of a reservoir and a pump for the dissolution medium, a flow-through cell, and a water bath that maintains the dissolution medium at 37 $\pm 0.5\,^0C$    .

The pump forces the dissolution medium upwards through the flow-through cell. The pump has a delivery range between 240 and 960 mL per hour, with standard flow rates of 4, 8, and 16 mL per minute. It must deliver a constant flow ($\pm$ 5 % of the nominal flow rate); the flow profile is sinusoidal with a pulsation of $120 \pm 10$ pulses per minute.

The flow-through cell, of transparent and inert material, is mounted vertically with a filter system (specified in the individual monograph) that prevents escape of undissolved particles from the top of the cell; standard cell diameters are 12 and 22.6 mm; the bottom cone is usually filled with small glass beads of about 1-mm diameter with one bead of about 5 mm positioned at the apex to protect the fluid entry tube; and a tablet holder is available for positioning of special dosage forms, for example, inlay tablets. The cell is immersed in a water bath, and the temperature is maintained at $37 \pm 0.5\,^0C$ (British Pharmacopoeia, 1998; United States Pharmacopoeia/National Formulary, 2007)

**Fig 2.9:** Apparatus 1 (Basket Apparatus)

NOTES-
(1) A and B dimensions are not to vary more than 0.5 mm when part is rotated on center line axis.
(2) Tolerances are ± 1.0 mm unless otherwise stated.

9.4 to 10.1 mm diameter

41.5 mm radius

1.2 ± 0.2 mm radius

A — 35.8 mm

19.0 mm ± 0.5 mm

B

42.0 mm

4.0 ± 1.0 mm

74.0 mm to 75.0 mm
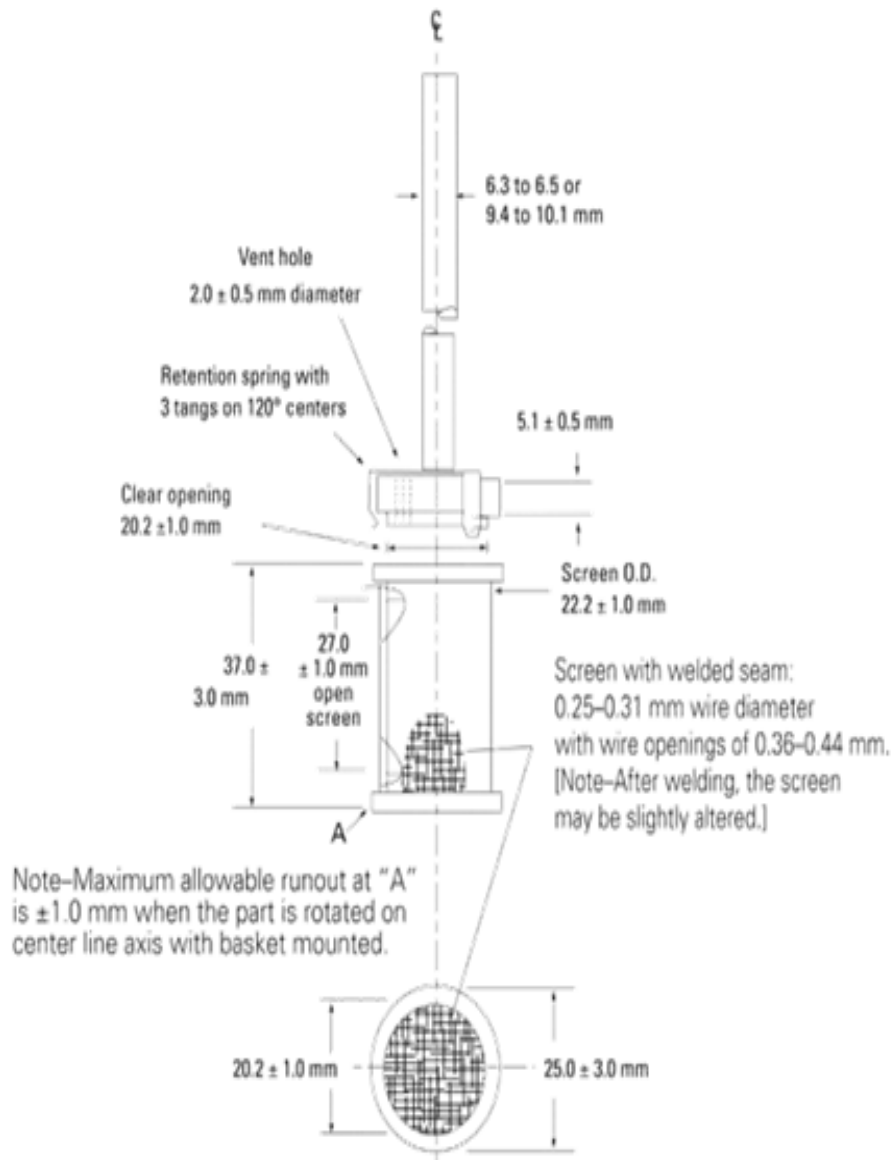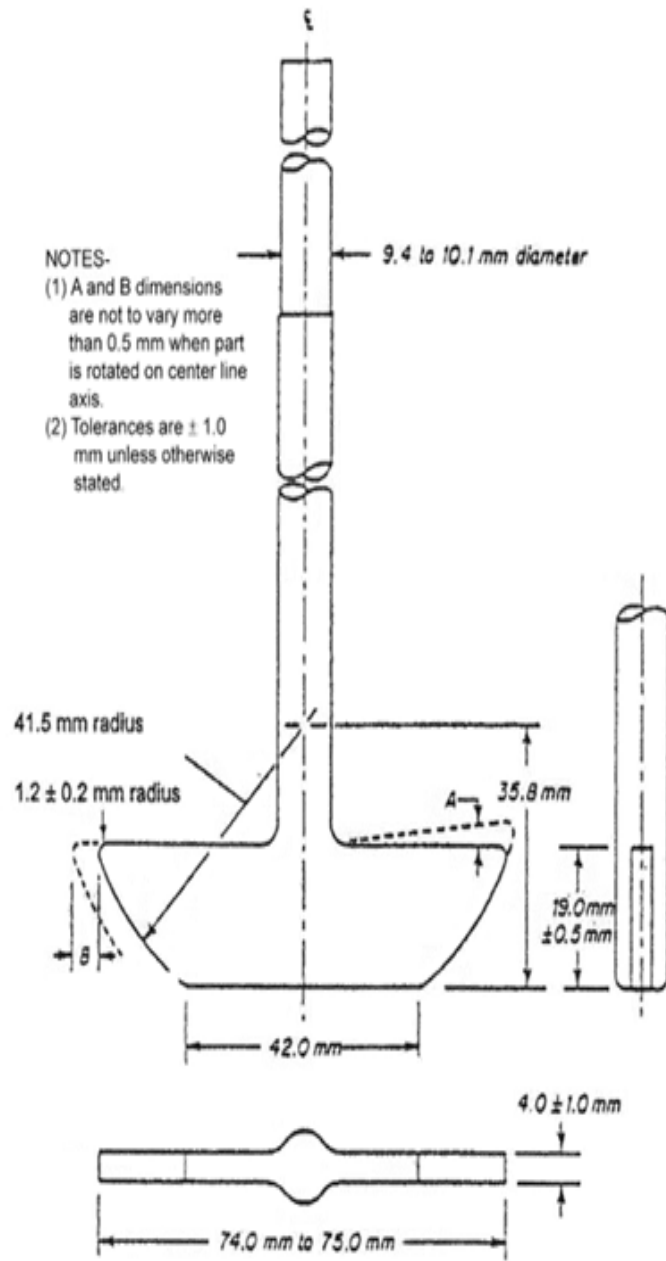
**Fig 2.10:** Apparatus 2 (Paddle Apparatus)

75
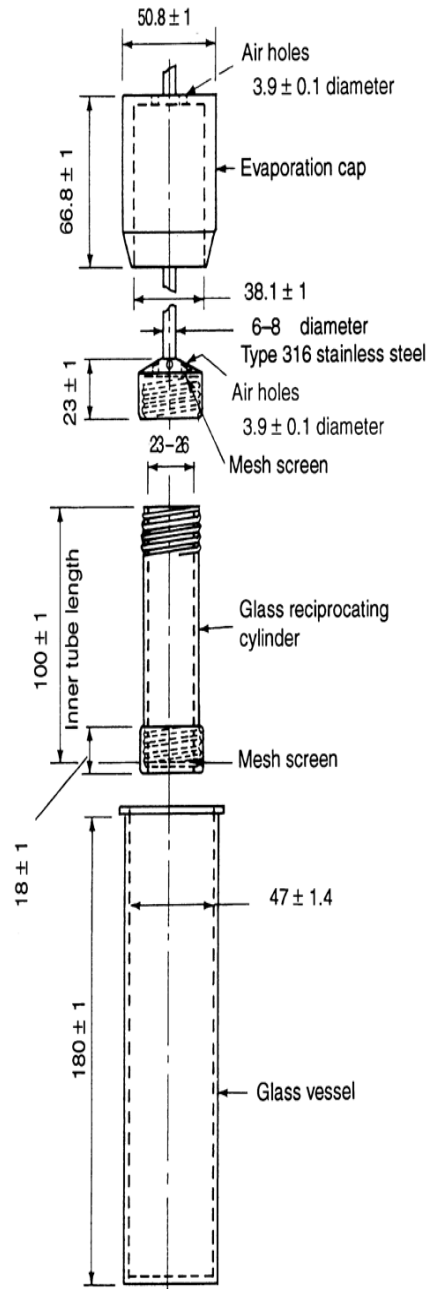
**Fig 2.11:** Apparatus 3 (Reciprocating Cylinder)

Filter chamber

Sieve 40 mesh
d=0.2 w=0.45

Ø20±0.2

Ø22.6±0.2

Score for the
tablet holder

5

35.5±0.5

15

40°±1°

(Ø3)

min.3

Ø0.8±0.05

Ø=diameter

0.5

6.5

9.5

R3

7.5

2.5±0.25

+0.5
24.0 0
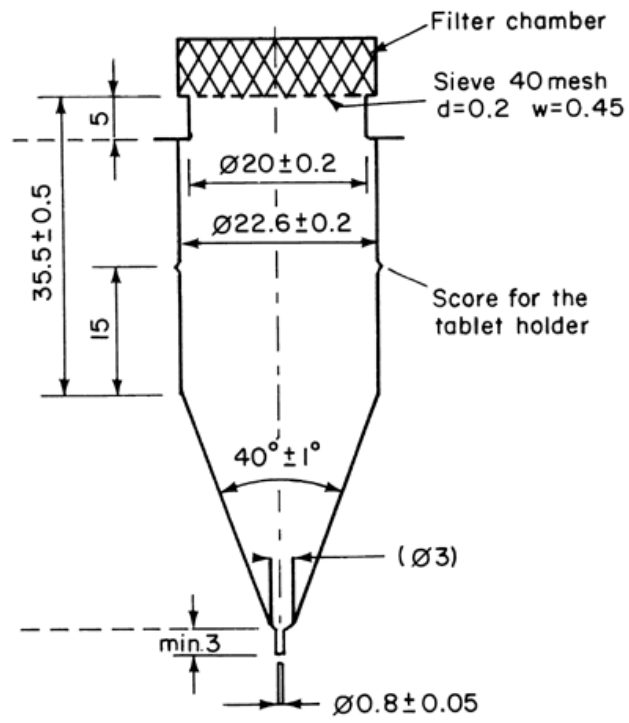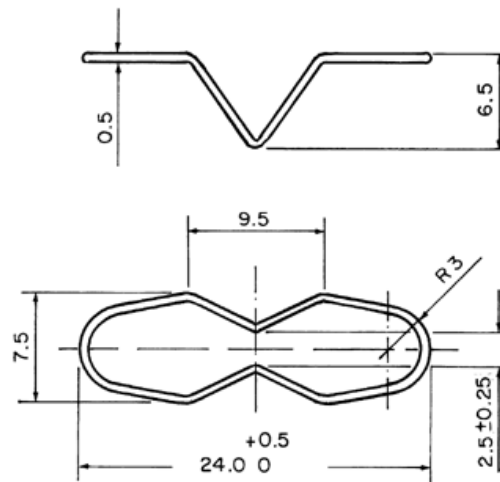
**Fig 2.12:** Apparatus 4 (Flow Through Cell)

All the aforementioned apparatuses have been found to be inadequate to study dissolution rate of drugs from the new modified drug delivery systems. They are also not able to mimic, in its absolute sense, the conditions of the gastro intestinal tract to produce the exact *in vivo* behavior of the dosage form. Hence, there is not yet a universally acceptable dissolution apparatus (Pillay and Fassihi, 1999).

The dissolution test has become an integral part of the control process for the manufacture of tablets. There are examples of drug products that do not meet compendia standards for dissolution but provided adequate bioavailability. On the other hand, there are no examples of a tablet or drug product that has met compendia dissolution standards and showed poor bioavailability characteristics (McGiney and Omelezuk, 2002).

### 2.15.3    Correlation between Disintegration Time and Dissolution Rate of Tablets

Many investigators have studied the correlations between the disintegration and dissolution rates of tablets (Najib and Jalal, 1988; Singh *et al*, 2007). Najib and Jalal (1988) discovered that both processes have been found to exhibit ''S''- shaped curves. However, the turbulent agitation employed during the disintegration test is not comparable with the smooth agitation or stirring employed in the dissolution test. In addition, factors such as particle size, crystalline form and solubility of drug substance that are known to affect dissolution rate have little or no effect on the disintegration process.

In spite of the differences in factors that influence the two processes, Singh *et al* (2007) reported a good correlation between the disintegration and dissolution rates of lorazepam tablets containing 5 %w/w Nymcel ZSB-16 as disintegrant. In addition, Najib and Jalal (1988) investigated the disintegration and dissolution rates of acetaminophen tablets in the same USP dissolution apparatus. A linear relationship was obtained between the time for 90 % disintegration and dissolution rates of the acetaminophen tablets. Their results suggested that the commonly observed lack of correlation between disintegration and dissolution rates were primarily a result of the difference in the hydrodynamic effect of the test apparatus (Najib and Jalal, 1988).

The use of the Kitazawa plots (Kitazawa *et al*, 1975) in the analysis of dissolution data usually produces two straight regression lines of slopes $K_1$ and $K_2$, being the initial (pre-disintegration) and final (post-disintegration) rate constants respectively. The time

where the two lines meet ($t_1$) has been found to show good correlation with the tablet disintegration time ($D_T$) even though the two are usually different in magnitude (Itiola and Pilpel, 1986). The relative values of $D_T$ and $t_1$ for a particular formulation seems to be binder and disintegrant type and agitation intensity dependent (Itiola and Pilpel, 1986). It should be noted, however, that the dissolution rate constant, (K), may be up to three or more in some cases (Kitazawa *et al*, 1975).

## 2.16    Matrix Tablets

A matrix tablet is the type of tablet which is designed to releases its contents regarding first order kinetics or zero order kinetics due to special arrangement and combination of hydrophobic and hydrophilic polymers as an excipient to form a matrix system (Varshosaz *et al*, 2006).

### 2.16.1  Classification of Matrix Tablets

Matrix tablets can be classified based on the retardant material used in the matrix system or the porosity of the matrix (Varshosaz *et al*, 2006; Avachat and Kotwal, 2007).

### 2.16.1.1  Classification based on the Retardant Material Used

Matrix tablets can be divided into 5 types on the basis of the type of retardant material used in the matrix system (Varshosaz *et al*, 2006):

### (i) Hydrophobic Matrices

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959 (Nashihata *et al*, 1995). In this method of obtaining sustained release from an oral dosage form, the drug is mixed with an inert or hydrophobic polymer and then compressed into a tablet. Sustained release is produced due to the fact that the dissolving drug must diffuse through a network of channels that exist between compacted polymer particles.  The rate-controlling step in these formulations is liquid penetration into the matrix. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their

copolymers. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

**(ii) Lipid Matrices**

These matrices are prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Reja *et* al (2003) documented the use of carnauba wax in different combinations with stearyl alcohol as retardant bases for many sustained release formulations.

**(iii) Hydrophilic Matrices**

The formulation of drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release.

The polymers used in the preparation of hydrophilic matrices are divided into three broad groups namely (Reja *et* al 2003):

(a) Cellulose derivatives such as methylcellulose, hydroxyethylcellulose (HEC), hydroxy propylcellulose (HPC), hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose.

(b) Non-cellulose, natural or semisynthetic polymers such as agar-agar, khaya gum, alginates, molasses, polysaccharides of mannose and galactose, chitosan and modified starches.

(c) Polymers of acrylic acid exemplified by corbapol 934, which is the most used variety.

**(iv) Biodegradable Matrices**

These consist of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymatic process into monomers that can be metabolised or excreted. Examples are natural polymers such as proteins and

polysaccharides, modified natural polymers and synthetic polymers such as aliphatic polyesters and polyanhydrides.

**(v) Mineral Matrices**

These consist of polymers which are obtained from various species of seaweeds. A good example is alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (*Phaephyceae*).

**2.16.1.2  Classification based on the Porosity of Matrix**

Matrix systems can also be classified according to their porosity and consequently, macroporous, microporous and non-porous systems can be identified:

**i) Macroporous Systems**

In such systems, the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm.

**ii) Microporous System**

Diffusion in this type of system occurs essentially through pore size ranges between 50 – 200 $A^{\circ}$.

**(iii) Non-porous System**

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

**2.16.2  Mechanism of Drug Release from Matrix Tablets**

There are three primary mechanisms by which active agents can be released from a delivery system; these are diffusion, erosion and swelling followed by diffusion.

The release of drug from the tablet matrix depends on the nature and concentration of the polymer (Varshosaz *et al*, 2006; Avachat and Kotwal, 2007). When the drug-containing porous polymer system produced by compression of two solids in powder form is brought in contact with water, a series of mass transport phenomenon occur. First, the

pores near the surface of the matrix are filled with water and initial drug diffusion is controlled by the dissolution of the solute in the water filled pores and by its continuous diffusion in water (Gurny *et al*, 1982). This type of unsteady diffusion for tablets that do not exhibit polymer swelling may be expressed by equation (31) as discussed by Swan and Peppas (1981) and Gurny *et al* (1982):

$$dc/dt = D_{eff} . (d^2c/d^2x) + (C_s - C) \tag{31}$$

Here, C is the solubility of the drug in the water filled pores, k is the dissociation constant, and $D_{eff}$ is the effective diffusivity in the pores expressed according to the equation:

$$D_{eff} = D_{iw} \, \text{Є}/\tau \tag{32}$$

where Є is the porosity of the system, $\tau$ is the turtuosity of the diffusional path and $D_{iw}$ is the diffusivity of the drug in water.

However, when the polymer is hydrophilic, progressive swelling of the polymer particles is observed, leading to considerable structural changes. These include change of the mobility of the macromolecular chains, macromolecular relaxation, and the changes of the porous structure including alteration of the shape and size distribution of the pores.

Finally, as swelling progresses, diffusion of the drug occurs both through the water filled pores with diffusibility, $D_{iw}$, and through the swollen polymer. Diffusion through the polymer depends on the physical structure of the polymer and is affected by properties such as cross-linking density and degree of crystallinity as well as thermodynamic interactions between polymer and solute (Korsmeyer and Peppas, 1981).

## 2.17    Mucoadhesion

Mucoadhesion can be defined as a state in which two components, of which one is of biological origin, are held together for extended periods of time by the help of interfacial forces (Pranshu and Satheesh-Madhav, 2011). Mucoadhesion involves drug delivery systems that utilize the property of bioadhesion of certain water insoluble polymers, which become adhesive on hydration and hence, can be used for targeting a drug to a particular

region of the body for extended periods of time (Chowdary and Srinivas, 2000). The term mucoadhesive is commonly used for materials that bind to the mucin layer of a biological membrane. The mucosal layer lines a number of regions of the gastrointestinal (GI) tract, the airways, the ear, nose, and the eye, and these areas represent potential sites for attachment of any bioadhesive system (Ahuja *et al*, 1998; Rahamatullah *et al*, 2011).

### 2.17.1  Mucoadhesive Polymers

Mucoadhesive polymers are water-soluble or water-insoluble polymers, which are swellable networks, joined by cross-linking agents (Vitaliy, 2011). These polymers possess optimal polarity, to make sure that they permit sufficient wetting by the mucous, and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucous to take place. Mucoadhesive polymers that adhere to the mucin-epithelia surface can be conveniently divided into three broad classes (Chowdary and Srinivas, 2000):

i.   Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
ii.  Polymers that adhere through non-specific, non-covalent interactions which are primarily electrostatic.
iii. Polymers that bind to specific receptor site on the cell surface.

### 2.17.2  Mucoadhesive Theories

Many theories have been proposed to describe mucoadhesion (Vitaliy, 2011). These theories are:

i.   Wetting theory
ii.  Electronic theory
iii. Fracture theory
iv.  Adsorption theory
v.   Diffusion theory

### 2.17.2.1 Wetting Theory

The wetting theory is perhaps the oldest established theory of adhesion. It is best applied to liquid or low-viscosity bioadhesives. The ability of bioadhesive or mucous to spread and develop intimate contact with its corresponding substrate is an important factor in bond formation. The wetting theory was developed predominantly in regard to liquid adhesives, uses interfacial tension to predict spreading and in turn adhesion (Mikos and Peppas, 1989; Baszkin, *et al*., 1990). The study of surface energy of polymers and tissues to predict mucoadhesive performance has been given considerable attention (Lele and Hoffman, 2000).The contact angle ($\varphi$) which should ideally be zero for adequate spreading and spontaneous wetting to occur is related to interfacial tension (g) as seen in eq (33):

$$g_{tg} = g_{mt} + g_{bg} \cos \varphi \tag{33}$$

Where the subscripts t, g and m represent tissue, gastrointestinal contents and mucoadhesive polymer respectively (Mathiowitz, *et al*., 2010)

For the mucoadhesion to take place the spreading coefficient must be positive, hence it is advantageous to maximize the interfacial tension at the tissue-GI contents interface and minimize the surface tension at the other two interfaces. The interfacial tension can be measured by methods like the Wilhelmy plate method ( Bateup, 1989). Thus, by the wetting theory it is possible to calculate spreading coefficients for various mucoadhesives over biological tissues and predict the intensity of the mucoadhesive bond.

### 2.17.2.2 Electronic Theory

The electronic theory is based on the assumption that the mucoadhesive material and the target biological material have different electronic surface characteristics. Based on this, when two surfaces come in contact with each other, electron transfer occurs resulting in the formation of a double layer of electrical charge at the interface of the mucoadhesive and the biologic surface. The bioadhesive force is believed to be present due to the attractive forces across this double layer (Vitaliy, 2011).

### 2.17.2.3 Fracture Theory

This is by-far the most accepted theory on mucoadhesion. It explains the forces required to separate the two surfaces after adhesion has taken place. It measures the maximum tensile stress, sm, produced during detachment as follows (Mathiowitz *et al.*, 2010):

$$sm = Fm/Ao \qquad (34)$$

Where Fm and Ao represent the maximum force of detachment and the total surface area respectively.

In a uniform single-component system, fracture strength, sf, which is equal to the maximum stress of detachment, sm, is proportional to the fracture energy ,gc, Young's modulus of elasticity, E, and the critical crack length ,c, of the fracture site as follows (Kammer, 1983):

$$sf = (gcE/c) \text{ x } 0.5 \qquad (35)$$

Fracture energy can be obtained by the sum of the reversible work of adhesion, Wr (work done to produce new fracture surfaces) and the irreversible work of adhesion, Wi (work of plastic deformation),

$$gc = Wr + Wi \qquad (36)$$

### 2.17.2.4 Adsorption Theory

This theory states that the bioadhesive bond formed between an adhesive substrate and the tissue is due to the weak van der waals forces and hydrogen bond formation. It is one of the most widely accepted theories of bioadhesion (Vitaliy, 2011).

### 2.17.2.5 Diffusion Theory

The concept of the interpenetration and entanglement of the bioadhesive polymer chains and mucous polymer chains is supported by the diffusion theory. The bond strength increases with increase in the degree of the penetration. This penetration is dependent on the concentration gradient and the diffusion coefficient. It is believed that interpenetration in the range of 0.2-0.5µm is required to produce effective bond strength (Vitaliy, 2011).

### 2.17.3  Characteristics of an Ideal Mucoadhesive Polymer

Mucoadhesive polymers have numerous hydrophilic groups, such as hydroxyl, carboxyl, amide, and sulfate. These groups attach to mucous or the cell membrane by various interactions such as hydrogen bonding and hydrophobic or electrostatic interactions. Hence, a mucoadhesive polymer is expected to combine several properties in order to exhibit the proposed therapeutic efficacy of the active drug it is formulated to deliver. An ideal mucoadhesive polymer should, thus, have the following characteristics (Ahuja *et al*, 1998; Patil *et al*, 2006):

i.   The polymer and its degradation products should be non toxic and should be non absorbable from the GI tract.

ii.   It should be non irritant to the mucous membrane.

iii.   It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.

iv.   It should adhere quickly to most tissues and should possess some site specificity.

v.   It should allow easy incorporation of the drug and should offer no hindrance to its release.

vi.   The polymers must not decompose on storage or during the shelf life of the dosage form.

vii.   The cost of polymer should not be high.

### 2.17.4  Mechanism of Mucoadhesion

Mucoadhesion is believed to occur in two stages involving three steps as shown in Fig 1.13 (Jose *et al*, 2011):

i.   Wetting.

ii.   Interpenetration.

iii.   Mechanical interlocking.

Wetting involves an intimate contact between the mucoadhesive and the mucous membrane with spreading and swelling of the formulation to initiate deep contact with the mucous layer ( Hogerstrom *et al*, 2003). This stage is a prerequisite for the development of strong adhesive bonds, where wetting equilibrium and the dynamic behavior of the mucoadhesive polymer with the mucous are critical.

Interpenetration occurs after contact is established, and involves penetration of the chains of the mucoadhesive with those of the mucous. The mucin and mucoadhesive are then locked mechanically. Thus, for mucoadhesion to occur, the attractive interaction should be larger than non-specific repulsion (Chowdary and Srinivas, 2000; Jose *et al*, 2011).
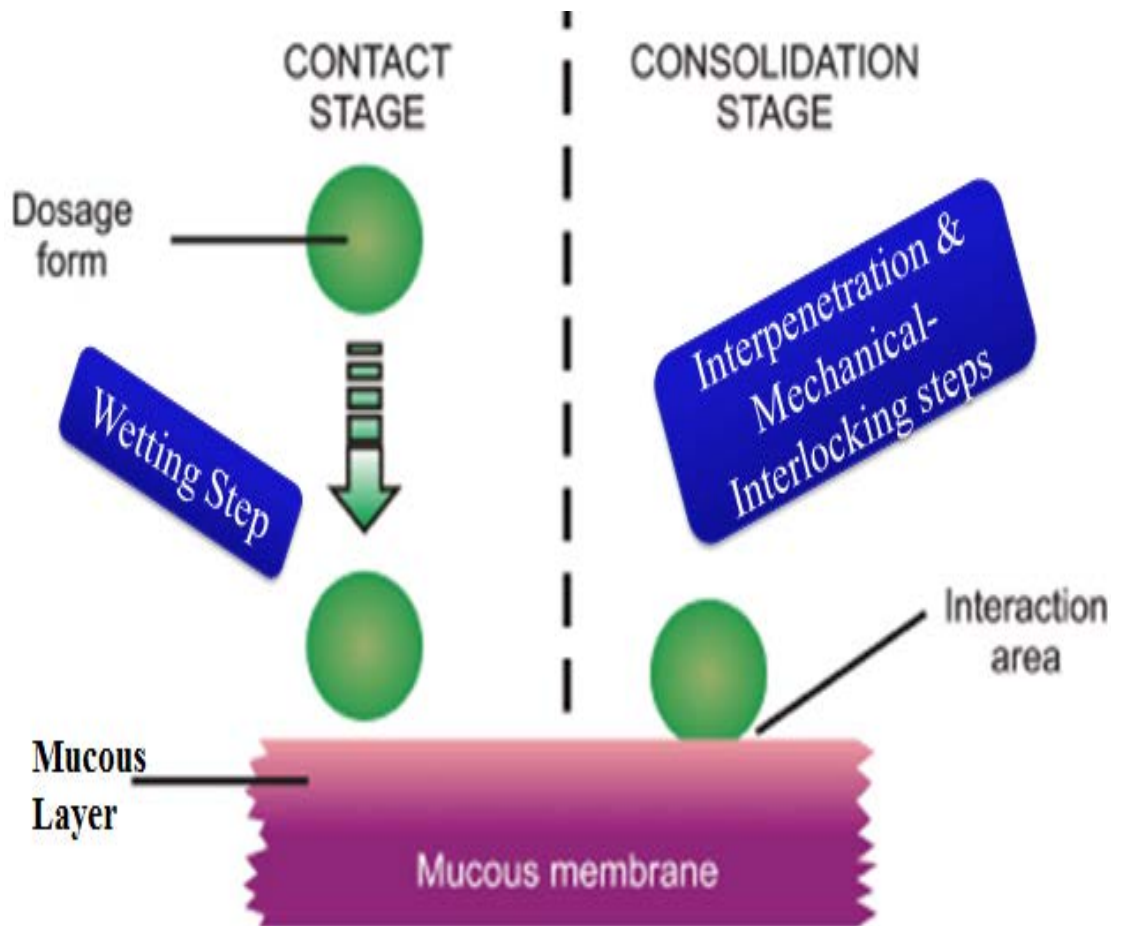
**Fig 2.13:** The Two Steps of The Mucoadhesion Process (Jose *et al*, 2011)

**2.17.5  Factors Affecting Mucoadhesion**

The mucoadhesion of a drug carrier system to the mucous membrane depends on a number of factors. These factors are grouped based on the characteristics of the mucoadhesive polymer, the conditions associated with the site of delivery and the physiological conditions of the drug carrier system and the mucous membrane (Jose *et al*, 2011).

**2.17.5.1  Polymer Related Factors**

**(i) Molecular Weight***:* The optimum molecular weight for maximum mucoadhesion depends upon the type of mucoadhesive polymer concerned. It is generally understood that the threshold required for successful mucoadhesion is, at least, 100,000 molecular weight (Chen *et al*, 2009). For example, polyethylene glycol (PEG), with a molecular weight of 20,000 has little adhesive character, whereas PEG with molecular weight of 200,000 has improved adhesive character, while PEG with molecular weight of 400,000 has superior adhesive properties. The fact that bioadhesiveness improves with increasing molecular weight for linear polymers implies two things: (1) interpenetration is a critical factor for low molecular weight polymers, and (2) entanglement is important for high molecular weight polymers. Adhesiveness of a nonlinear structure, by comparison, follows a quite different trend (Chowdary and Srinivas, 2000). The adhesive strength of non linear dextran, with a high molecular weight of 19,500,000 is similar to that of PEG, with a molecular weight of 200,000. The reason for this similarity may be that the helical conformation of dextran may shield many of the adhesive groups, which are primarily responsible for adhesion, unlike the conformation of PEG (Chen *et al*, 2009; Jose *et al*, 2011).

**(ii) Concentration of Active Polymer**: There is an optimum concentration for bioadhesive polymer to produce maximum adhesion. In highly concentrated systems, beyond the optimal level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium, so that the chain available for interpenetration becomes limited (Duchene, *et al*, 1998; Vitaliy, 2011).

**(iii) Flexibility of Polymer Chains***:* Chain flexibility is critical for interpenetration and entanglement. As water-soluble polymers become cross-linked, mobility of an individual chain decreases and thus, the effective length of chain that can penetrate into the mucous layer decreases, which reduces bioadhesive strength ( Vitaliy, 2011).

**iv) Spatial Conformation***:* Besides molecular weight or chain length, spatial conformation of a molecule is also important. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation (Ahuja *et al*, 1998; Rahamatullah, 2011).

**(v) Swelling***:* Swelling characteristics are related to the bioadhesive itself and its environment. Swelling depends on the polymer concentration, the ionic strength and the presence of water. During the dynamic process of bioadhesion, maximum bioadhesion *in vitro* occurs with optimum water content. Over hydration results in the formation of a slippery mucilage without adhesion (Chen *et al*, 2009; Rahamatullah, 2011).

**2.17.5.2  Environmental Related Factors**

**(i) pH  of  Polymer-Substrate Interface**: pH can influence the formal charge on the surface of the mucous  as well as certain ionizable mucoadhesive polymers. Mucous will have a different charge density, depending on the pH, due to difference in the dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. Some studies have shown that the pH of the medium is important for the degree of hydration of cross linked polyacrylic acid, showing consistently increased hydration from pH 4 through 7, and then a decrease as alkalinity or ionic strength increases. For example, polycarbophil does not show a strong mucoadhesive property above pH 5, because uncharged, rather than the unionized, carboxyl group reacts with mucin molecule, presumably through numerous hydrogen bonds. However, at higher pH, the chain is fully extended due to electrostatic repulsion of the carboxylate anions (Ch'ng *et al*, 1985; Hirofumi *et al*, 2010).

**(ii) Applied Strength***:* Whatever the polymer, the adhesion strength increases with applied strength or with the duration of its application, up to an optimum. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interactions with the mucin (Ahuja *et al*, 1998; Rahamatullah, 2011).

**(iii) Initial Contact Time***:* Contact time between the mucoadhesive and mucous layer determines the extent of swelling and interpenetration of the mucoadhesive polymer chains. Mucoadhesive strength increases as the initial contact time increases (Park, 1989; Rahamatullah, 2011).

### 2.17.5.3 Physiological Factors

**(i) Mucin Turnover***:* The natural turnover of mucin molecules from the mucous layer is important for at least two reasons. First, the mucin turnover is expected to limit the residence time of the mucoadhesives on the mucous layer. No matter how high the mucoadhesive strength, mucoadhesives are detached from the surface due to mucin turnover. The turnover rate may be different in the presence of mucoadhesives. Secondly, mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with mucoadhesives before they have the chance to interact with the mucin layer. Surface fouling is unfavorable for mucoadhesion to the tissue surface. Mucin turnover may depend on the other factors such as the presence of food. The gastric mucosa accumulates secreted mucin on the luminal surface of the tissue during the early stages of fasting. The accumulated mucin is subsequently released by freshly secreted acid or simply by the passage of ingested food. The ciliated cells in the nasal cavity are known to transport the mucous to the throat at the rate of 5 mm/min. the muciliary clearance in the trachea region has been found to be at the rate of 4-10 mm/min (Taylor, 2007; Lingmin *et al*, 2010).

**(ii) Disease State***:*  The physiochemical properties of the mucous are known to change during disease conditions, such as the common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacteria and fungi infections of the female reproductive tract, and inflammatory conditions of the eye ( Rahamatullah, 2011.).

### 2.17.6   Evaluation Methods to Study Mucoadhesion

Mucoadhesive polymers can be characterized by testing their adhesion strength by *in vitro* and *in vivo* tests. These tests are necessary not only for screening a large number of candidates for mucoadhesive exploits, but also to study their mechanisms. The various methods that have been reported are as follows (Asane, *et al*, 2008).

### 2.17.6.1  *In Vitro* Methods

*In vitro* tests were initially designed to screen potential mucoadhesives with a view to performing *in vivo* testing, if successful. Currently, more emphasis is being placed on elucidating the precise mechanisms of mucoadhesion because an evaluation of mucoadhesive properties is fundamental to the development of new mucoadhesives. The most commonly employed *in vitro* techniques are (Asane *et al*, 2008; Neeray *et al*, 2010):

  i.   Methods Based on the Measurement of Tensile Strength
 ii.   Methods Based on the Measurement of Shear Strength
iii.   Adhesion Weight Method
 iv.   Fluorescent Probe Method
  v.   Flow Channel Method
 vi.   Mechanical Spectroscopic Method
vii.   Falling Liquid Film Method
viii.   Electrical conductance Method

**(i)      Methods Based on the Measurement of Tensile Strength**

Methods using tensile strength usually measure the force required to break the adhesive bond between a model membrane and test polymers. The instruments usually employed are modified balances or tensile testers. A typical example is the method employed by Robinson *et al* (1985) and Neeray *et al,* (2010). In this method, the force

required to separate the mucoadhesive sample from excised rabbit stomach tissue was determined using modified tensiometers. A section of tissue, having the mucous side exposed, was secured on a weighted glass vial placed in a beaker containing USP-simulated gastric fluid. Another section of the same tissue was placed over a rubber stopper, again with the mucous side exposed, and secured with a vial cap. Then, a small quantity of polymer was placed between the two mucosal tissues. The force used to detach the polymer from the tissue was then recorded. The results of the study provided information regarding the effects of charge density, hydrophobicity, and experimental conditions such as pH, ionic strength, mucocytic agents, and applied pressure on mucoadhesion (Park *et al*, 1985; Taylor, 2007).

**(ii)    Methods Based on the Measurement of Shear Strength**

Shear stress has been referred to as a measure of force that causes the mucoadhesive to slide with respect to the mucous layer in a direction parallel to the plane of contact. The Wilhelmy plate method uses a glass plate suspended from a microbalance that is dipped in a temperature-controlled mucous sample. The force required to pull the plate out of the solution is determined under constant experimental conditions (Smart *et al*, 1984; Wang *et al,* 2011).

**(iii)    Adhesion Weight Method**

Neeray *et al* (2010) developed a test system where suspensions of ion exchange resin particles flowed over the inner mucosal surface of a section of guinea-pig intestine and the weight of the particles was determined. Although the method was of limited value due to reproducibility resulting from fairly rapid degeneration and biological variation of the tissue, it was possible to determine the effect of particle size and charge on adhesion after 5 minutes contact with porcine intestine.

**(iv)    Fluorescent Probe Method**

Park and Robinson (1984) studied polymer interaction with the conjuctival epithelial cell membrane using fluorescent probes. The study was done in an attempt to understand structural requirements for mucoadhesion in order to design mucoadhesive

polymers for oral use. The membrane lipid bilayer and membrane proteins were labelled with pyrene and fluorescein isothiocyanate, respectively. The cells were then mixed with the mucoadhesive material, and the changes in fluorescence spectra were monitored. This gave a direct indication of polymer binding and its influence on polymer adhesion.

**(v)        Flow Channel Method**

Mikos and Peppas (1989) developed a flow channel method that utilized a thin channel made of glass and filled with 2 %w/w aqueous solution of bovine submaxillary mucin, thermostated at 37 $^0$C. Humid air at 37 $^0$C was passed through the glass channel. A particle of a mucoadhesive polymer was placed on the mucin gel. The static and dynamic behavior was measured using the electrical conduct at frequent intervals, using a camera.

**(vi)        Mechanical Spectroscopic Method**

Mortazavi *et al* (1995) used Carri-med CSL 100 rheometer with a 4cm parallel plate to investigate the effect of introduction of carbopol 934P on the rheological behavior of mucous gelatin. They also investigated the role of mucous glycoprotein and the effect of various factors such as ionic concentration, polymer molecular weight, its concentration, and the introduction of anionic, cationic, and the neutral polymers on the mucoadhesive mucous interface.

**(vii)        Falling Liquid Film Method**

Niazy *et al* (1989) developed a falling liquid film method. Small intestine segments from rats were placed at an inclination of a tygon tube flute. The adhesion of particles to the surface was monitored by passing the suspension of particles over the surface. By comparing the fraction of particles adhering to the tissue, the adherence strength of different polymers can be determined.

**(viii)        Electrical Conductance**

Asane *et al* (1997) used electrical conductance as a parameter for testing semi solid mucoadhesive ointments. The adhesion of orabase, Guar gum, Carbopol and methylcellulose to artificial biomembrane and artificial saliva was studied by using a

modified rotational viscometer capable of measuring conductance. This parameter, measured as a function of time, was found to be influenced by the sample, artificial saliva and artificial biomembrane. In the presence of adhesive material, the conductance was relatively low. As the adhesive was removed, the value increased to a final value corresponding to the conductance of the saliva, which indicated the absence of the adhesive.

### 2.17.6.2 *In Vivo* Methods

The most common *in vivo* techniques to monitor mucoadhesion include the following:

  i.    Use of Radioisotopes
  ii.   Use of Gamma Scintigraphy
  iii.  Use of Electron Paramagnetic Resonance (EPR)   Oximetry
  iv.   X-ray Studies

**(i)     Use of Radioisotopes**

Ch'ng *et al* (1985) developed in vivo methods in order to investigate the GI transit of mucoadhesive beads. Cr-55 (isotope) was used in labelling mucoadhesive material in the stomach of rats. Radioactivity was measured in cut segments of the intestine. This method was improved on by Taylor (2007).

**(ii)    Use of Gamma Scintigraphy**

Krishnaiah *et al* (1998) demonstrated this method as a valuable tool in the development of pharmaceutical dosage forms. With this method, it is possible to obtain information noninvasively. This technique gives information in terms of oral dosage forms across the different regions of the GI tract, the time and site of disintegration of dosage forms, the size of drug absorption, and also the effect of food, disease, and the size of the dosage form on the in vivo performance of the dosage forms.

Gamma scintigraphy is especially useful in exploring sources of intersubject variation, especially in examining food effects in pharmacokinetic estimations and establishing windows of absorption from oral delivery. It is  a modern technique which

needs to be exploited to the maximum for its potentials in the evaluation of new molecular entities, drug delivery systems, and therapeutic drug monitoring.

**(iii)     Use of Electron Paramagnetic Resonance (EPR)   Oximetry**

Rahamatullzh *et al* (2011) performed the in vivo study of different ointments for drug delivery into the oral mucosa by electron paramagnetic resonance (EPR) oximetry. Three ointments with bioadhesive properties, orabase, carbapol 935P, and polymethylmetacrylate, and the ointment Miglyol without such properties were used. Benzyl nicotinate was used as an active ingredient that causes hyperemia. The kinetics of drug action was measured by EPR oximetry *in vivo* using the paramagnetic probe (lithium phthalocycrine) implanted beneath the epithelium of the buccal mucosa in rats.

**(iv)     X-ray Studies**

The in vivo adhesive testing of barium sulphate matrix tablets containing polymer and drug was studied in rabbits by Sudhakar *et al* (2006). It was found that the tablet was mucoadhesive even after 8 hours. Enteric coating did not show any effect on mucoadhesion after passing through the stomach.

**2.18    Natural Gum**

Gum is a widely available, naturally occurring substance, obtained from the trunk or branches of specific plants (Evans, 2004). Uzeala (1988) classified gums on the basis of their source of origin as plant seeds (examples include locust bean, guar gum and macuna gum), seaweed extracts (examples include alginates, agar and carrageenan), tree exudates (examples include tragacanth gum, khaya gum, acacia gum and raphia gum), citrus fruits (e.g. pectin), animal skin and bones (e.g. gelatin), and gums obtained by fermentation processes (examples include xanthan and lichen gum). Alur *et al* (1999) described gums as materials that can be dissolved or dispersed in water to form more or less viscous colloidal dispersion.

Plant gums are made up of polysaccharides or salts of polysaccharides, which contain various uronic acids (Adeleye *et al*, 2011). Most gum polysaccharides occur with other plant substances such as fat, protein and other biological substances. Purification of

gum is therefore achieved by preparing a solution of the gum, filtering and precipitating with a suitable solvent (Alur *et al,* 1999). The galactomanans, which are branched polysaccharides composed of D-galactose and D-mannose are commonly found in the endosperm of leguminosae where they serve as food reserve. In higher seed plants, the mucilage is made up of galactomanans with $\beta_{1-4}$ and $\beta_{1-6}$ linkages. Polysaccharide gums are often complex branched structures, and it is common to find more than three different types of monosaccharide molecules (Uzeala, 1988)

In recent years, plant gums have evoked tremendous interest due to their diverse pharmaceutical applications e.g. binders, disintegrants in tablets, thickeners in oral liquids, protective colloids in suspensions, gelling agents and bases in suppositories. Gums are biocompatible, cheap and easily available, thus, making them attractive substitutes for costly semi-synthetic and synthetic excipients (Al-Saidan *et al* , 2005). Natural gums have also been widely used in the preparation of controlled release dosage forms. Such works that have been carried out on natural gums were reported by Odeku and Fell (2004) for Khaya gum and Al-Saidan *et al* (2005) for guar gum. Haskell *et al* (1992) also observed that locust bean gum, extracted from the seed of *Ceratonia siliqua* (Carob tree), reduced elevated plasma cholesterol in healthy male subjects, while Venkataraju (2007) evaluated locust bean gum as a controlled release agent in matrix formulations. Talukdar and Kinget (1995) also reported the use of xanthan gum in controlled release formulations.

### 2.18.1 *Entandophragma angolense* Gum

*Entandophragma angolense* tree (Family Meliaceae) (Fig 2.14) is a huge tree up to 60 m high, with a strong bore, buttressed to 5 m height, sometimes slightly curved and elliptical in cross-section. The sap-wood of the tree is creamy-white to pale-pink, while the heart-wood is reddish brown, darkening on exposure. It is slightly aromatic, moderately resistant to decay and very resistant to impregnation. *Entandophragma angolense* tree seasons quite easily and it is deemed a timber of first importance in Ghana. In Uganda, it is the best cabinet wood of all the East African Meliaceae (Burkhill, 1997). The tree is mainly used for export in Nigeria. The gum obtained as exudates from the incised trunk of *Entandophragma angolense* tree has application in the adhesive industry, especially among furniture and upholstery workers in Sub Saharan Africa (Uzeala, 1988).

*Entandophragma angolense* gum has also been used extensively in battery electrolytes and printing inks as thickeners (Uzeala, 1988). The characteristics of the gum do show some variation. Samples of the gum from Ivory Coast have been marketed in the furniture industry under the trade name, *acajou frise,* because of its high specific density. Dark colored *Entandophragma angolense* trees in Uganda produce a reasonable quantity of gum while the light coloured trees lack gum (Burkhill, 1997). In Ivory Coast, the gum obtained by bark-slashing is somewhat sticky, faintly scented, and has a bitter taste (Uzeala, 1988); the gum, when pulped with salt and the seeds of melegueta pepper (*Aframomum melegueta,* Family: Zingiberacea), and is boiled in water, finds an application as a febrifuge drink. In Nigeria, the gum has analgesic properties, and is used by traditional medical practitioners to counter stomach and fever pains after thorough boiling. Similarly in Congo (Brazzaville), the bark- sap is mixed with the filtered gum for treating stomach and kidney pains, for ear ache and in external embrocation for rheumatism, muscular and arthritic pain (Burkhill, 1997)

(a)                                                    (b)

**Fig 2.14:** (a) *Entandophragma angolense* tree (b) Portion of the incised trunk

### 1.19    Chlorpheniramine Maleate

Chlorpheniramine maleate belongs to the group of drugs generally referred to as Histamine-type-1($H_1$) receptor antagonists (Katzung, 2001). As an antihistamine, chlorpheniramine maleate has sedative properties, and is thus classified as a first generation antihistamine (British National Formulary, March 2010, WHO Model Formulary, 2003) with the following chemical structure (Olaniyi, 1989)
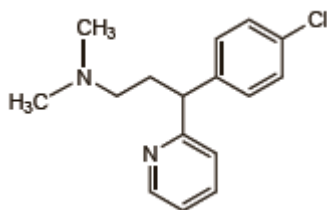


Chlorpheniramine maleate is a white crystalline odourless powder with a bitter taste. A 1 % solution of the drug has a pH of about 4.5. The drug is soluble, at 20 $^0$C, in 4 parts of water, in 10 parts of alcohol, and in 10 parts of chloroform; it is very slightly soluble in ether.

### 1.20    Ibuprofen

Ibuprofen was derived from propionic acid by the research arm of Boots Group during the 1960s. It was discovered by Andrew RM Dunlop, with colleagues Stewart Adams, John Nicholson, Vonleigh Simmons, Jeff Wilson and Colin Burrows, and was patented in 1961. The drug was launched as a treatment for rheumatoid arthritis in the United Kingdom in 1969, and in the United States in 1974. Boots was awarded the Queen's Award For Technical Achievement for the development of the drug in 1987 (Bower and Riltz, 2011).

Ibuprofen ($C_{13}H_{18}O_2$) has the systematic name 2-(4-isobutylphenyl) propionic acid, making it an organic compound in the class of propionic acid derivatives. Its melting point is 74 – 77 °C. It is a stable white crystalline powder, slightly soluble in water and

very soluble in ethanol. Ibuprofen is a chiral molecule, meaning that two mirror-image forms (called enantiomers) are possible.

$$(CH_3)_2CHCH_2 - C_6H_4 - CH(CH_3)COOH$$
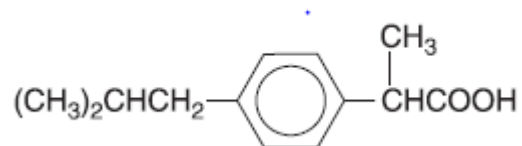
In the human body, only the S- enantiomer of Ibuprofen is active, but an enzyme readily converts the R- enantiomer to the active S- enantiomer. Thus, drug manufacturers do not bother to separate the enantiomers in their formulations; a mixture of the two (called a racemic mixture) is usually applicable (Bower and Riltz, 2011).

# CHAPTER THREE

## MATERIALS AND METHODS

### 3.1        Materials

The materials used were chlorpheniramine maleate powder BP, (Sigma Chemicals, St. Louis, MO), ibuprofen powder BP, (BDH Chemicals Ltd., Poole, U.K.) gelatin , lactose BP, magnesium stearate BP, and hydroxypropylcellulose (HPC) (Aqualon, Hercules Incorporated, USA), all supplied by Bond Pharmaceuticals Limited Nigeria. Analytical grade chloroform water (D/S), ethanol, diethylether and distilled water were obtained from the Research Laboratories of the departments of Pharmaceutics and Industrial Pharmacy, and Pharmaceutical chemistry, University of Ibadan, Ibadan, Nigeria. The gum was obtained from the early morning exudates of the trunk of *Entandophragma angolense* (family: Meliaceae syn; *Swietenia angolensis*), available as a tree crop in the Botanical Gardens of the University of Ibadan, Ibadan, Nigeria, and also within the complex of the Forestry Research Institute of Nigeria, Jericho, Ibadan. The tree was authenticated at the Forest Herbarium, Ibadan (FHI No: 108883), located in the Forestry Research Institute of Nigeria, Jericho, Ibadan, Nigeria.

### 3.2        Collection and Purification of Gum Extract

The brown coloured gum, collected as early morning exudates from previous incisions made on the trunk of *Entandophragma angolense* tree (family: Meliaceae), which has been sprayed with ethephon (2 chloroethyl phosphorinic acid) according to the method of Nair (2007), was weighed, allowed to dry and then thoroughly washed in chloroform water (D/S) to remove associated earth particles. The washed exudates were spread on sterile drainers at room temperature for a period of 3 hours, before being transferred to sterile tiles and dried in hot air oven at a temperature of $40^0$C for 48 hours. The dried gum was then crushed with a mortar and pestle to break up the gum. The gum was hydrated in double strength chloroform water for 5 days while stirring intermittently.

The resulting mucilage was strained through a clean calico cloth and the gum obtained was precipitated with 95 %v/v ethanol. The precipitated gum was filtered, washed with diethylether and then dried in a hot air oven at a temperature of 40 $^0$C for 24 hours. The dried gum was pulverized and passed through a number 60 mesh sieve (250µm) (Alur *et al*, 1999; Odeku and Itiola, 2003; Bamiro *et al*, 2010). The percentage weight of the purified and dried gum obtained from the exudates was then calculated. The dried gum (0.005g) was dissolved in water, mounted on the microscope and observed for the presence of any foreign organic matter to determine the level of gum purity (Sofowora, 1993).

### 3.3     Determination of Phytochemical Characteristics

### 3.3.1   Molisch's Test for Carbohydrates

Two drops of α-naphthol solution was added to 2 mL of *Entandophragma angolense* gum (1 %w/v). 1 mL of concentrated sulphuric acid solution was then carefully poured down the side of the tube (Evans, 2004).


### 3.3.2   Fehling's Test for Reducing Sugar

A 2 mL quantity of Fehling's solution was added to 2 mL of *Entandophragma angolense* gum (1 %w/v) and then boiled in a water bath for 30 min (Evans, 2004).

### 3.3.3   Selivanoff's Test for Ketones

A crystal of resorcinol was added to 2mL of *Entandophragma angolense* gum (1 %w/v) and warmed on a water bath with an equal volume of concentrated hydrochloric acid (Evans, 2004).

### 3.3.4   Test for Alkaloids

A 2 mL quantity of 10 % HCl was added to 2 g of *Entandophragma angolense* gum powder and boiled on a water bath. The resulting mucilage was filtered and the following tests were carried out on the filtrate (Evans, 2004):

i.   **Wagner's Test**: A small quantity of iodine in potassium iodide solution was added dropwise to 0.5 mL of the filtrate.

ii.  **Dragendorff's Test**: A small quantity of bismuth potassium iodide solution was added dropwise to 0.5 mL of the filtrate.

### 3.3.5 Determination of the Presence of Saponins

*Entandophragma angolense* gum (1 g) was boiled with 10 mL of distilled water in a test tube. This was filtered while still hot and 2.5 mL of the resulting filtrate was diluted with 10 mL of water, before shaking vigorously for two min (Sofowora, 1993).

### 3.3.6 Determination of the Presence of Anthraquinones

*Entandophragma angolense* gum (1 g) was extracted with 10 mL ether, filtered while hot and 10 mL of 10 % Ammonia solution was added to the filtrate in the test tube (Sofowora, 1993).

### 3.3.7 Determination of the Presence of Tannins

*Entandophragma angolense* gum (1 g) was boiled with 10 mL of distilled water for 5 min, filtered while hot and cooled. A few drops of ferric chloride reagent were added to the filtrate (Sofowora, 1993).

### 3.3.8 Keller-Killiani Test for the Presence of Glycosides

*Entandophragma angolense* gum (2 g) was dissolved in 5 mL of acetic acid containing a trace of ferric chloride and transferred to the surface of concentrated sulphuric acid (Evans, 2004)

### 3.3.9 Determination of Mucilaginous Properties (Ruthenium Red Test)

*Entandophragma angolense* gum (2 g) was dissolved in 7 mL of aqueous potassium hydroxide solution and warmed slightly (Evans, 2004)

### 3.3.10 Shinoda Test for Flavonoids

*Entandophragma angolense* gum (3 g) was dissolved in 5 mL of aqueous potassium hydroxide solution. A 1.5 mL quantity of glacial acetic acid was added to the resulting solution (Evans, 2004)

### 3.4 Powder Properties

### 3.4.1 Particle Size Distribution

The particle size distribution of the powdered samples of *Entandophragma angolense* gum, gelatin, hydroxypropylcellulose, chlorpheniramine maleate, ibuprofen and lactose, were determined by optical microscopy on approximately five hundred (500) particles for each sample. This was carried out by placing a quantity of each powder on a slide, which was then mounted and observed with the aid of a light microscope. The particle sizes of the powders were measured against a previously calibrated eye-piece micrometer and the projected mean diameter of the samples were calculated.

### 3.4.2 Particle Density Determination

Particle density determination was carried out for all the samples using the pycnometer method with xylene as the displacement fluid. An empty 50 mL pycnometer bottle was weighed (W), and then filled with non-solvent displacement fluid. Excess non-solvent was wiped off and the weight of the bottle and the non-solvent was determined ($W_1$). The difference between the weights (i.e. $W_1$-W) was calculated as $W_2$. A quantity (2 gm) of the sample was weighed ($W_3$) and quantitatively transferred into the pycnometer bottle. The excess fluid was wiped off and the bottle weighed again ($W_4$). The particle density, $\rho_s$, was calculated using the following equation:

$$\rho_s = \quad (W_2 \times W_3) / [50(W_3 - W_4 + W_2 + W)] \tag{37}$$

### 3.4.3 Bulk and Tapped Densities

The bulk density was determined by weighing 30 g (W) of *Entandophragma angolense* gum into a 50 mL measuring cylinder of internal diameter 21 mm (Itiola, 1991). The height, h (cm) of the powder bed and internal radius, r (cm) of the measuring cylinder were used to compare the loose bulk volume, $V_0$.

$$V_0 = \pi r^2 h \tag{38}$$

The value obtained was used to calculate the loose bulk density $\rho_0$ (g/cm$^3$)

$$\rho_0 = W/V_0 \tag{39}$$

Tapped density was determined by applying 100 taps to the 30 gm of *Entandophragma angolense* gum powder at a standard rate of 38 taps per minute according to British standard 1460 (British Pharmacopoeia, 1998). All determinations were done in quadruplicate.

### 3.4.4    Hausner's Ratio

This was calculated as the ratio of the tapped density to the bulk density of each of the samples (Emeje *et al*, 2007).

### 3.4.5   Angle of Repose

The angle of repose, θ, was measured according to the fixed funnel and free standing cone method (Itiola, 1994; Ohwoavworhua and Adelakun, 2005). A funnel was clamped with its tip 2 cm above a graph paper placed on a flat horizontal surface. A known weight of each of the powder samples of *Entandophragma angolense* gum, gelatin or HPC was separately and carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The height, h, of the powder cone and the mean diameter, D, of the base of the powder cone were determined and the tangent of the angle of the angle of repose calculated using the equation:

$$\text{Tan } \theta = 2h/D \tag{40}$$

### 3.4.6   Compressibility Index

This was calculated for each sample using the equation below:

$$\text{Compressibility Index} = \left[\frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}}\right] \times 100 \tag{41}$$

### 3.4.7   Determination of pH

A 1 %w/v (32 $^{0}$C) solution of the dried *Entandophragma angolense* gum was made. A glass-rod stirrer was used to gently stir the solution for about 5 min  prior to

determination of the pH using an Accumet pH meter (Denver Corporations, New York) (Emeje *et al*, 2007; Sinko, 2011).

## 3.5 Determination of Physicochemical Characteristics

### 3.5.1 Determination of Elemental Constituents

The elemental constituents of *Entandophragma angolense* gum were determined using an atomic absorption spectrophotometer Z-2000 (Hitachi HiTech, Tokyo, Japan).

### 3.5.2 Determination of Protein Content

Protein content of *Entandophragma angolense* gum was estimated from the nitrogen content determined by elemental analysis, using a conversion factor of 6.25 (Gebre-Mariam and Schmidt, 1998).

### 3.5.3 Determination of Moisture Content

A quantity of *Entandophragma angolense* gum (10 g) was weighed into a tared clean dish provided with a removable lid. The uncovered dish was placed in an oven maintained at $103 \pm 2\,^0C$. After 2 hours, the lid was placed on the dish and transferred to a dessicator at room temperature to cool. After cooling for 30 min, the sample was weighed as quickly as possible to 0.01 mg. The lid of the dish was replaced and placed in the oven for another 2 hours. This was repeated until the decrease in mass between successive weighing did not exceed 0.05 mg per g of sample (fresh weight basis). The loss in weight was recorded as moisture content (AOAC, 1990):

$$\text{Percentage Moisture content} = [(M_1 - M_2) / (M_1 - M_0)] \times 100 \qquad (42)$$

where $M_0$ is the weight of the dish and lid (in grams), $M_1$ is the weight of the dish, lid and gum (in grams) before drying and $M_2$ is the weight of the dish, lid and gum after drying (in grams) (AOAC, 1990).

### 3.5.4 Determination of Degree of Swelling and Solubility

A quantity of *Entandophragma angolense* gum (1 g) was placed in a 100 mL conical flask. Distilled water (15 mL) was added and swirled gently for 5 min. The slurry

was heated in a water bath fitted with a thermostat for about 40 min, with gentle stirring to prevent formation of lumps till the temperature rose to 80 $^0$C.

Centrifuge tubes and cans were weighed to constant weight. The slurry was transferred into the tared centrifuge tubes and weighed. 7.5 mL of distilled water was added, and the resulting solution was centrifuged at 2,200 revolutions per minute (rpm) for 20 min. The supernatant was decanted immediately after the centrifuging into the tared can. The weight of the sediment was determined (AOAC, 1990):

$$\text{Swelling} = \frac{\text{Weight of Sediment}}{\text{Initial weight of gum} - \text{Weight of soluble fraction}} \qquad (43)$$

$$\text{Solubility Index (\%)} = \frac{\text{Weight of soluble fraction}}{\text{Initial weight of gum}} \times 100 \qquad (44)$$

The procedure was also carried out at 27 $^0$C. determinations were made in quadruplicate.


### 3.5.5    Determination of Total Ash

A quantity of *Entandophragma angolense* gum (4 g) was placed in a tared silica crucible. The gum sample was evenly spread in the crucible and ignited by gradually increasing the heat to 500-600 $^0$C until it became white, indicating the absence of carbon. The residue was cooled in a desiccator and weighed. The total ash content was calculated in mg per gram of the air-dried gum. The procedure was carried out in quadruplicate (AOAC, 1990)


### 3.5.6    Determination of Acid-insoluble Ash

A 25 mL quantity of HCl (0.1M) was added to the crucible containing the total ash. The crucible was covered with a watch-glass and boiled gently for 5 min on a water bath. The watch-glass was rinsed with 5ml of hot water directly into the crucible. The insoluble matter was collected on an ashless filter paper and washed with hot water until the filtrate became neutral. The filter paper containing the insoluble matter was transferred into the original crucible, dried on a hotplate and ignited to constant weight. The residue

was cooled in a suitable desiccator for 30 min and weighed immediately. The content of acid-insoluble ash was calculated in mg per gram of the dried gum (AOAC, 1990)

### 3.5.7     Determination of Water-Insoluble Ash

A quantity of distilled water (25 mL) was added to the crucible containing the total ash and boiled for 5 min. The resulting insoluble matter was collected on an ashless filter paper, washed with about 5mls of hot water and ignited in a crucible for 15 min at a temperature of $400 \pm 5\ ^0C$. The content of water insoluble ash, in mg of gram of the air-dried gum, was calculated by subtracting the weight of the residue in mg from the weight of total ash (AOAC, 1990).

### 3.5.8 Fourier Transform Infrared (FTIR) Determination

Spectra were obtained for the *Entandophragma angolense* gum, gelatin or HPC and the model drugs (chlorpheniramine maleate or ibuprofen) using a Magna-IR, 560 spectrometer (Emeje *et al*, 2007).

A quantity (5 mg) of each of the completely dried powdered samples was weighed and then dispersed in 200 mg potassium bromide (pellet procedure). Signal averages were obtained at a resolution of $4\ cm^{-1}$.

### 3.5.9   X-ray powder Diffraction

The X-ray diffraction pattern was recorded with a copper anode x-ray tube (Cu $K_{\alpha 1}$ and $K_{\beta}$ radiation) using a XPERT-PRO PW3064/60 diffractometer (Stoe and Cie GmbH, Darmstadt, Germany) shown in Fig 3.1.  The polymers were tightly packed in sample holders and exposed to the X-ray spinning beam at a generator setting of 40 kV and 30 mA. The scanning diffraction angle ($2\theta$) was $5.01^0$-$99.07^0$ at a continuous scan step time of 6.35 sec.

**Fig 3.1:** XPERT-PRO PW3064/60 Diffractometer

## 3.6    Determination of Rheological Properties

Rheological characteristics were determined with a Rapid Visco Analyzer (RVA), (model RVA 3D$^+$, Network Scientific, Australia). A quantity (0.625 g) of polymer sample (*Entandophragma angolense*, gelatin or hydroxypropylcellulose) was weighed into a pre-dried empty canister; distilled water (25 mL) was dispensed into the canister containing the sample to form 2.5 %w/v slurry. The slurry was heated to 95 °C followed by cooling to 50 °C with 2 min holding time. The rate of heating and cooling were at a constant rate of 11.25 °C min$^{-1}$. Peak viscosity, trough, breakdown, final viscosity, set back, peak time and pasting temperature were read with the aid of a thermocline for windows software connected to a computer (Newport Scientific, 1998). The entire process was repeated for 5.0, 7.5 and 10.0 %w/v of each sample.

## 3.7    Evaluation of Toxicity

Toxicity studies were carried out according to the method reported by Kumar *et al* (2009). Male albino rats weighing 180-200 g were divided into two groups comprising of six animals each. The control group received a daily oral dose of 2.50 mg/kg of *Entandophragma angolense* gum suspension in normal saline (prepared by dissolving 0.9 g of sodium chloride in 100 mL of distilled water). The other group received a daily oral dose of 400 mg/kg of *Entandophragma angolense* gum suspension in normal saline. The animals were observed continuously for behavioral changes for the first 4 hours and then observed for mortality for 48 hours. The body weights were recorded for both groups at intervals of 10 days over 30 days. At the end of the 30-day period, hematological parameters were studied in both groups, and the blood samples were analysed in quadruplicate.

## 3.8    UV Determination

Various mixtures of *Entandophragma angolense* gum, gelatin or hydroxypropylcellulose and the model drugs (chlorpheniramine maleate or ibuprofen) were scanned in the wavelength range 190-300 nm. The maxima at 265 nm and 221 nm were monitored for wavelength shifts on a model DU-7400 spectrophotometer (Beckman, Fullerton, CA) (Alur *et al*, 1999).

### 3.9    Tablet Preparation

### 3.9.1    Preparation of Granules

Batches (250 gm) of a basic formulation comprising of chlorpheniramine maleate (or water insoluble ibuprofen), lactose, and *Entandophragma angolense* gum (or gelatin or hydroxypropylcellulose), at a ratio of 6:3:1 respectively were dry mixed for 5 min in a planetary mixer (Model A120, Hobart Manufacturing Co., U.K.) and  moistened with appropriate amount of paste of the binding agent *Entandophragma angolense* (or gelatin or hydroxypropylcellulose) to produce samples containing different concentrations of the binder.

Massing was continued for about five minutes and the wet masses were granulated by passing them manually through a no. 12 mesh sieve (1,400 µm). The granules were dried in hot air oven for 16 hours at 60 $^0$C. The dried granules were then re-sieved through a number 16 mesh sieve (1,000 µm), before they were stored in air-tight containers.

### 3.9.2    Granule Size Distribution

Size distribution analysis of the granules was performed using standard sieves of the following sizes; 12 mesh (1400 µm), 14 mesh (1,250 µm), 16 mesh (1,000 µm), 22 mesh (710 µm), 30 mesh (500 µm), 44 mesh (355 µm), 60 mesh (250 µm) and the receiver.

The cleaned sieves were arranged in descending order of aperture size with the receiver at the bottom. A quantity (100 g) of granules was placed on the uppermost sieve, the cover was firmly placed and the stack of sieves was shaken for fifteen minutes on a sieve shaker (J.Englsmann AG, Ludwigehafan/Phan. Germany).

The quantity of granules retained on each sieve was carefully weighed and the cumulative percentage oversize was calculated and plotted, and the mean granule size which corresponds to the sieve size (µm) at 50 % cumulative weight percentage oversize was determined. The granules of size 500-1,000 µm were collected and stored in air tight containers.

### 3.9.3 Loose Bulk Density

The determination of the loose bulk density (at zero pressure) of each sample, $\rho_0$, was carried out by pouring a known weight of sample at an angle of 45 $^0$C through a funnel into a measuring cylinder with a diameter of 25mm and a volume of 50 mL

Determinations were carried out in quadruplicate and the loose bulk density, $\rho_0$, values were calculated using the following equation:

$$\rho_0 = w/\pi r^2 h \tag{45}$$

where  w  = weight of the sample in the cylinder.

  r  = radius of the cylinder.

  h  = height of the sample in the cylinder.

### 3.9.4 Direct Compression

The formulae for the directly compressed tablets are listed in Table 2.1, and were prepared initially by premixing the *Entandophragma angolense* (or gelatin or hydroxypropylcellulose and Chlorpheniramine maleate (or Ibuprofen) for 15 min. Subsequently, lactose and talc were incorporated and the resulting composition was mixed for a further 15 min. Compression was carried out at predetermined loads using a Carver hydraulic hand press (model C, Carver Inc, Menomonee falls, Wisconsin, U.S.A), equipped with a 10.5 mm flat faced punch and die set lubricated with a 1 % dispersion of magnesium stearate in acetone prior to compression.

### 3.9.5 Compression of Granules

Granule size fractions (500 – 1,000 µm) from the already prepared granules (section 3.9.1) were used to prepare the tablets (400mg ±5mg) using a Carver hydraulic hand press (model C, Carver Inc, Menomonee falls, Wisconsin, U.S.A), equipped with a 10.5mm flat faced punch and die set lubricated with a 1 % dispersion of magnesium stearate in acetone prior to compression.

Different compression pressures were employed to obtain different relative densities, $\rho_r$, for the tablets. Tablets with holes were also prepared by employing an upper

punch with a hole through the centre and a lower punch fitted with a pin. The tablets (with and without holes) were stored over silica gel for 24 hours to allow for elastic recovery and hardening prior to measuring their weights and dimensions. The packing fractions (relative densities), $\rho_r$, of the tablets were calculated using the equation:

$$\rho_r = W / V\rho_s \qquad (46)$$

where V = volume of tablets.

W= weights of tablets.

$\rho_s$ = particle density of formulation.

**Table 3.1:** Formulae for directly compressed tablets (mg)

| Formulations  (% w/w) | A | B | C | D | E |
|---|---|---|---|---|---|
| Chlorpheniramine maleate (or Ibuprofen) | 5 | 5 | 5 | 5 | 5 |
| Polymer (*Entandophragma angole*nse or gelatin or hydroxypropylcellulose) | - | 2.5 | 5.0 | 7.5 | 10.0 |
| Talc | 2 | 2 | 2 | 2 | 2 |
| Spray dried lactose | 93 | 90.5 | 88 | 85.5 | 83 |

### 3.11 Heckel Plots

Heckel plots of In $(1/1-\rho_r)$ against the applied pressure (P) were plotted for the different formulations. Values of K and A were obtained from the slope and intercept respectively. The mean yield pressure, $P_y$, was determined as the reciprocal of the slope while the relative density, $\rho_{rA}$, was obtained from equation (12). Values for the relative density at low pressures, $\rho_{rB}$, were obtained from the difference between $\rho_{rA}$ and $\rho_{r0}$ (equation 14).

### 3.12 Kawakita Plots

The volume of the formulations at zero pressure, $V_0$, was determined using equation 38. The volume of the tablets at different compression pressures, $V_p$, were also calculated. The degree of volume reduction, C, was calculated from equation 15. Kawakita plots of P/C against applied pressure, P, were plotted for the different formulations.  Values of 'a' and 'ab' were obtained from the slope and intercept respectively.

### 3.13 Tensile Strength Measurement

The tensile strengths of the normal tablets, T, and the tablets with a hole , $T_0$, were determined using the Erweka Hardness Tester (Model TBH 28, Apparatebau, GMBH, Germany) (Fell and Newton, 1970). Measurements were made in quadruplicate on individual tablets and the results of the crushing strength were accepted only if the tablets split clearly into two halves.

The tensile strength values were calculated using equation (17).

### 3.14 Brittle Fracture Index

The brittle fracture index values (BFI) of the tablets were calculated using equation (18).

### 3.15 Friability Test

The friability test of the tablets was done using the Veego tablet friability testing apparatus (Veego Scientific Devices, Mumbai, Maharashtra, India). To achieve this, ten

tablets were randomly selected, weighed together and then placed in the friabilator, and the apparatus was operated at 25 rpm for 4 min (100rpm). The tablets were collected, dusted and weighed again. Determinations were made in quadruplicate and the percentage weight loss was calculated.

### 3.16    Disintegration Test

The disintegration times of the tablets were determined in 900 mL of distilled water at a temperature of $37 \pm 0.5\ ^{0}C$ using the Apex disintegration testing apparatus (Apex Construction Ltd; Northflect gravescent and Dartford, Kent, U.K.).

Six tablets from each batch were placed in the cylindrical tubes of the basket. The time taken for the tablets to break up into particles and pass through the mesh was recorded and the mean disintegration time was calculated.

### 3.17    Dissolution Test

The *in vitro* dissolution test was determined in 900 mL of 0.1M HCl and 900 mL of phosphate buffer (pH 7.4) for chlorpheniramine maleate and ibuprofen tablets respectively,  at a temperature of $37 \pm 0.5\ ^{0}C$ using the Rotating Basket (USP Apparatus I) method (Fig 1.10) at a rotation of 100 rpm. The pre-weighed tablet was then introduced into the dissolution medium and at different time intervals; 10 mL of the sample was withdrawn and replaced with 10 mL of fresh medium.

Samples (10 mL) that were removed at the designated intervals were subjected to UV spectrometric analysis of drug content (265 nm and 221 nm for chlorpheniramine maleate ibuprofen tablets respectively). The absorbance of the removed samples was measured and the total concentration of the drug in each medium was determined.

### 3.17.1  Dissolution Profiles and Kitazawa Plots

Typical dissolution profiles of percentage (%) of drug dissolved against time (mins) were plotted for the different formulations. The data obtained was subjected to kitazawa analysis, which involved the use of the integrated form of the Noyes-Whitney equation (Noyes and Whitney, 1897) as shown in equation (24). Values of In $[C_S/C_S\text{-}C)]$ were plotted against t for different formulations.

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### 3.18    Mucoadhesion Studies

Mucoadhesion studies were carried out to quantitate the time of detachment (mucoadhesive strength) of chlorpheniramine maleate or ibuprofen tablets attached to freshly excised intestinal mucosa of pig.

The rotating cylinder method,which is a slightly modified dissolution apparatus described in the USP was used (Fig 3.2). An intestinal segment of the mucosa was fixed on a stainless-steel cylinder with the basolateral side facing the cylinder. The tablets were pressed on the apical side and the cylinder was transferred into a medium containing 500 mL of phosphate buffer, pH 7.4 (or 500 mL of 0.1M HCl, pH 1.2) medium. The rotation speed was set to 60 rpm. The time taken for the tablets to detach from the mucosa was observed for tablets prepared by the direct compression and wet granulation techniques.

### 3.19    Preparation of Matrix Tablets

*Entandophragma angolense* gum matrices (400 mg ±5 mg) were prepared by direct compression at a compression force and compression time of 1 ton and 30 seconds, respectively, using the same Carver hydraulic hand press (model C, Carver Inc, Menomonee falls, Wisconsin, U.S.A) described in Section 3.9.4, to determine the effect of polymer concentration on the matrix tablets. The hydrophilic matrices were formulated to contain 10, 20, 30 and 40 % of chlorpheniramine maleate and 90, 80, 70 and 60 % respectively of the polymers (*Entandophragma angolense* gum, gelatin or hydroxypropylcellulose)    *In-vitro* drug release studies from the matrix tablets were conducted for 14 hours at 37 $^0$C in a dissolution medium with a rotating basket providing agitation of 100 rpm. 0.1M HCl was used as the dissolution media.
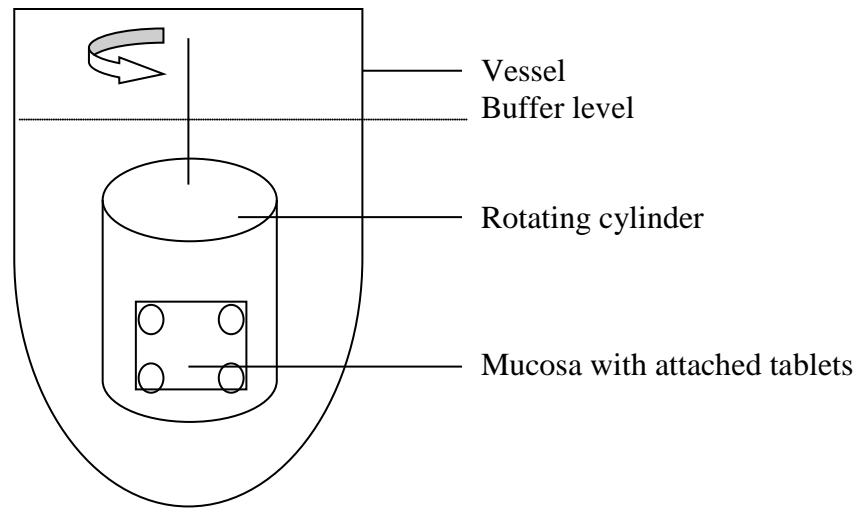
**Fig. 3.2:** Rotating Cylinder Apparatus for Mucoadhesion Studies.

### 3.20 Factorial Experimental Design

To study the effects of nature of binder (denoted by N), concentration of binder (denoted by C), relative density (denoted by D) and tabletting technique (denoted by M) on the disintegration time, tensile strength, brittle fracture index and mucoadhesion time of the tablets, the experiments were performed based on the statistical modulation proposed by Woolfall (1964). The basis of the experiment was to utilize a two-level factor using the four variables, that is $2^4$, and maintain a factorial structure. The levels are "high" level (denoted by the subscript H) and "low" level (denoted by the subscript L)

Using the above nomenclature, the expected combinations are represented by the following:

$N_H C_H D_H M_H$,   $N_H C_L D_L M_L$,   $N_H C_H D_L M_L$,   $N_H C_H D_H M_L$

$N_H C_L D_H M_L$,   $N_H C_L D_L M_H$,   $N_L C_H D_H M_H$,   $N_L C_L D_H M_H$

$N_L C_L D_L M_H$,   $N_L C_L D_L M_L$,   $N_L C_H D_L M_H$,   $N_L C_H D_L M_L$

$N_H C_H D_L M_H$,   $N_H C_L D_H M_H$,   $N_L C_L D_H M_L$,   $N_L C_H D_H M_L$


Where: $N_L$ = Nature of polymer (*Entandophragma angolense*)

$\quad\quad$ $N_H$ = Nature of polymer (Hydroxypropylcellulose)

$\quad\quad$ $C_L$ = Concentration of polymer (2.5%w/w)

$\quad\quad$ $C_H$ = Concentration of polymer (10.0%w/w)

$\quad\quad$ $D_L$ = Relative Density of tablet at 0.85

$\quad\quad$ $D_H$ = Relative Density of tablet at 0.90

$\quad\quad$ $M_L$ = Direct compression technique

$\quad\quad$ $M_H$ = Wet granulation technique


By grouping the results into a number of sets, it was possible to assess the effect that each of the four variables had separately on the disintegration time, tensile strength, brittle fracture index and mucoadhesion time of the tablets (Woolfall, 1964; Montgomery, 1991).

According to Woolfall (1964), the effect of increasing the excipient N, from its 'low' level to its 'high' level on the disintegration time, tensile strength, brittle fracture index or mucoadhesion time can be determined by summing up all the values of

disintegration time (or tensile strength, brittle fracture index, or mucoadhesion time) of samples containing 'high' level of N and subtracting the sum of the values containing 'low' levels of N. That is:

$$1/4 \, [(N_H C_H D_H M_H) + (N_H C_L D_L M_L) + (N_H C_H D_L M_L) + (N_H C_H D_H M_L) +$$
$$(N_H C_L D_H M_L) + (N_H C_L D_L M_H) + (N_H C_H D_L M_H) + (N_H C_L D_H M_H) \; -$$
$$(N_L C_H D_H M_H) + (N_L C_L D_H M_H) + (N_L C_L D_L M_H) + (N_L C_L D_L M_L)$$
$$(N_L C_H D_L M_H) + (N_L C_H D_L M_L) + (N_L C_L D_H M_L) + (N_L C_H D_H M_L)]$$

In the same way, the effect of increasing the concentration of polymer (C), changing the relative density (D) or the compression technique (M) from 'low' to 'high' levels can also be determined using the adaptation of the method proposed by Woolfall (1964).

To determine whether there was any interaction between two variables, the results of the combination in which they appear together at either high or low levels were summed and the sum of the other combinations were subtracted from this to obtain the interaction effects. For example, the interactive effects of N and C on the disintegration time were obtained as follows:

$$1/4 \, [(N_H C_H D_H M_H) + (N_H C_H D_L M_L) + (N_H C_H D_H M_L) + (N_H C_H D_L M_H) +$$
$$(N_L C_L D_H M_H) + (N_L C_L D_L M_H) + (N_L C_L D_L M_L) + (N_L C_L D_H M_L) \; -$$
$$(N_H C_L D_L M_L) + (N_H C_L D_H M_L) + (N_H C_L D_L M_H) + (N_H C_L D_H M_H)$$
$$(N_L C_H D_H M_H) + (N_L C_H D_L M_H) + (N_L C_H D_L M_L) + (N_L C_H D_H M_L)]$$

Montgomery (1991) designed a computer-based software to determine the various effects of these variables. The software (Minitab© 16), though based on the principles of Woolfall's work on product formulation (1964), has been able to optimize performance in experimental processes and thus, reduced the manual calculation associated with previous processes.

Montgomery (1991) also applied the $2^k$ factorial experiment involving k factors at only two levels per factor (settings normally coded as either high or low). Factorial

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experimental design allows estimation and testing of the statistical significance of the main effects and the interactions between factors. If two factors interact, then it implies that the effects of one factor depend on the setting of the other. Factor settings are very important in the presence of interactions since effects will not be additive in nature (Woolfall, 1964; Montgomery, 1991).

### 3.21    Analysis of Results

Statistical analysis was done to compare the binding, mucoadhesive and controlled release properties of *Entandophragma angolense* gum and the reference polymers (gelatin or hydroxypropylcellulose) on the tablet properties using the analysis of variance (ANOVA) on a computer software; Graphpad Prism 4 (Graphpad Software Incorporation, San Diego, USA). Variable multiple comparison tests (quantitative) were used to compare the differences between the different polymers. At 95% confidence interval, p values $\leq$ 0.05 were considered significant. Different kinetic models were applied to interpret the dissolution data obtained from the *in-vitro* drug release studies from the matrix tablets in order to determine the best fit for the formulations.

# CHAPTER FOUR

## CHARACTERIZATION OF *Entandophragma angolense* GUM

### 4.1          Gum Yield

The percentage yield of the dried gum obtained from exudates of the incised trunk of *Entandophragma angolense* tree was 48.46 %w/w. This value is considerably high for a natural product (Bellal *et al*, 2005), thus further establishing the potential for use in the pharmaceutical industry.

### 4.2    Phytochemical Screening of *Entandophragma angolense* Gum

The results of the phytochemical screening of *Entandophragma angolense* gum (ENTA) are presented in Table 4.1. The results show the presence of carbohydrates and confirm that the gum has mucilage properties, suggesting that *Entandophragma angolense* gum is a polysaccharide. Absence of tannins and alkaloids in the gum is an indication that the gum does not contain compounds that could have potential pharmacological effects.

### 4.3    Powder Properties of *Entandophragma angolense* Gum and the other Polymers

The particle density, bulk density and tapped density of the *Entandophragma angolense*, Gelatin and Hydroxypropylcellulose are presented in Table 4.2. The ranking of the loose bulk densities of the individual powders was Gelatin > Hydroxypropylcellulose > *Entandophragma angolense* gum, while the ranking for the tapped densities was Hydroxypropylcellulose > Gelatin > *Entandophragma angolense* gum. The bulk density of a powder describes its packing behavior. Higher bulk density is advantageous in tabletting because of a reduction in the fill volume of the die. The tapped density indicates the rate and extent of packing that would be experienced by the material during the various unit operations of tabletting (Wray, 1992). The difference observed in the tapped density values could be due to the difference in the particle shape and particle size distribution, both of which affect the packing arrangement of particles.

**Table 4.1:** Phytochemical screening of *Entandophragma angolense* gum

| Tests | Observation |
| --- | --- |
| Test for Carbohydrates (Molisch's test) | + |
| Test for reducing sugars (Fehling's test) | - |
| Test for ketones (Selivanoff's test) | - |
| Test for alkaloids (Wagner's and Dragendorff's  tests) | - |
| Test for saponins | - |
| Test for anthraquinones | - |
| Test for Tannins (Ferric Chloride test) | - |
| Test for glycosides (Keller-Killiani test) | - |
| Test for mucilage (Ruthenium red test) | + |
| Test for flavonoids (Shinoda test) | - |
| Mounting in 95% alcohol | Transparent angular masses seen under the microscope |
| Mounting in iodine | Colour of iodine retained (no blue coloured particles seen (starch is absent) |

The value of the compressibility index is a measure of the flowability and compressibility of a powder. Thus, *Entandophragma angolense* gum would be expected to have better flow properties, but lower compressibility than Gelatin, based on the result shown in Table 4.2. Compressibility index of 5-10, 12-16, 18-21, and 23-28 represent excellent, good, fair and poor flow properties respectively (Carr, 1965; Emeje *et al,* 2009).

The ranking of the compressibility index was Hydroxypropylcellulose > ENTA > Gelatin, thus indicating that Hydroxypropylcellulose had the lowest flow properties with the highest compressibility.

The Hausner's ratio (tapped to bulk density) provides an indication of the degree of densification which could result from the vibration of the feed hopper, for example, during tabletting. Higher values of Hausner's ratio predict significant densification of powders. The ranking of Hausner's ratio was Hydroxypropylcellulose > ENTA > Gelatin, thus suggesting that ENTA exhibited a higher degree of densification with tapping than Gelatin.

The packing and cohesive properties of powdered materials influence the various aspects of their processing such as milling, blending, flow from hoppers, compression and packing into capsule shells or containers. These properties depend to a large extent on the particle size distribution and shape of the granules made from such powdered materials (Itiola, 1994).

The angle of repose, $\theta$, has been used as a qualitative measure of the cohesiveness or the tendency of the powdered or granulated materials to flow, for instance, from hoppers through the feed frame into the tabletting machine. Such uniformity of flow will minimize weight variations in tablets produced (Varthalis and Pilpel, 1976). Angles of $30^0$ or below is usually an indication that the powder is free flowing, while angle of $40^0$ or above indicates poor flow characteristics (Adolfsson and Nystron, 1996). The angle of repose is affected by the particle size distribution and usually increases with a decrease in particle size. The ranking of the angle of repose was Hydroxypropylcellulose > ENTA > Gelatin. This ranking is inversely related to the ranking of their particle size. Thus, ENTA with a smaller mean projected particle diameter was more cohesive when compared with gelatin, but less cohesive when compared with hydroxypropylcellulose. In general, the smaller the particle size, the more cohesive the particles. The angle of repose for all the

polymers (Table 4.2) is well below $30^0$ indicating that the polymers have good flow properties.

Knowledge of the pH of an excipient is an important parameter in determining its suitability in formulations since the stability and physiologic activities of most preparations depend on pH (Luiz *et al*, 2005). The observed pH of the *Entandophragma angolense* gum (Table 4.2) indicates that the gum will be stable at acidic pH.

## 4.4    Physicochemical Characteristics of *Entandophragma angolense* Gum

### 4.4.1    Moisture Content Determination

The moisture content of *Entandophragma angolense* gum was low , thus suggesting that the *Entandophragma angolense* gum can be incorporated as an excipient in formulations containing moisture sensitive drugs. Water content for safe storage of materials is prescribed to be within the range of 10-13% (Kurup and Pilpel, 1979). Higher levels of water can lead to microbial spoilage and subsequent deterioration in gum quality. In addition, water has been known to affect the flow and mechanical properties of powdered materials (Alur *et al*, 1999), hence, control of relative humidity is important during tablet production to obtain powders and granules with optimum flow and compaction properties. Moisture, depending on the temperature, could be an aiding factor for the proliferation of microorganisms in pharmaceutical products, thereby affecting the shelf life of such a product (Adetunji *et al*, 2006). It is important to have a thorough understanding of the moisture content of a material because of the economic importance of an excipient for industrial application, which relies not only on the easy availability and affordability of the material, but also on the optimization of production processes such as drying, packaging and storage, which are all based on the qualitative assurance of the material (Sonnergard, 1999).

### 4.4.2   Elemental Analysis

The elemental constituents of *Entandophragma angolense* gum are presented in Table 4.3. The result shows the absence of heavy metals such as nickel, arsenic and lead in *Entandophragma angolense* gum powder. Undesirable presence of heavy metals may limit the use of gums as excipients in the preparation of oral solid dosage forms; this is because

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these heavy metals are hazardous to health. Variations within gum samples may occur since the mineral composition of a particular gum sample could be a function of the soil on which the plant grows (Bellal *et al*, 2005).

**Table 4.2:** Physicochemical Composition of Polymers (mean ±SD, n=4)

| Parameters | *Entandophragma angolense* gum | HPC | Gelatin |
|---|---|---|---|
| Swelling capacity in water at $27^0$C (%) | 51.3±0.01 | 9.8±0.03 | 11.7±0.01 |
| Swelling capacity in water at $80^0$C (%) | 82.7±0.02 | 21.5±1.04 | 37.7±1.00 |
| Solubility in water at $27^0$C (%) | 38±0.01 | 29±1.01 | 21±0.23 |
| Solubility in water at $80^0$C (%) | 53±0.01 | 57±0.01 | 41±0.17 |
| Loss on drying (%w/w) | 0.1±0.01 | 0.2±0.03 | 0.1±0.01 |
| Total ash (%w/w) | 1.26±0.04 | 1.29±0.02 | 2.0±0.03 |
| Acid insoluble ash (%w/w) | 0.1±0.02 | 0.1±1.00 | 0.03±1.04 |
| Water insoluble ash (%w/w) | 0.3±0.02 | 0.2±1.00 | 0.19±1.04 |
| pH of 1% solution at $32^0$C | 4.27±1.08 | 6.24±0.03 | 7.5±1.17 |
| Mean projected particle diameter (µm) | 13.1±0.02 | 11.3±0.02 | 14.1±0.02 |
| Particle density (g cm$^{-3}$) | 1.69±0.01 | 1.62±0.03 | 1.71±0.11 |
| Bulk density (g cm$^{-3}$) | 0.61±0.03 | 0.64±0.02 | 0.67±0.06 |
| Tapped density (g cm$^{-3}$) | 0.72±0.04 | 0.79±0.04 | 0.77±0.01 |
| Hausner's ratio | 1.18±0.03 | 1.23±0.03 | 1.15±1.04 |
| Compressibility index (%) | 15.28±0.04 | 18.98±0.12 | 12.99±0.03 |
| Angle of repose (degrees) | 12.53±2.02 | 17.42±1.87 | 12.48±1.72 |
| Moisture content (%) | 9.2±0.01 | 8.7±0.15 | 1.73±0.01 |

HPC: Hydroxypropylcellulose

**Table 4.3:** Elemental constituents of *Entandophragma angolense* gum powder

| Element | mg/100 gm |
|---|---|
| Nickel (Ni) | 0.00 |
| Selenium (Se) | 0.00 |
| Nitrogen (N) | 0.48 |
| Calcium (Ca) | 47.21 |
| Potassium (K) | 640.09 |
| Lead (Pb) | 0.00 |
| Phosphorous (P) | 43.04 |
| Bromine (Br) | 0.18 |
| Iron (Fe) | 5.42 |
| Silicon (Si) | 0.00 |
| Aluminium (Al) | 0.00 |
| Copper (Cu) | 0.25 |
| Manganese (Mn) | 29.86 |
| Zinc (Zn) | 43.28 |
| Arsenic (As) | 0.00 |

### 4.4.3 Swelling and Solubility Characteristics

The swelling characteristics and solubility of the gums in distilled water were studied, and the results indicate that the swelling characteristics, at both $27^0C$ and $80^0C$, was in the ranking ENTA > Hydroxypropylcellulose > Gelatin. The water solubility of the gums (at $27\,^0C$) was in the ranking Hydroxypropylcellulose > Gelatin > ENTA, while at $80\,^0C$, it was ENTA > Hydroxypropylcellulose > Gelatin. The swelling characteristics and solubility of the gums provide evidence of the magnitude of interaction within the lattice structure of the gum and between water molecules. It has also been suggested that the swelling characteristics of a pharmaceutical polymer could be used in the preliminary determination of some excipient properties (Emeje *et al*, 2009).

### 4.4.4 Fourier Transform Infrared (FTIR) Spectrum

The results of the FTIR spectrum obtained for the powdered mixtures of *Entandophragma angolense* gum with chlorpheniramine maleate (or ibuprofen), and *Entandophragma angolense* gum alone using a Magna-IR, 560 spectrometer are shown in Figs 4.1- 4.3. The functional group region (4000 to 1300 $cm^{-1}$) showed sharp peaks at 2926.85 $cm^{-1}$ and 2853.19 $cm^{-1}$ (Fig 4.1). These sharp peaks are characteristic of methyl C-H stretching associated with aromatic rings and carboxylic acids. The sharp peaks at 2359.93 and 2341.37 $cm^{-1}$ are indications of asymmetric C-O stretch. The peaks obtained at 1573.69 and 1558.36 showed similar functional groups consisting of strong N=O nitroso and weak C-O stretch.

The fingerprint region consists of a characteristic peak at 1070.72 $cm^{-1}$ (Fig 4.1). This peak confirms the presence of strong aromatic characters consisting of C-O, C=O, C-N and C-F stretches, and weak P-H bending groups, which are present in materials like carbohydrates, starch, and natural polymers (Malik *et al,* 2002). The results revealed the presence of methyl, amine, phosphine and hydroxyl groups, in *Entandophragma angolense* gum, and suggested the absence of a chemical reaction between *Entandophragma angolense* and chlorpheniramine maleate (or ibuprofen).
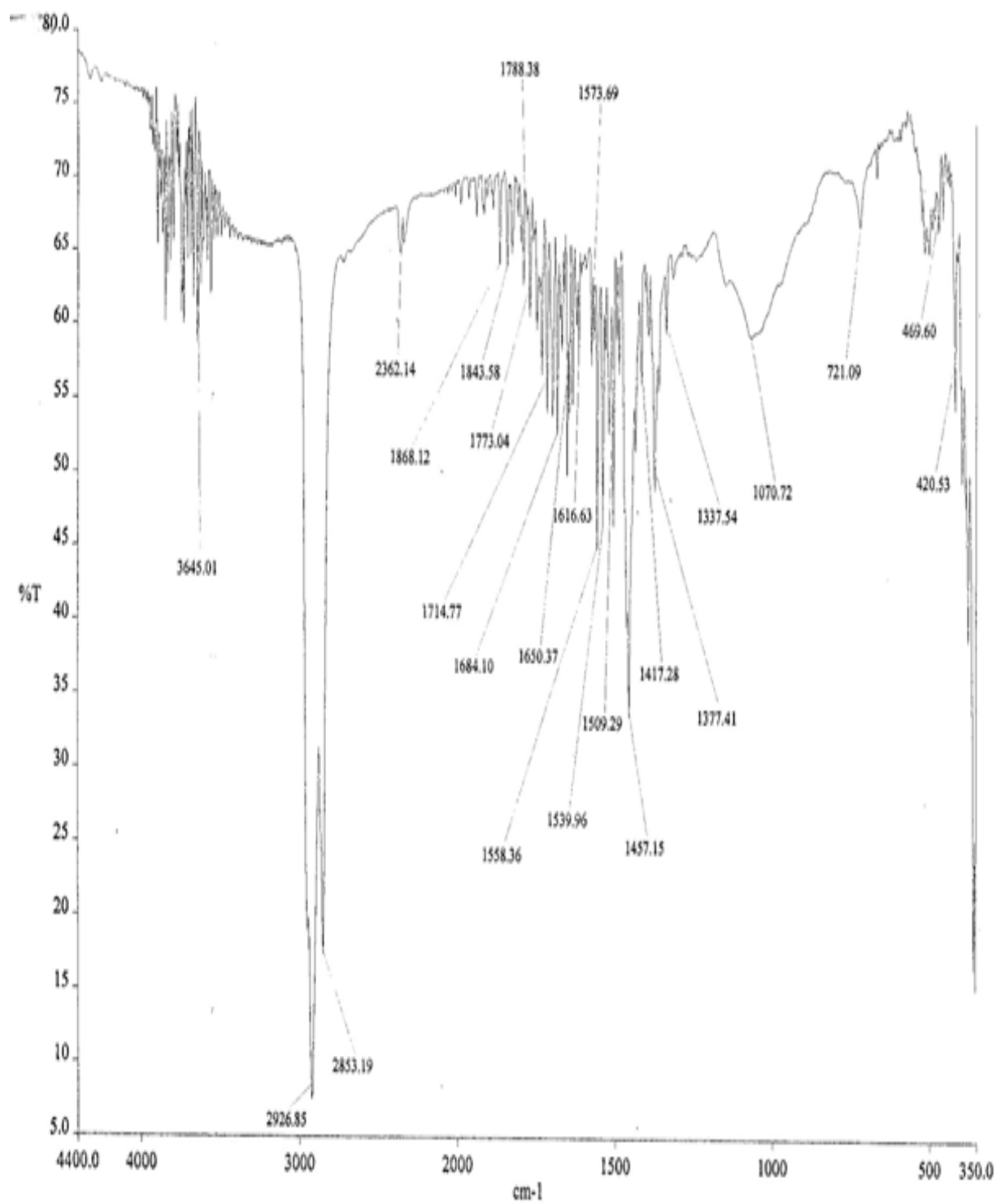
**Fig 4.1:** FTIR Spectroscopy pattern for *Entandophragma angolense* gum
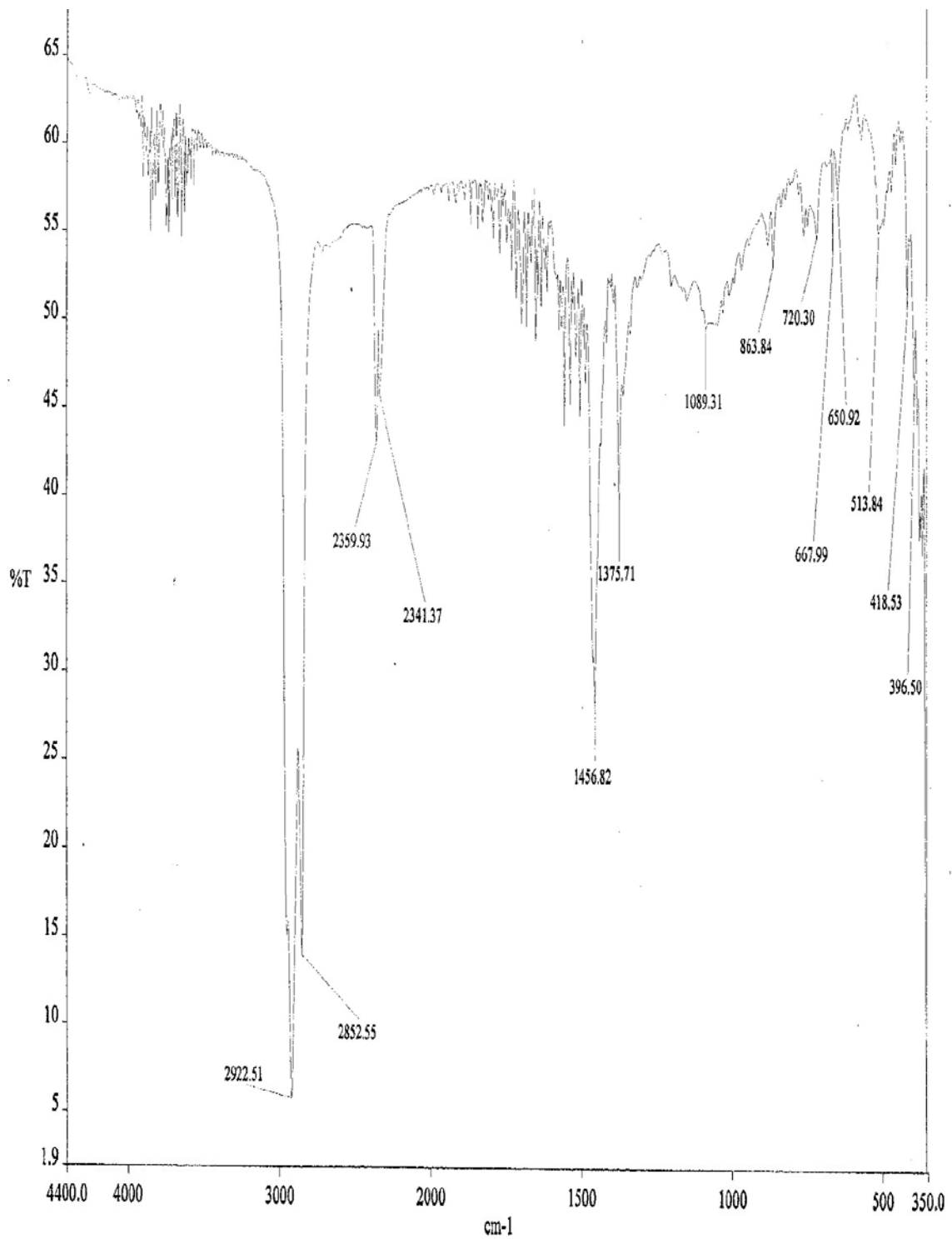
**Fig 4.2:** FTIR spectroscopy pattern for the physical mixture containing *Entandophragma angolense* gum and chlorpheniramine maleate powders
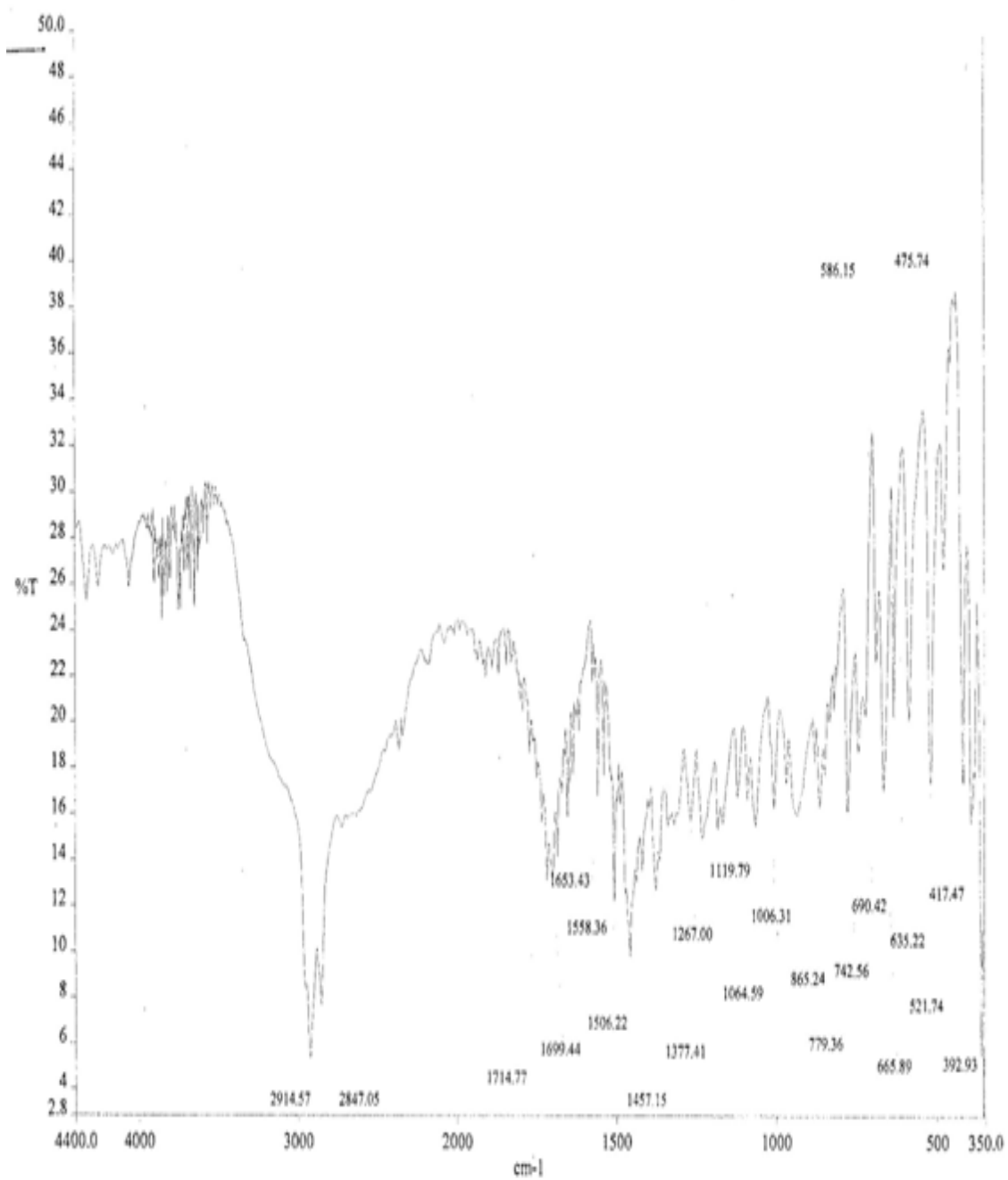
**Fig 4.3:** FTIR Spectroscopy pattern for the physical mixture containing *Entandophragma angolense* gum and Ibuprofen powders

### 4.4.5  X-ray Diffraction Pattern

The X-ray diffraction pattern was used to characterize the crystal packing in the *Entandophragma angolense* gum granules. The X-ray diffraction pattern of *Entandophragma angolense* gum is shown in Fig 4.4. Ideally, every possible crystalline orientation is represented equally in a powdered sample. The resulting orientational averaging causes the three-dimensional reciprocal space that is studied in single crystal diffraction to be projected onto a single dimension. In practice, it is sometimes necessary to rotate the sample orientation to eliminate the effects of texturing and achieve true randomness (Percharsky *et al*, 2008). *Entandophragma angolense* gum showed peaks at $20.99^0$, $26.68^0$, $26.73.^0$ $27.59^0$ and $69.21^0$, all at $2\Theta$. These reflection patterns show that *Entandophragma angolense* gum is a mixture of polymorphs (Scappin, 2006).

### 4.5     Viscosity Profile

Table 4.4 shows the rheological properties of the polymers, while Figure 4.5 shows a representative plot of apparent viscosity (RVU) versus time for 5.0 %w/v of the polymers. During the test, which involved the use of the Rapid Visco Analyser (RVA), the polymer formed a jelly with subsequent rise in viscosity when subjected to high temperature and controlled shearing during which its stability was revealed and then cooled to provide an indication of setback time.  As the concentration of the polymer was increased, the apparent viscosity also increased. Viscosity is the measure of the internal friction of a fluid. This friction becomes apparent when a layer of fluid is made to move in relation to another layer. The greater the friction, the greater the amount of force required to cause this movement, which is called shear. Shearing occurs whenever the fluid is physically moved or distributed, as in pouring, spreading, spraying, mixing, etc. Highly viscous fluids, therefore, require more force to move than less viscous materials.

Knowledge of a material's rheological characteristics is valuable in predicting pourability, performance in a dipping or coating operation, or the ease with which it may be handled, processed, or used.
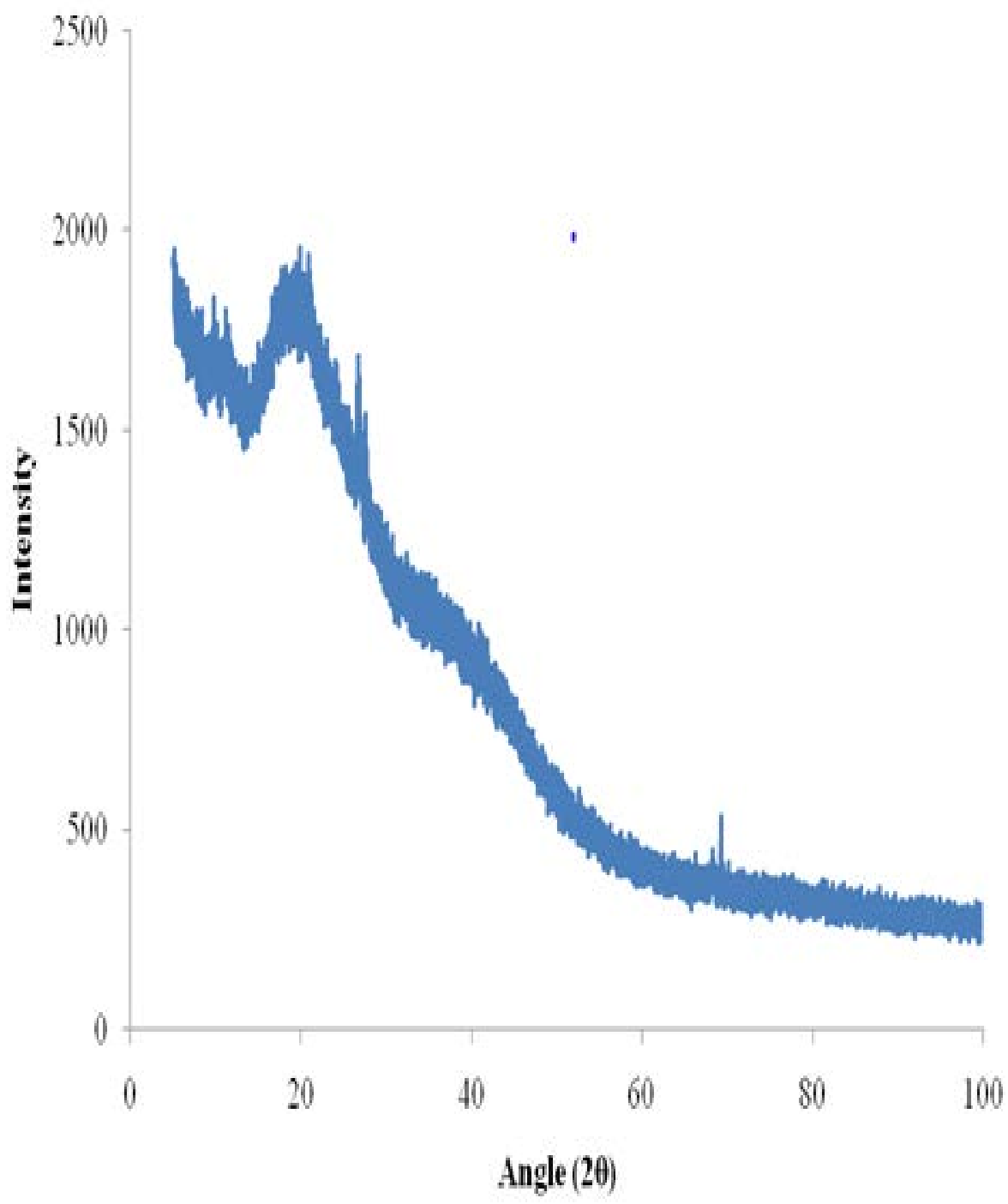
**Fig 4.4**: X-ray diffraction pattern of *Entandophragma angolense* gum

**Table 4.4:** Rheological properties of polymers

| Polymers | %w/v | Peak Viscosity (RVU) | Trough Viscosity (RVU) | Breakdown Viscosity (RVU) | Final Viscosity (RVU) | Set back (mins) | Peak time (mins) | Peak Temperature ($^0$C) |
|----------|------|----------|----------|-----------|----------|--------|--------|-------------|
| ENTA gum | 2.5 | 287.13 | 187.23 | 129.03 | 255.13 | 98.67 | 4.53 | 62.47 |
| | 5.0 | 276.04 | 185.43 | 128.24 | 258.17 | 95.13 | 4.43 | 62.48 |
| | 7.5 | 273.62 | 163.21 | 128.17 | 261.22 | 92.06 | 4.37 | 62.36 |
| | 10.0 | 251.26 | 124.42 | 128.03 | 269.13 | 88.62 | 4.33 | 61.45 |
| Gelatin | 2.5 | 255.27 | 155.04 | 127.51 | 247.05 | 89.13 | 4.47 | 63.09 |
| | 5.0 | 241.13 | 146.18 | 127.43 | 251.37 | 88.34 | 4.40 | 63.04 |
| | 7.5 | 238.35 | 134.63 | 128.04 | 256.28 | 83.14 | 4.42 | 62.18 |
| | 10.0 | 227.18 | 104.12 | 127.32 | 257.13 | 81.08 | 4.39 | 62.11 |
| HPC | 2.5 | 238.26 | 127.26 | 123.18 | 241.68 | 86.58 | 4.25 | 62.09 |
| | 5.0 | 222.08 | 124.15 | 118.24 | 244.26 | 86.42 | 4.33 | 61.27 |
| | 7.5 | 221.16 | 121.05 | 119.13 | 247.13 | 85.12 | 4.31 | 61.23 |
| | 10.0 | 207.25 | 119.62 | 121.25 | 256.24 | 82.42 | 4.28 | 61.09 |

ENTA: *Entandophragma angolense*

HPC: Hydroxypropylcellulose
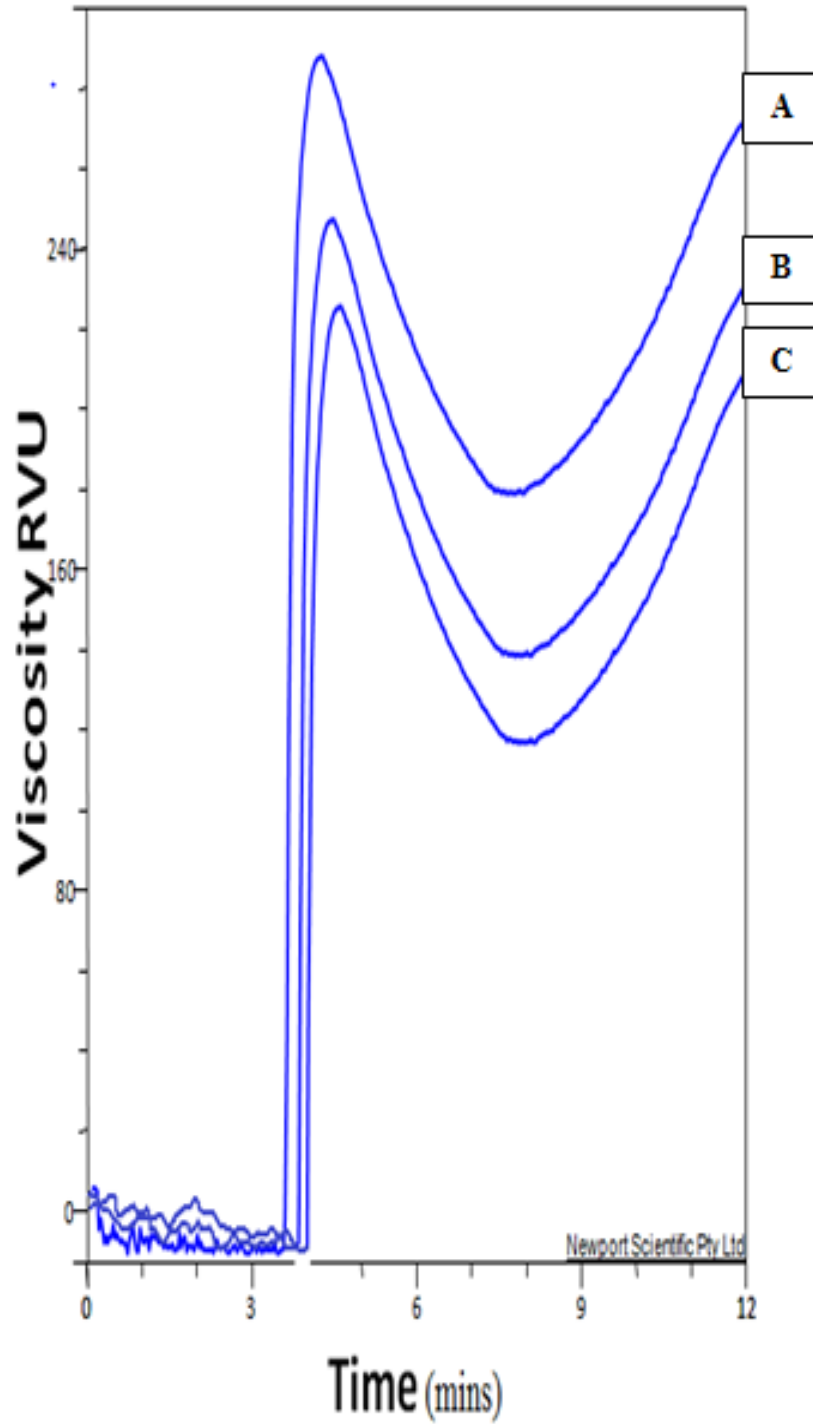
**Fig 4.5:** Plot of Viscosity (RVU) against time (mins) for 5.0%w/w of polymers

**A**: *Entandophragma angolense* gum, **B**: Gelatin, **C**: Hydroxypropylcellulose

**4.6    Toxicity Evaluation of *Entandophragma angolense* gum**

The determination of the safety level of *Entandophragma angolense* gum revealed no behavioral changes and no mortality throughout the course of the period. Toxic symptoms were not observed even at the dose level of 4000mg/kg body weight after 24 hours, which could be a measure of the safety of the gum. It was found that the body weight of both test and control albino rats and the rate of increase were comparable. The effect of *Entandophragma angolense* gum on hematological parameters is summarized in Table 4.5

**4.7    Material properties of *Entandophragma angolense* gum**

The results of the photomicrographs revealed irregular shaped particles of the polymers (Fig. 4.6). It was observed that hydroxypropylcellulose and gelatin had clustered particles, while those of *Entandophragma angolense* gum were scattered. Also, the particles of gelatin were the biggest out of the three polymers observed. Particle shape can influence compaction characteristics as it affects the packing behavior of the gums. This is because there is tendency for particle rearrangement to occur in the initial stages of the compaction process (Wray, 1992). The more irregular the particle shape of a material, the higher the tendency of the particle to fragment during compaction and the better the compatibility. Powdered materials with finer particles tend to have a higher number of particles per unit weight which is indicative of a higher potential of achieving homogeneity when mixing the substance with the active pharmaceutical ingredients (Odeku, 2005). Particle size also has significant effect on the densification of gums during die filling, particle rearrangement, fragmentation propensity and elastic/plastic deformation (Opakunle and Spring, 1977; Wray, 1992).

**Table 4.5:** Hematological values of male albino rats that received the mucilage of *Entandophragma angolense* gum for 30 days (Mean± SD, n = 4)

| Parameters | Mucilage treated | Control |
|---|---|---|
| RBC (x $10^6$ cells/mm$^3$) | 9.67±0.18 | 9.61±0.06 |
| WBC (x $10^6$ cells/mm$^3$) | 5.03±0.39 | 5.01±0.16 |
| Hemoglobin (g/dl) | 17.11±0.04 | 17.05±0.22 |
| Platelet ( x $10^3$ cells/mm$^3$) | 961±0.16 | 957±0.03 |
| Neutrophil (%) | 19.04±0.11 | 18.96±0.45 |
| Eosinophil (%) | 1.77±0.25 | 1.73±0.15 |
| Lymphocytes (%) | 62.31±0.41 | 62.27±0.22 |
| Monocyte (%) | 11.68±0.05 | 11.36±0.04 |
| Basophil (%) | 4.59±0.32 | 4.47±0.14 |
| Hematocrit (%) | 51.22±0.41 | 51.19±0.07 |
| MCV (µm$^3$/red cell) | 59.64±0.27 | 58.96±0.05 |
| MCH (g/dL/red cell ) | 21.05±0.04 | 21.03±0.06 |
| MCHC (g/dL/red cell) | 31.86±0.08 | 31.77±0.11 |
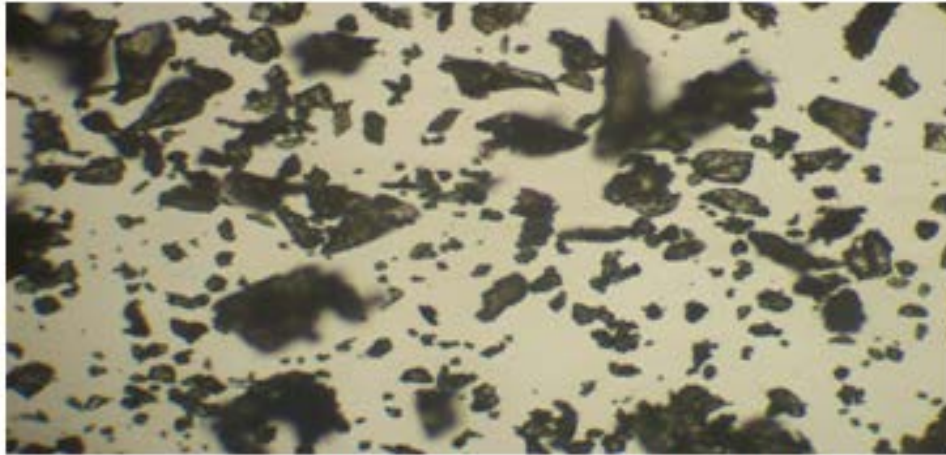
*Entandophragma angolense gum x 300*
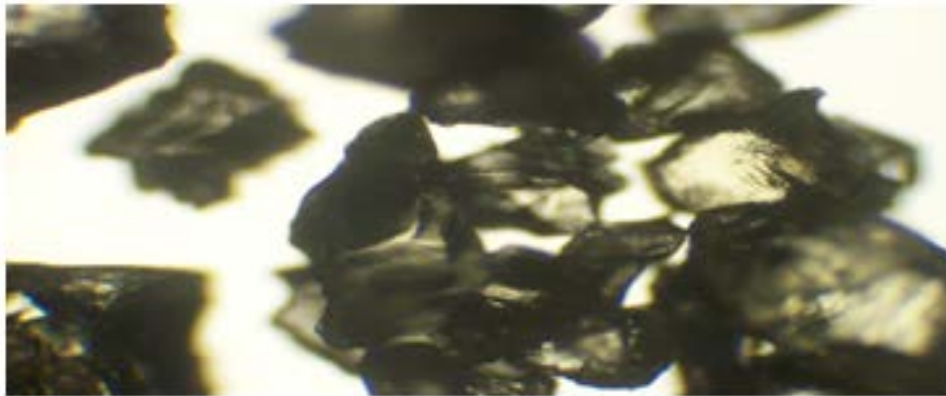


Gelatin x 300
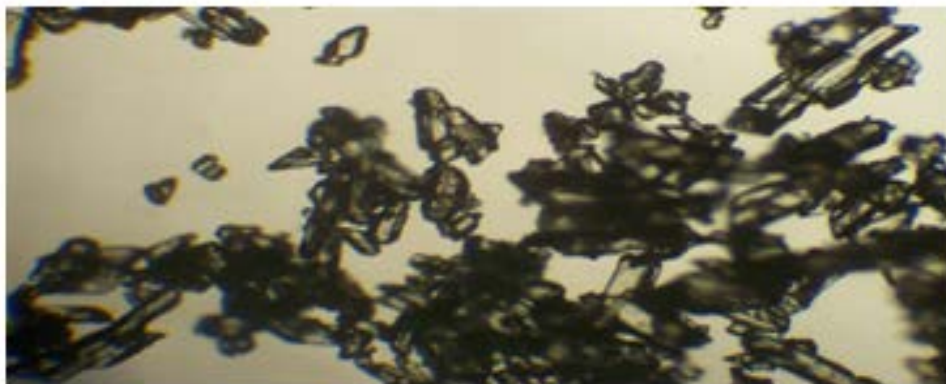


Hydroxypropylcellulose x 300

**Fig 4.6:** Photomicrographs of Polymers

**4.8          UV Determinations**

The results of the peaks at wavelength range 190-300 nm monitored using a model DU-7400 spectrophotometer (Beckman, Fullerton, CA) for *Entandophragma angolense* gum powder in combination with chlorpheniramine maleate powder at 265 nm (or ibuprofen powder at 221 nm) suggest the absence of any reaction between *Entandophragma angolense* and chlorpheniramine maleate (or Ibuprofen).

# CHAPTER FIVE

## CHARACTERISTICS OF FORMULATIONS

### 5.1 Granule Properties

Tables 5.1 - 5.3 show the sieve analysis data and size distribution of granules for the various formulations containing different concentrations of the polymers as binder. Representative plots of the granule size distribution of the various formulations containing different concentrations of polymers are shown in Figs 5.1 and 5.2. The granule size corresponding to 50 % on each plot was taken as the mean projected granule diameter (G) and the values are presented in Table 5.4. Plots of G against concentration of binder are shown in Figs 5.3 and 5.4. Generally, there was an increase in granule size as the concentration of polymer increased. This could be attributed to the strengthening of bonds between the particles as there would be more binder per bond as the concentration is increased. This has been previously reported in literature (Femi-Oyewo, 1987; Alebiowu and Itiola, 2002; Adetunji *et al*, 2006). It was observed that ibuprofen exhibited larger granules than chlorpheniramine maleate. In addition to this, the nature of the polymer was also observed to affect the granule size. The ranking of the granule size was of the order *Entandophragma angolense* gum > Hydroxypropylcellulose > Gelatin.

Granule size may influence the compression properties of granules and subsequently have an effect on some mechanical properties of the tablets they are formulated with. Dense hard granules may require higher compressive loads to produce a cohesive compact, but are usually less friable.

### 5.2 Precompression Density

The values of the precompression density, i.e. the relative density at zero pressure, $\rho_0$ for the gums are presented in Table 5.5 and 5.6. The ranking of the values of $\rho_0$ was Hydroxypropylcellulose > *Entandophragma angolense* gum > Gelatin. This implies that Hydroxypropylcellulose and *Entandophragma angolense* exhibited higher degree of initial packing in the die as a result of die filling.

**Table 5.1**: Granule size distribution of chlorpheniramine maleate and Ibuprofen formulations containing no binder

| Sieve Size (µm) | Cumulative weight % Oversize | |
| :---: | :---: | :---: |
| | Chlorpheniramine maleate | Ibuprofen |
| 1400 | 6.27 | 7.13 |
| 1250 | 12.11 | 11.28 |
| 1000 | 14.23 | 15.77 |
| 710 | 64.16 | 49.22 |
| 500 | 73.98 | 71.48 |
| 355 | 89.67 | 83.14 |
| 250 | 95.12 | 96.38 |
| Receiver (0) | 100.00 | 100.00 |

**Table 5.2**: Granule size distribution of chlorpheniramine maleate formulations containing different concentrations of the polymer as binder

| Binder | Sieve Size (µm) | 2.5% (w/w) | 5.0% (w/w) | 7.5% (w/w) | 10.0% (w/w) |
|---|---|---|---|---|---|
| *Entandophragma angolense* gum | 1400 | 3.71 | 4.95 | 5.22 | 12.07 |
| | 1250 | 19.19 | 27.62 | 34.67 | 39.02 |
| | 1000 | 29.31 | 29.62 | 35.12 | 48.42 |
| | 710 | 52.06 | 58.27 | 52.73 | 53.71 |
| | 500 | 72.70 | 76.38 | 80.67 | 62.94 |
| | 355 | 73.42 | 82.61 | 91.22 | 88.61 |
| | 250 | 86.28 | 93.42 | 96.71 | 96.93 |
| | Receiver (0) | 100.00 | 100.00 | 100.00 | 100.00 |
| Hydroxypropylcellulose | 1400 | 3.82 | 4.73 | 5.17 | 12.23 |
| | 1250 | 21.68 | 28.52 | 35.17 | 38.36 |
| | 1000 | 28.13 | 31.62 | 38.11 | 46.22 |
| | 710 | 49.15 | 49.77 | 53.28 | 58.08 |
| | 500 | 63.22 | 65.13 | 69.12 | 71.73 |
| | 355 | 71.27 | 73.26 | 76.26 | 83.16 |
| | 250 | 84.18 | 89.96 | 94.11 | 95.36 |
| | Receiver (0) | 100.00 | 100.00 | 100.00 | 100.00 |
| Gelatin | 1400 | 4.72 | 5.48 | 8.21 | 14.22 |
| | 1250 | 18.63 | 22.42 | 24.67 | 38.33 |
| | 1000 | 33.22 | 39.12 | 38.76 | 42.41 |
| | 710 | 61.46 | 63.13 | 68.37 | 68.99 |
| | 500 | 71.27 | 76.37 | 79.24 | 80.03 |
| | 355 | 79.42 | 81.38 | 83.21 | 86.37 |
| | 250 | 84.33 | 91.41 | 91.87 | 92.33 |
| | Receiver (0) | 100.00 | 100.00 | 100.00 | 100.00 |

**Table 5.3**: Granule size distribution of Ibuprofen formulations containing different concentrations of the polymer as binder

| Binder | Sieve Size (µm) | 2.5% (w/w) | 5.0% (w/w) | 7.5% (w/w) | 10.0% (w/w) |
|---|---|---|---|---|---|
| *Entandophragma angolense* gum | 1400 | 4.72 | 4.93 | 6.28 | 8.13 |
| | 1250 | 8.99 | 18.26 | 22.73 | 28.33 |
| | 1000 | 14.16 | 19.13 | 28.14 | 36.78 |
| | 710 | 32.37 | 38.23 | 43.34 | 54.73 |
| | 500 | 82.70 | 86.33 | 84.18 | 89.37 |
| | 355 | 82.88 | 88.24 | 93.12 | 98.13 |
| | 250 | 91.26 | 92.44 | 96.13 | 96.42 |
| | Receiver(0) | 100.00 | 100.00 | 100.00 | 100.00 |
| Hydroxypropylcellulose | 1400 | 4.11 | 5.21 | 6.03 | 11.58 |
| | 1250 | 24.18 | 29.22 | 37.07 | 37.71 |
| | 1000 | 26.47 | 33.09 | 37.34 | 42.35 |
| | 710 | 48.90 | 51.17 | 58.42 | 62.23 |
| | 500 | 64.09 | 67.73 | 71.62 | 74.44 |
| | 355 | 75.07 | 77.16 | 79.22 | 81.25 |
| | 250 | 81.27 | 84.93 | 96.04 | 97.11 |
| | Receiver(0) | 100.00 | 100.00 | 100.00 | 100.00 |
| Gelatin | 1400 | 4.12 | 5.44 | 5.83 | 6.28 |
| | 1250 | 14.17 | 18.92 | 19.33 | 21.22 |
| | 1000 | 15.88 | 22.44 | 29.43 | 40.88 |
| | 710 | 61.11 | 62.43 | 69.11 | 69.94 |
| | 500 | 63.43 | 71.07 | 72.13 | 70.04 |
| | 355 | 80.11 | 81.06 | 83.48 | 89.42 |
| | 250 | 81.27 | 84.62 | 88.63 | 92.16 |
| | Receiver(0) | 100.00 | 100.00 | 100.00 | 100.00 |

**Table 5.4**: Values of mean granule size (G) for formulations containing different binders

| Binder | Concentration (%w/w) | Mean Granule Size (µm) | |
| --- | --- | --- | --- |
| | | Chlorpheniramine maleate | Ibuprofen |
| | 0.0 | 593.12 | 601.18 |
| *Entandophragma angolense* | 2.5 | 660.96 | 648.64 |
| | 5.0 | 673.24 | 819.10 |
| | 7.5 | 729.17 | 928.59 |
| | 10.0 | 781.91 | 996.69 |
| Hydroxypropylcellulose | 2.5 | 611.23 | 569.55 |
| | 5.0 | 647.29 | 607.67 |
| | 7.5 | 713.28 | 693.77 |
| | 10.0 | 722.28 | 725.97 |
| Gelatin | 2.5 | 514.57 | 509.76 |
| | 5.0 | 519.39 | 573.67 |
| | 7.5 | 562.33 | 568.64 |
| | 10.0 | 577.61 | 580.92 |
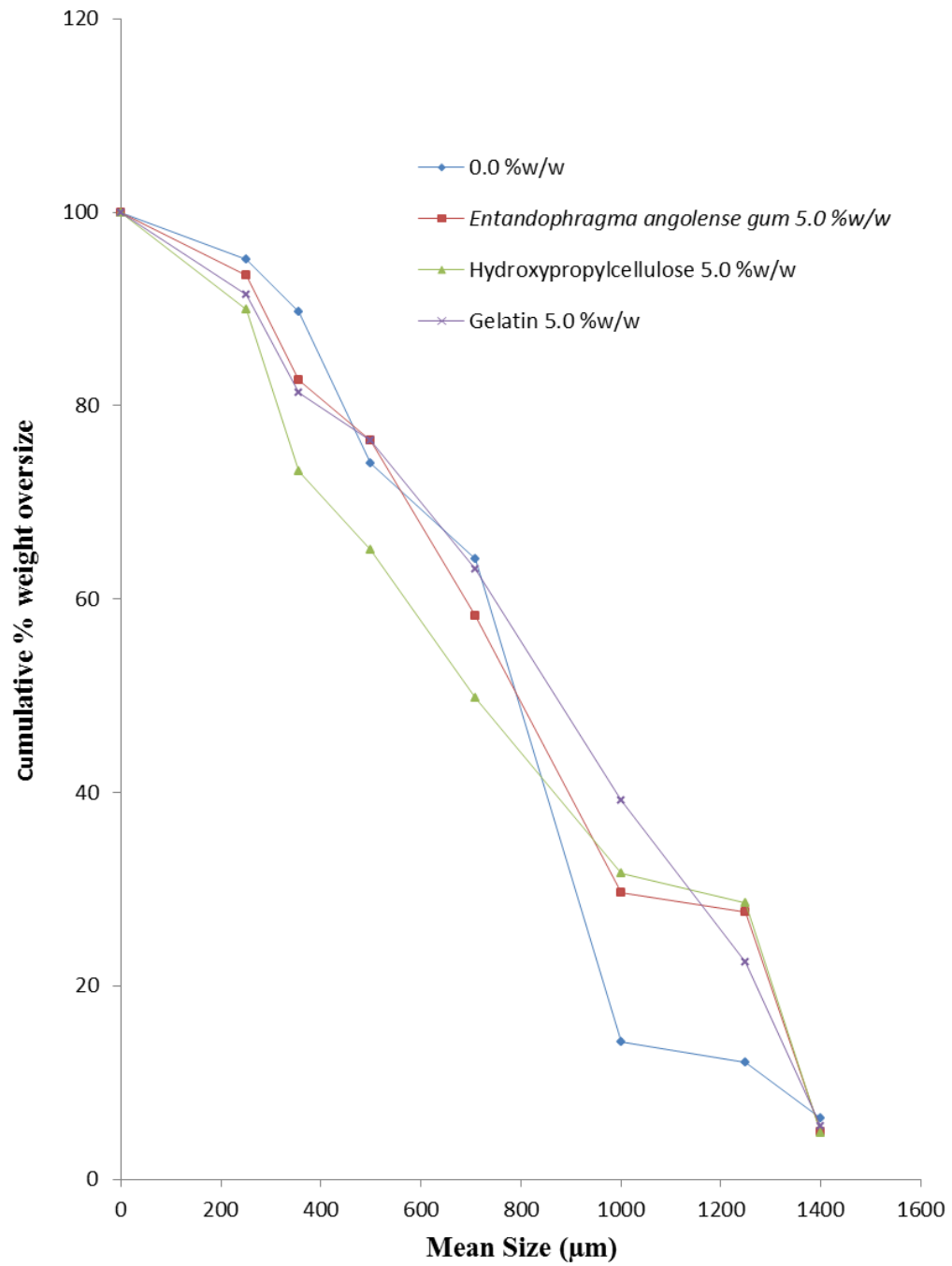
**Fig 5.1**: Granule size distribution for chlorpheniramine maleate formulations containing 0% and 5.0%w/w binders
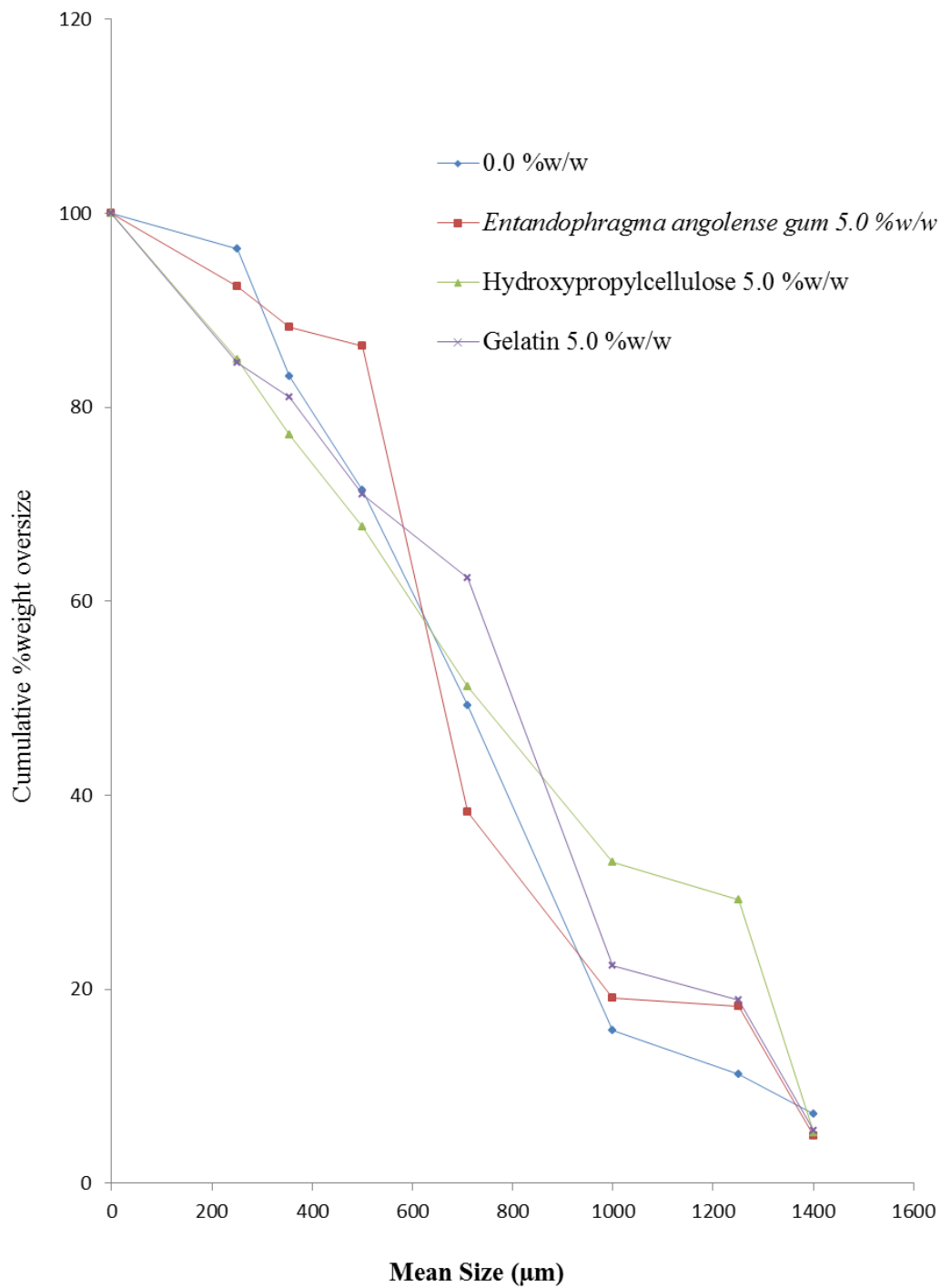
**Fig 5.2**: Granule size distribution for Ibuprofen formulations containing 0 % and 5.0 %w/w of binders
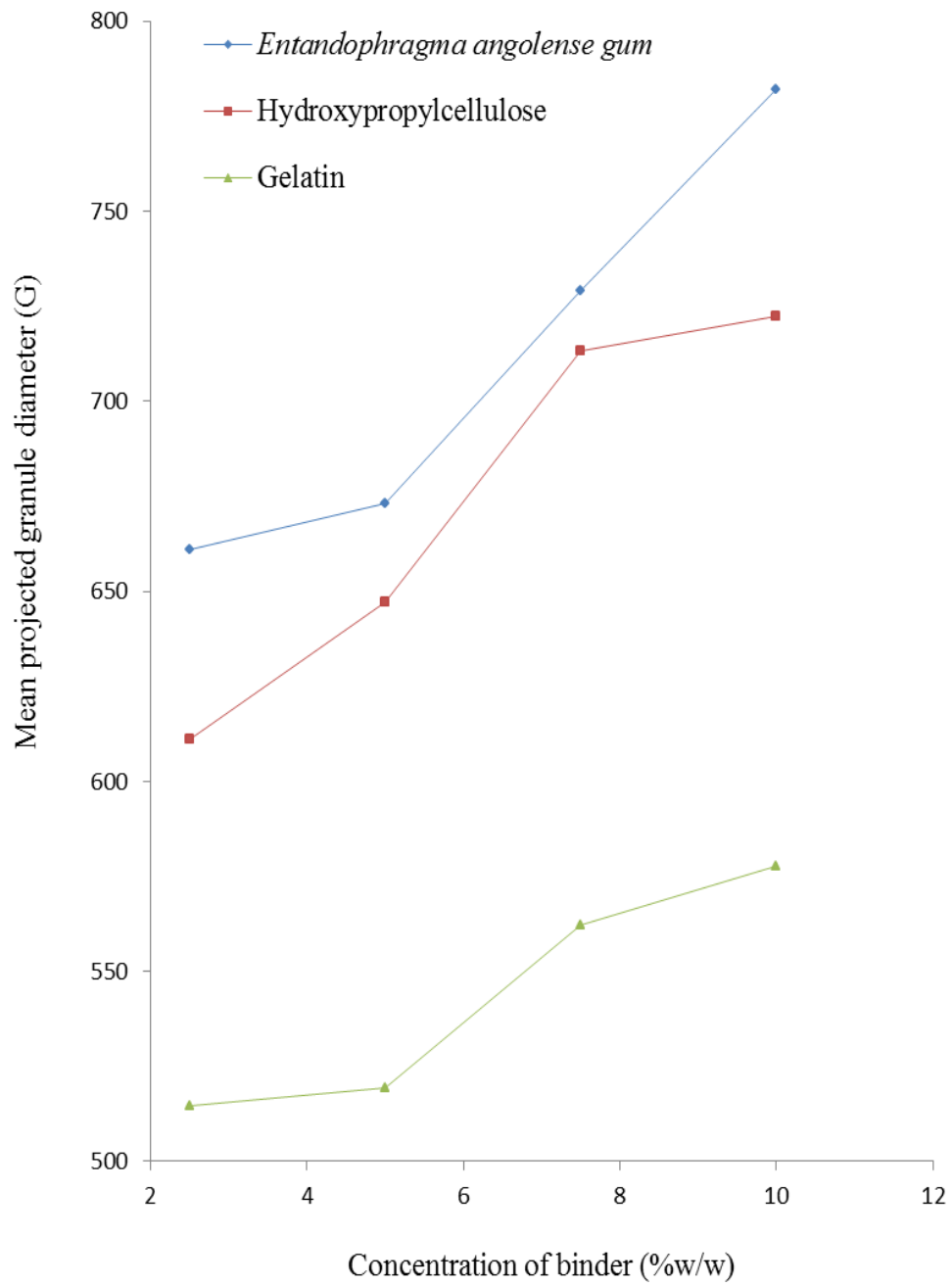
**Fig 5.3**: Plot of Mean projected granule diameter (G) against concentration of binder (%w/w) for chlorpheniramine maleate formulations
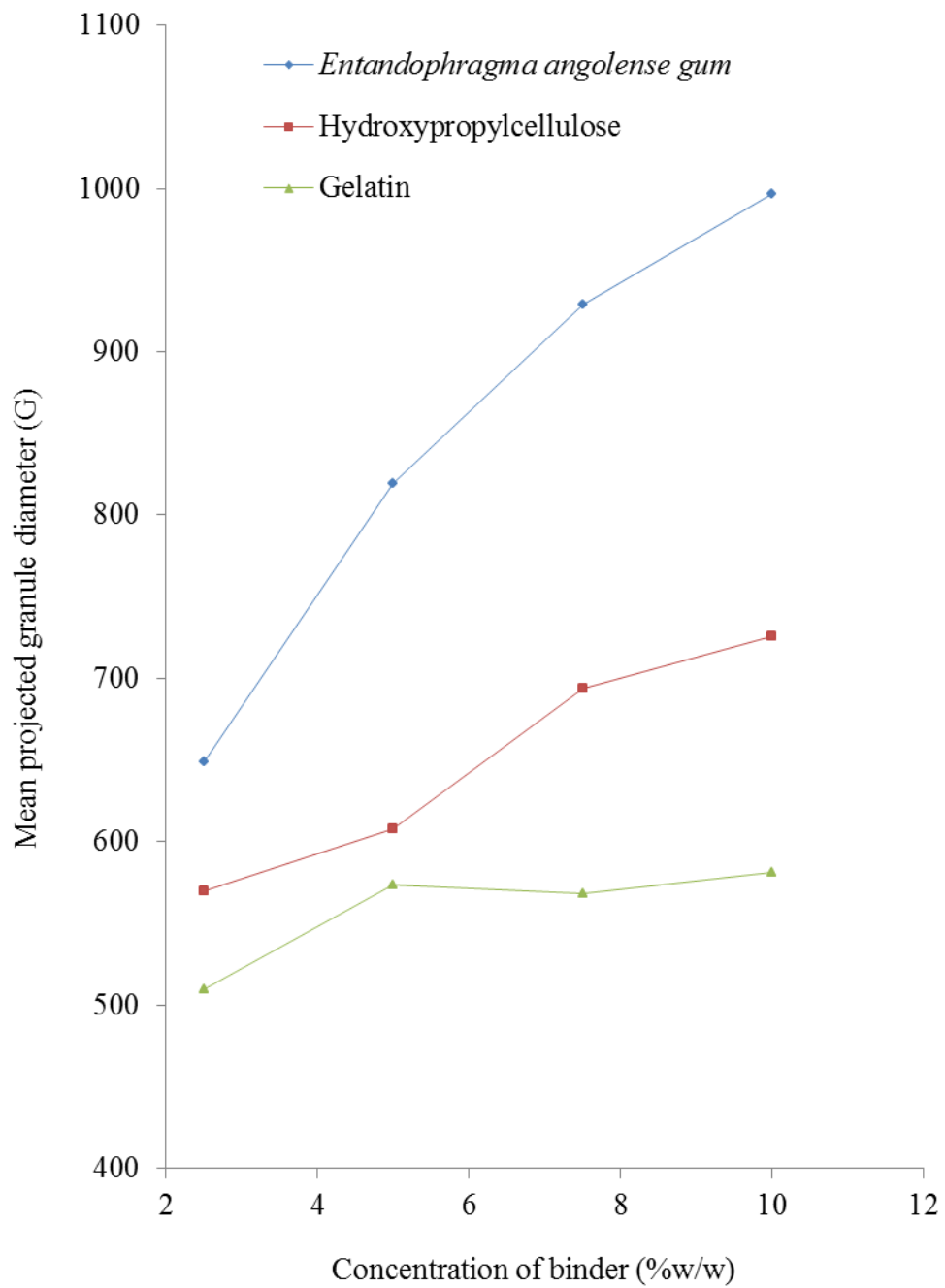
**Fig 5.4**: Plot of mean projected granule diameter (G) against concentration of binder (%w/w) for Ibuprofen formulations

**Table 5.5**: Values of particle density for chlorpheniramine maleate formulations containing different binders

| Binder | Concentration (% w/w) | Particle Density, $\rho_s$ ($gcm^{-3}$). |
|---|---|---|
| *Entandophragma angolense* gum | 0.0 | 1.680 |
| | 2.5 | 1.657 |
| | 5.0 | 1.655 |
| | 7.5 | 1.653 |
| | 10.0 | 1.651 |
| Hydroxypropylcellulose | 2.5 | 1.846 |
| | 5.0 | 1.844 |
| | 7.5 | 1.841 |
| | 10.0 | 1.838 |
| Gelatin | 2.5 | 1.558 |
| | 5.0 | 1.554 |
| | 7.5 | 1.552 |
| | 10.0 | 1.551 |

**Table 5.6**: Values of particle density for ibuprofen formulations containing different binders

| Binder | Concentration (% w/w) | Particle Density $\rho_s$ ($gcm^{-3}$). |
|---|---|---|
| | 0.0 | 1.680 |
| *Entandophragma angolense* gum | 2.5 | 1.546 |
| | 5.0 | 1.544 |
| | 7.5 | 1.543 |
| | 10.0 | 1.540 |
| | | |
| Hydroxypropylcellulose | 2.5 | 1.786 |
| | 5.0 | 1.783 |
| | 7.5 | 1.782 |
| | 10.0 | 1.779 |
| | | |
| Gelatin | 2.5 | 1.568 |
| | 5.0 | 1.560 |
| | 7.5 | 1.551 |
| | 10.0 | 1.548 |

**5.3**      **Compression Characteristics of Granules**

**5.3.1**      **Heckel Plots**

Values of applied pressure and In $(1/1-\rho_r)$ for the different formulations are presented in Table 5.7. Representative Heckel plots of In $(1/1-\rho_r)$ versus applied pressure are presented in Figs 5.5 to 5.7. The values for K and A were obtained from the slope and intercept of extrapolation of the linear regions of the plots respectively. The mean yield pressure $P_y$ was calculated from region of the plots showing the highest correlation coefficient for linearity of $> 0.997$ for all the polymers. Values of $P_y$, $\rho_{r0}$, $\rho_{rA}$ and $\rho_{rB}$ for all the polymers are presented in Tables 5.8 and 5.9.

The mean yield pressure is inversely related to the ability of the material to deform plastically under pressure. The ranking of $P_y$ for the polymers was Hydroxypropylcellulose >*Entandophragma angolense* gum > Gelatin. This indicates that *Entandophragma angolense* gum exhibited faster onset of plastic deformation than hydroxypropylcellulose, but slower than gelatin. The rate of deformation of polymers is of importance since most tabletting machines have short dwell or compression time and the phenomenon of plastic deformation is time-dependent (Odeku and Itiola, 2003).

The values of $\rho_{rA}$ represent the total degree of packing achieved at zero and low pressures as a result of rearrangement process before an appreciable amount of interparticulate bonding takes place (Odeku, 2005). The ranking of $\rho_{rA}$ was Hydroxypropylcellulose > *Entandophragma angolense* gum > Gelatin. Thus, *Entandophragma angolense* gum showed a higher degree of packing at zero and low pressures when compared with Gelatin, while Hydroxypropylcellulose exhibited the highest degree of packing at zero and low pressures.

The relative density $\rho_{rB}$, describes the phase of rearrangement of particles during the initial stages of compression. Values of $\rho_{rB}$ values tend to indicate the extent of fragmentation of particles or granules, although fragmentation can occur concurrently with plastic and elastic deformation of constituent particles. The ranking of $\rho_B$ values was Hydroxypropylcellulose > *Entandophragma angolense* gum > Gelatin. Formulations containing ibuprofen displayed higher values of $P_y$, $\rho_{r0}$, $\rho_{rA}$ and $\rho_{rB}$ values than formulations containing chlorpheniramine maleate.

**Table 5.7:** Values of Applied pressure (MNm$^{-2}$) and In (1/1-$\rho_r$) for different formulations

| Formulation Type | Polymer Concentration (%w/w) | Applied pressure (MNm$^{-2}$) | In (1/1-$\rho_r$) |
|---|---|---|---|
| CPM/ENTA (WG) | 2.5 | 56.62 | 2.104 |
| | | 84.93 | 2.112 |
| | | 113.23 | 2.516 |
| | | 141.54 | 2.635 |
| | | 169.85 | 2.763 |
| | | 198.16 | 2.833 |
| | | 224.47 | 2.919 |
| | 5.0 | 56.62 | 1.981 |
| | | 84.93 | 2.146 |
| | | 113.23 | 2.831 |
| | | 141.54 | 3.016 |
| | | 169.85 | 3.058 |
| | | 198.16 | 3.270 |
| | | 224.47 | 3.576 |
| | 7.5 | 56.62 | 2.112 |
| | | 84.93 | 2.216 |
| | | 113.23 | 2.865 |
| | | 141.54 | 3.381 |
| | | 169.85 | 3.411 |
| | | 198.16 | 3.650 |
| | | 224.47 | 4.017 |
| | 10.0 | 56.62 | 2.283 |
| | | 84.93 | 2.293 |
| | | 113.23 | 3.147 |
| | | 141.54 | 3.270 |
| | | 169.85 | 3.650 |
| | | 198.16 | 3.863 |
| | | 224.47 | 4.075 |

**Table 5.7** continued:

| Formulation Type | Polymer Concentration (%w/w) | Applied pressure (MNm$^{-2}$) | In (1/1-$\rho_r$) |
|---|---|---|---|
| CPM/ENTA (DC) | 2.5 | 56.62 | 1.904 |
| | | 84.93 | 2.056 |
| | | 113.23 | 2.087 |
| | | 141.54 | 2.120 |
| | | 169.85 | 2.551 |
| | | 198.16 | 2.830 |
| | | 224.47 | 3.016 |
| | 5.0 | 56.62 | 1.973 |
| | | 84.93 | 2.040 |
| | | 113.23 | 2.071 |
| | | 141.54 | 2.146 |
| | | 169.85 | 2.180 |
| | | 198.16 | 2.937 |
| | | 224.47 | 3.058 |
| | 7.5 | 56.62 | 2.071 |
| | | 84.93 | 2.120 |
| | | 113.23 | 2.154 |
| | | 141.54 | 2.180 |
| | | 169.85 | 2.198 |
| | | 198.16 | 3.124 |
| | | 224.47 | 3.271 |
| | 10.0 | 56.62 | 2.235 |
| | | 84.93 | 2.244 |
| | | 113.23 | 2.293 |
| | | 141.54 | 3.244 |
| | | 169.85 | 3.576 |
| | | 198.16 | 3.772 |
| | | 224.47 | 4.510 |

**Table 5.7: continued**

| Formulation Type | Polymer Concentration (%w/w) | Applied pressure (MNm$^{-2}$) | In (1/1-$\rho_r$) |
|---|---|---|---|
| IBUP/ENTA (WG) | 2.5 | 56.62 | 2.025 |
| | | 84.93 | 2.096 |
| | | 113.23 | 2.163 |
| | | 141.54 | 2.172 |
| | | 169.85 | 2.498 |
| | | 198.16 | 2.593 |
| | | 224.47 | 2.631 |
| | 5.0 | 56.62 | 2.064 |
| | | 84.93 | 2.163 |
| | | 113.23 | 2.226 |
| | | 141.54 | 2.419 |
| | | 169.85 | 2.604 |
| | | 198.16 | 2.703 |
| | | 224.47 | 3.037 |
| | 7.5 | 56.62 | 2.137 |
| | | 84.93 | 2.104 |
| | | 113.23 | 2.181 |
| | | 141.54 | 2.226 |
| | | 169.85 | 2.797 |
| | | 198.16 | 3.411 |
| | | 224.47 | 3.563 |
| | 10.0 | 56.62 | 2.293 |
| | | 84.93 | 2.419 |
| | | 113.23 | 2.538 |
| | | 141.54 | 2.617 |
| | | 169.85 | 3.442 |
| | | 198.16 | 4.075 |
| | | 224.47 | 4.293 |

**Table 5.7** continued:

| Formulation Type | Polymer Concentration (%w/w) | Applied pressure (MNm$^{-2}$) | In (1/1-$\rho_r$) |
|---|---|---|---|
| IBUP/ENTA (DC) | 2.5 | 56.62 | 1.945 |
| | | 84.93 | 2.033 |
| | | 113.23 | 2.048 |
| | | 141.54 | 2.079 |
| | | 169.85 | 2.129 |
| | | 198.16 | 2.416 |
| | | 224.47 | 2.513 |
| | 5.0 | 56.62 | 2.033 |
| | | 84.93 | 2.048 |
| | | 113.23 | 2.071 |
| | | 141.54 | 2.096 |
| | | 169.85 | 2.501 |
| | | 198.16 | 2.738 |
| | | 224.47 | 2.759 |
| | 7.5 | 56.62 | 2.040 |
| | | 84.93 | 2.112 |
| | | 113.23 | 2.137 |
| | | 141.54 | 2.477 |
| | | 169.85 | 2.617 |
| | | 198.16 | 3.016 |
| | | 224.47 | 3.297 |
| | 10.0 | 56.62 | 2.283 |
| | | 84.93 | 2.293 |
| | | 113.23 | 2.343 |
| | | 141.54 | 2.631 |
| | | 169.85 | 2.765 |
| | | 198.16 | 2.937 |
| | | 224.47 | 3.037 |

**Table 5.7** continued:

| Formulation Type | Polymer Concentration (%w/w) | Applied pressure (MNm$^{-2}$) | In (1/1-$\rho_r$) |
|---|---|---|---|
| CPM/GEL (WG) | 2.5 | 56.62 | 2.017 |
| | | 84.93 | 2.033 |
| | | 113.23 | 2.235 |
| | | 141.54 | 2.273 |
| | | 169.85 | 2.333 |
| | | 198.16 | 2.914 |
| | | 224.47 | 3.111 |
| | 5.0 | 56.62 | 2.079 |
| | | 84.93 | 2.146 |
| | | 113.23 | 2.163 |
| | | 141.54 | 2.273 |
| | | 169.85 | 2.674 |
| | | 198.16 | 2.937 |
| | | 224.47 | 3.437 |
| | 7.5 | 56.62 | 2.112 |
| | | 84.93 | 2.137 |
| | | 113.23 | 2.419 |
| | | 141.54 | 2.782 |
| | | 169.85 | 2.836 |
| | | 198.16 | 3.071 |
| | | 224.47 | 3.474 |
| | 10.0 | 56.62 | 2.226 |
| | | 84.93 | 2.235 |
| | | 113.23 | 2.273 |
| | | 141.54 | 2.881 |
| | | 169.85 | 3.079 |
| | | 198.16 | 3.458 |
| | | 224.47 | 3.510 |

**Table 5.7** continued:

| Formulation Type | Polymer Concentration (%w/w) | Applied pressure (MNm$^{-2}$) | In (1/1-$\rho_r$) |
|---|---|---|---|
| CPM/GEL (DC) | 2.5 | 56.62 | 1.945 |
| | | 84.93 | 1.959 |
| | | 113.23 | 1.981 |
| | | 141.54 | 2.071 |
| | | 169.85 | 2.237 |
| | | 198.16 | 2.431 |
| | | 224.47 | 2.564 |
| | 5.0 | 56.62 | 1.973 |
| | | 84.93 | 1.981 |
| | | 113.23 | 2.112 |
| | | 141.54 | 2.226 |
| | | 169.85 | 2.404 |
| | | 198.16 | 2.663 |
| | | 224.47 | 2.830 |
| | 7.5 | 56.62 | 1.988 |
| | | 84.93 | 1.995 |
| | | 113.23 | 2.087 |
| | | 141.54 | 2.226 |
| | | 169.85 | 2.749 |
| | | 198.16 | 2.831 |
| | | 224.47 | 2.882 |
| | 10.0 | 56.62 | 1.981 |
| | | 84.93 | 2.025 |
| | | 113.23 | 2.273 |
| | | 141.54 | 2.419 |
| | | 169.85 | 2.847 |
| | | 198.16 | 3.411 |
| | | 224.47 | 3.576 |

**Table 5.7** continued:

| Formulation Type | Polymer Concentration (%w/w) | Applied pressure (MNm$^{-2}$) | In (1/1-$\rho_r$) |
|---|---|---|---|
| IBUP/GEL (WG) | 2.5 | 56.62 | 2.064 |
| | | 84.93 | 2.087 |
| | | 113.23 | 2.198 |
| | | 141.54 | 2.226 |
| | | 169.85 | 2.603 |
| | | 198.16 | 2.692 |
| | | 224.47 | 2.896 |
| | 5.0 | 56.62 | 2.154 |
| | | 84.93 | 2.226 |
| | | 113.23 | 2.283 |
| | | 141.54 | 2.293 |
| | | 169.85 | 2.617 |
| | | 198.16 | 2.749 |
| | | 224.47 | 3.016 |
| | 7.5 | 56.62 | 2.265 |
| | | 84.93 | 2.283 |
| | | 113.23 | 2.781 |
| | | 141.54 | 2.847 |
| | | 169.85 | 3.101 |
| | | 198.16 | 3.411 |
| | | 224.47 | 3.863 |
| | 10.0 | 56.62 | 2.489 |
| | | 84.93 | 2.865 |
| | | 113.23 | 3.171 |
| | | 141.54 | 3.65 |
| | | 169.85 | 3.963 |
| | | 198.16 | 4.269 |
| | | 224.47 | 4.423 |

**Table 5.7** continued:

| Formulation Type | Polymer Concentration (%w/w) | Applied pressure (MNm$^{-2}$) | In (1/1-$\rho_r$) |
|---|---|---|---|
| IBUP/GEL (DC) | 2.5 | 56.62 | 2.011 |
| | | 84.93 | 2.079 |
| | | 113.23 | 2.172 |
| | | 141.54 | 2.180 |
| | | 169.85 | 2.198 |
| | | 198.16 | 2.535 |
| | | 224.47 | 2.673 |
| | 5.0 | 56.62 | 2.024 |
| | | 84.93 | 2.107 |
| | | 113.23 | 2.199 |
| | | 141.54 | 2.283 |
| | | 169.85 | 2.431 |
| | | 198.16 | 2.733 |
| | | 224.47 | 2.919 |
| | 7.5 | 56.62 | 2.079 |
| | | 84.93 | 2.129 |
| | | 113.23 | 2.226 |
| | | 141.54 | 2.354 |
| | | 169.85 | 2.489 |
| | | 198.16 | 2.957 |
| | | 224.47 | 3.352 |
| | 10.0 | 56.62 | 2.189 |
| | | 84.93 | 2.577 |
| | | 113.23 | 2.617 |
| | | 141.54 | 2.703 |
| | | 169.85 | 2.831 |
| | | 198.16 | 3.037 |
| | | 224.47 | 4.343 |

**Table 5.7** continued:

| Formulation Type | Polymer Concentration (%w/w) | Applied pressure (MNm$^{-2}$) | In (1/1-$\rho_r$) |
|---|---|---|---|
| CPM/HPC (WG) | 2.5 | 56.62 | 1.871 |
|  |  | 84.93 | 1.945 |
|  |  | 113.23 | 2.235 |
|  |  | 141.54 | 2.293 |
|  |  | 169.85 | 2.577 |
|  |  | 198.16 | 2.882 |
|  |  | 224.47 | 2.976 |
|  | 5.0 | 56.62 | 2.064 |
|  |  | 84.93 | 2.107 |
|  |  | 113.23 | 2.254 |
|  |  | 141.54 | 2.397 |
|  |  | 169.85 | 2.442 |
|  |  | 198.16 | 2.937 |
|  |  | 224.47 | 3.058 |
|  | 7.5 | 56.62 | 2.096 |
|  |  | 84.93 | 2.237 |
|  |  | 113.23 | 2.285 |
|  |  | 141.54 | 2.847 |
|  |  | 169.85 | 3.147 |
|  |  | 198.16 | 3.297 |
|  |  | 224.47 | 3.541 |
|  | 10.0 | 56.62 | 2.216 |
|  |  | 84.93 | 2.604 |
|  |  | 113.23 | 2.734 |
|  |  | 141.54 | 2.865 |
|  |  | 169.85 | 3.411 |
|  |  | 198.16 | 3.776 |
|  |  | 224.47 | 3.943 |

**Table 5.7** continued:

| Formulation Type | Polymer Concentration (%w/w) | Applied pressure (MNm$^{-2}$) | In (1/1-$\rho_r$) |
|---|---|---|---|
| CPM/HPC (DC) | 2.5 | 56.62 | 1.845 |
| | | 84.93 | 1.938 |
| | | 113.23 | 1.973 |
| | | 141.54 | 2.064 |
| | | 169.85 | 2.244 |
| | | 198.16 | 2.273 |
| | | 224.47 | 2.489 |
| | 5.0 | 56.62 | 1.973 |
| | | 84.93 | 2.056 |
| | | 113.23 | 2.198 |
| | | 141.54 | 2.273 |
| | | 169.85 | 2.283 |
| | | 198.16 | 2.442 |
| | | 224.47 | 2.645 |
| | 7.5 | 56.62 | 1.981 |
| | | 84.93 | 2.025 |
| | | 113.23 | 2.235 |
| | | 141.54 | 2.538 |
| | | 169.85 | 2.577 |
| | | 198.16 | 2.765 |
| | | 224.47 | 3.65 |
| | 10.0 | 56.62 | 1.995 |
| | | 84.93 | 2.226 |
| | | 113.23 | 2.283 |
| | | 141.54 | 2.882 |
| | | 169.85 | 3.270 |
| | | 198.16 | 3.381 |
| | | 224.47 | 3.895 |

**Table 5.7** continued:

| Formulation Type | Polymer Concentration (%w/w) | Applied pressure (MNm$^{-2}$) | In $(1/1-\rho_r)$ |
|---|---|---|---|
| IBUP/HPC (WG) | 2.5 | 56.62 | 2.087 |
| | | 84.93 | 2.254 |
| | | 113.23 | 2.263 |
| | | 141.54 | 2.273 |
| | | 169.85 | 2.293 |
| | | 198.16 | 2.843 |
| | | 224.47 | 3.184 |
| | 5.0 | 56.62 | 2.173 |
| | | 84.93 | 2.283 |
| | | 113.23 | 2.333 |
| | | 141.54 | 2.375 |
| | | 169.85 | 2.719 |
| | | 198.16 | 3.251 |
| | | 224.47 | 3.549 |
| | 7.5 | 56.62 | 2.198 |
| | | 84.93 | 2.617 |
| | | 113.23 | 2.703 |
| | | 141.54 | 2.919 |
| | | 169.85 | 3.316 |
| | | 198.16 | 4.265 |
| | | 224.47 | 4.343 |
| | 10.0 | 56.62 | 2.577 |
| | | 84.93 | 2.703 |
| | | 113.23 | 2.996 |
| | | 141.54 | 3.663 |
| | | 169.85 | 4.269 |
| | | 198.16 | 4.423 |
| | | 224.47 | 4.511 |

**Table 5.7** continued:

| Formulation Type | Polymer Concentration (%w/w) | Applied pressure (MNm$^{-2}$) | In (1/1-$\rho_r$) |
|---|---|---|---|
| IBUP/HPC (DC) | 2.5 | 56.62 | 1.802 |
| | | 84.93 | 1.995 |
| | | 113.23 | 2.087 |
| | | 141.54 | 2.189 |
| | | 169.85 | 2.216 |
| | | 198.16 | 2.244 |
| | | 224.47 | 2.293 |
| | 5.0 | 56.62 | 1.938 |
| | | 84.93 | 2.079 |
| | | 113.23 | 2.146 |
| | | 141.54 | 2.226 |
| | | 169.85 | 2.235 |
| | | 198.16 | 2.263 |
| | | 224.47 | 2.386 |
| | 7.5 | 56.62 | 1.988 |
| | | 84.93 | 2.096 |
| | | 113.23 | 2.216 |
| | | 141.54 | 2.538 |
| | | 169.85 | 2.703 |
| | | 198.16 | 3.352 |
| | | 224.47 | 3.389 |
| | 10.0 | 56.62 | 2.087 |
| | | 84.93 | 2.216 |
| | | 113.23 | 2.765 |
| | | 141.54 | 3.016 |
| | | 169.85 | 3.247 |
| | | 198.16 | 3.827 |
| | | 224.47 | 4.087 |
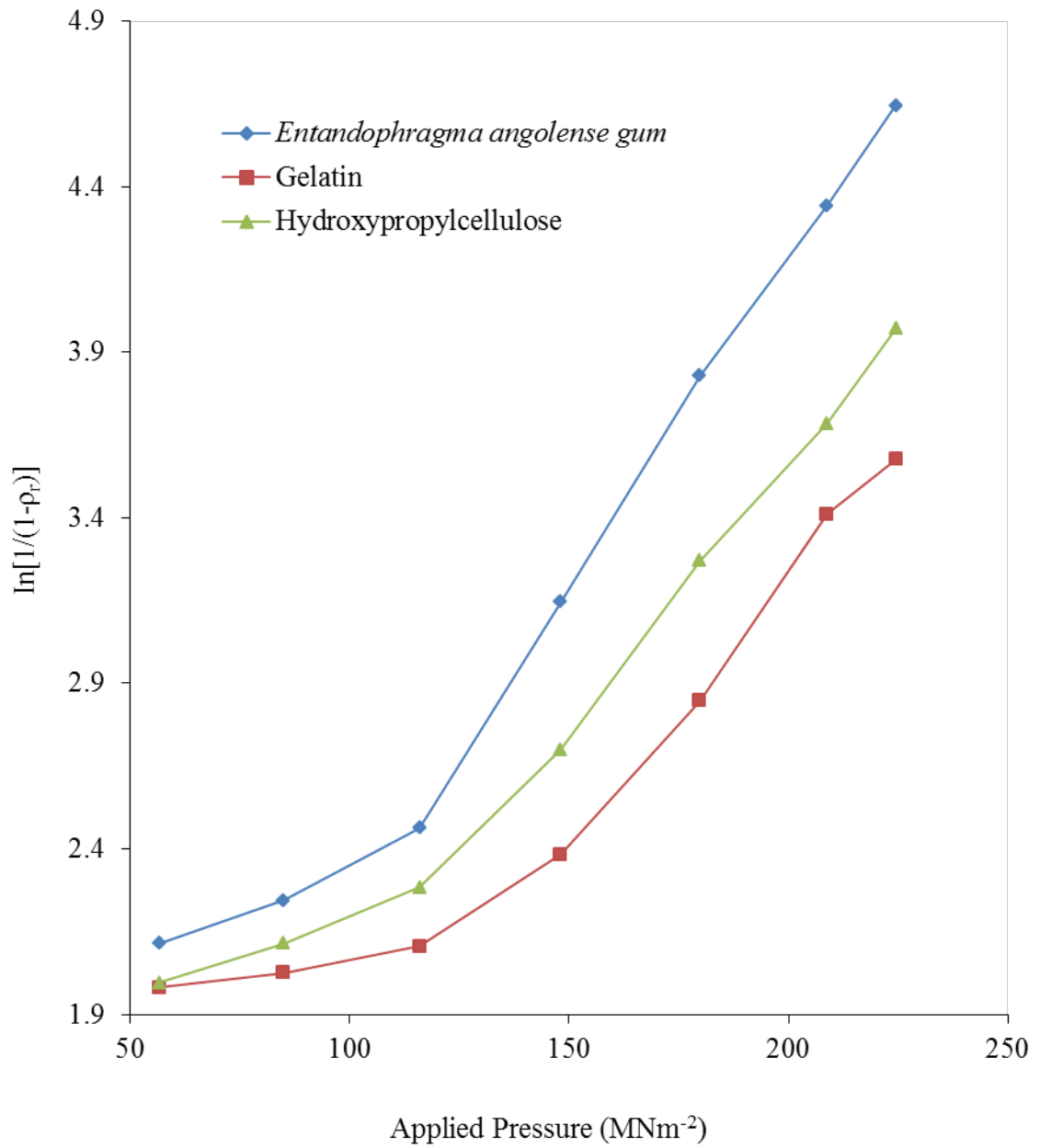
**Fig 5.5**: Heckel plots for chlorpheniramine maleate formulations containing 10.0 %w/w polymers prepared for direct compression
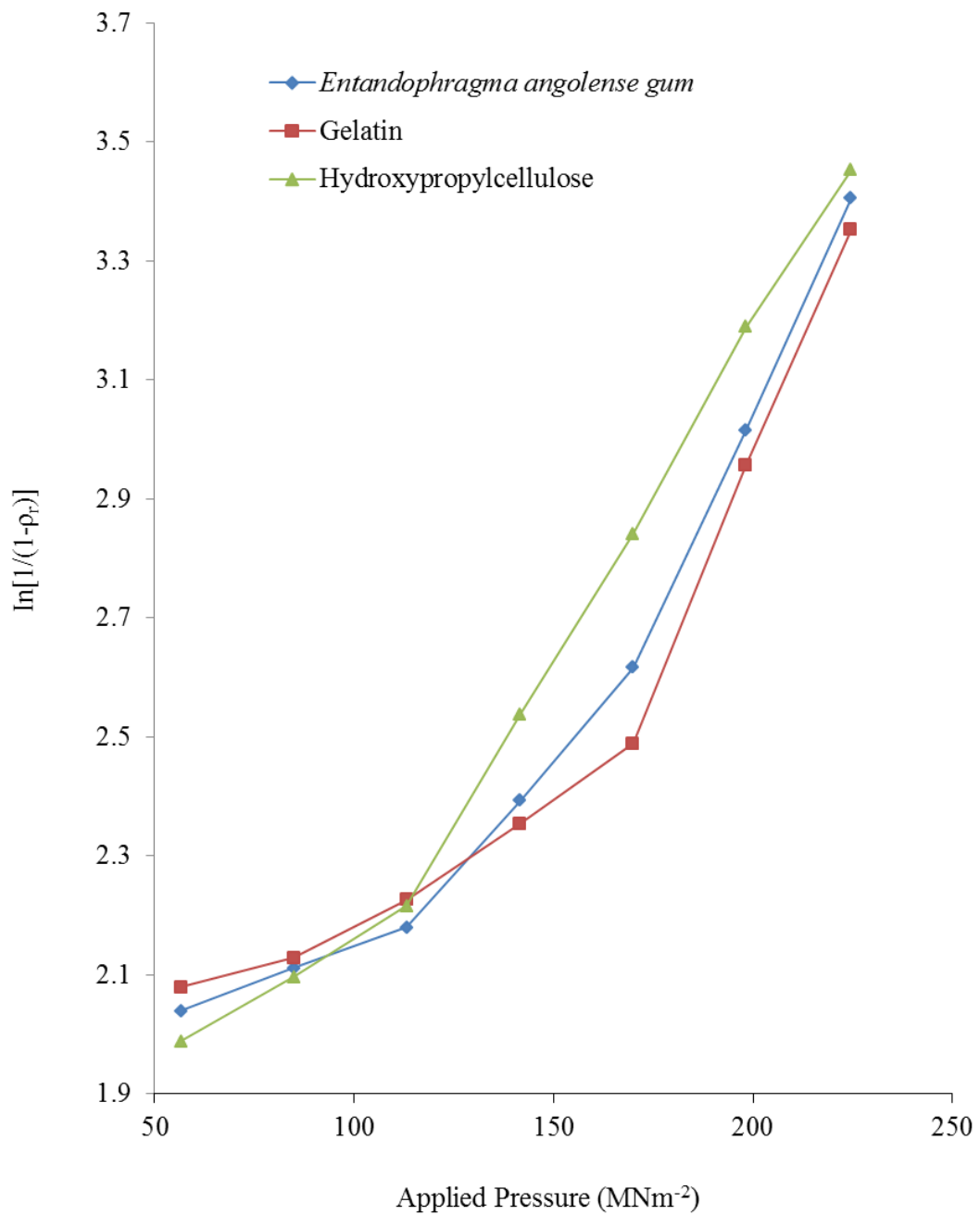
**Fig 5.6:** Heckel plots for Ibuprofen formulations containing 7.5 %w/w polymers prepared for direct compression
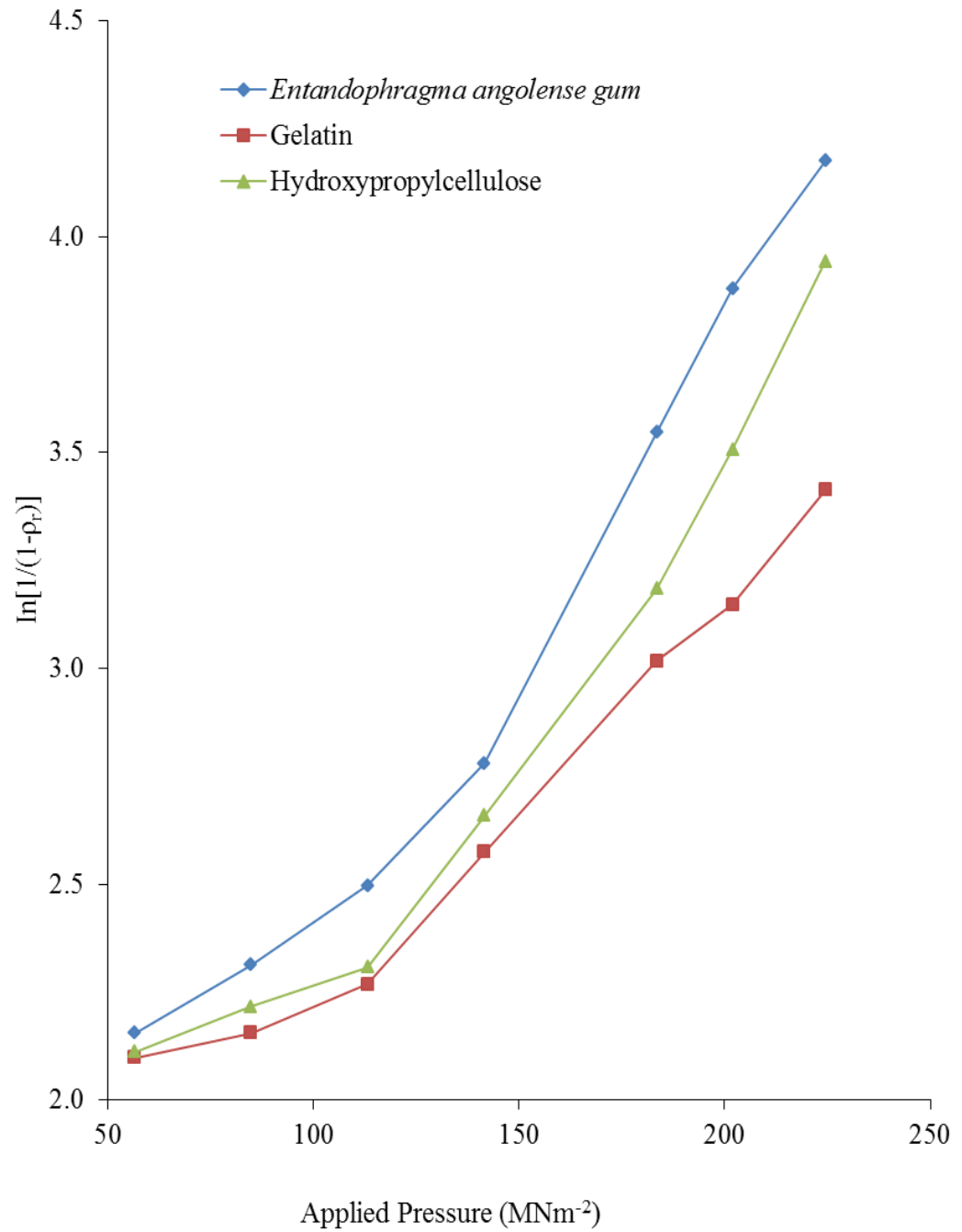
**Fig 5.7**: Heckel plots for Ibuprofen formulations containing 7.5 %w/w gum prepared for wet granulation

**Table 5.8**: Parameters derived from Heckel plots for chlorpheniramine maleate formulations

| Binder | Concentration (% w/w) | $P_y$ (MNm$^{-2}$) | $\rho_{rA}$ | $\rho_{r0}$ | $\rho_{rB}$ |
|---|---|---|---|---|---|
| | 0.0 | 119.33 | 0.875 | 0.417 | 0.458 |
| *Entandophragma Angolense* gum | 2.5 | 122.11 | 0.830 | 0.447 | 0.383 |
| | 5.0 | 113.26 | 0.823 | 0.454 | 0.369 |
| | 7.5 | 98.87 | 0.813 | 0.471 | 0.342 |
| | 10.0 | 90.91 | 0.774 | 0.476 | 0.298 |
| Gelatin | 2.5 | 121.46 | 0.822 | 0.444 | 0.378 |
| | 5.0 | 112.57 | 0.817 | 0.453 | 0.364 |
| | 7.5 | 96.47 | 0.806 | 0.474 | 0.332 |
| | 10.0 | 89.28 | 0.772 | 0.483 | 0.289 |
| Hydroxypropylcellulose | 2.5 | 126.43 | 0.834 | 0.445 | 0.389 |
| | 5.0 | 122.19 | 0.831 | 0.460 | 0.371 |
| | 7.5 | 113.28 | 0.828 | 0.475 | 0.353 |
| | 10.0 | 98.55 | 0.802 | 0.455 | 0.347 |

**Table 5.9**: Parameters derived from Heckel plots for Ibuprofen formulations

| Binder | Concentration (% w/w) | $P_y$ (MNm$^{-2}$) | $\rho_{rA}$ | $\rho_{r0}$ | $\rho_{rB}$ |
|---|---|---|---|---|---|
| | 0.0 | 120.08 | 0.847 | 0.455 | 0.392 |
| *Entandophragma Angolense* gum | 2.5 | 128.92 | 0.883 | 0.472 | 0.411 |
| | 5.0 | 126.63 | 0.875 | 0.482 | 0.393 |
| | 7.5 | 124.74 | 0.843 | 0.488 | 0.355 |
| | 10.0 | 121.56 | 0.788 | 0.491 | 0.297 |
| Gelatin | 2.5 | 126.17 | 0.843 | 0.469 | 0.374 |
| | 5.0 | 121.23 | 0.832 | 0.474 | 0.358 |
| | 7.5 | 120.51 | 0.797 | 0.488 | 0.309 |
| | 10.0 | 119.92 | 0.772 | 0.489 | 0.283 |
| Hydroxypropylcellulose | 2.5 | 129.73 | 0.892 | 0.472 | 0.420 |
| | 5.0 | 127.13 | 0.881 | 0.479 | 0.402 |
| | 7.5 | 125.29 | 0.836 | 0.479 | 0.357 |
| | 10.0 | 123.75 | 0.819 | 0.491 | 0.328 |

**5.3.2          Kawakita Plots**

The volume of chlorpheniramine maleate and ibuprofen formulations at zero pressure, $V_0$, and the change in applied pressure, $V_p$, for the formulations are presented in Tables 5.10 and 5.11. Representative kawakita plots are shown in Figs 5.8 and 5.9. Formulations containing chlorpheniramine maleate had lower values of $V_0$ and $V_p$. A linear relationship was obtained at all compression pressures employed with correlation coefficient of 0.999 for all formulations. The constants **a** and **b** were obtained from the slope and intercept of the plots respectively. The value of **a** is equal to the minimum porosity of the powder bed prior to compression (Adams *et al*, 1994) while **b** is related to the plasticity of the material (Lin and Cham, 1995). Values of **1-a** gave the packed initial relative density of the formulations $\rho_I$, while $P_k$ values were obtained from the reciprocal of the values of **b.**

The values of $P_K$ and $\rho_I$ are presented in Tables 5.12 and 5.13. The values of $P_K$ represent the pressure required to reduce the powder bed by 50% (Lin and Cham, 1995; Shivanand and Sprockel, 1992). Low values of $P_k$ indicate materials that are soft and readily deform plastically under pressure. It can be seen that the values of $P_k$ for the formulations decreased with an increase in binder concentration, with formulations containing Ibuprofen having higher $P_K$ values than formulations containing chlorpheniramine maleate.

The ranking of the $P_k$ values for the polymers was Hydroxypropylcellulose < *Entandophragma angolense* gum < Gelatin. Thus, formulations containing hydroxypropylcellulose and *Entandophragma angolense* gum exhibited higher amount of total plastic deformation than formulations containing gelatin. It has been shown that the lower the value of $P_k$, the more the total plastic deformation occurring during compression (Odeku, 2005).

The values of $\rho_I$, which is a measure of the packed initial relative density of the polymer with the application of small pressures or tapping (Odeku and Itiola, 1998), decreased with increase in concentration of binder, and were found to be lower for chlorpheniramine maleate formulations. These values were also higher than the corresponding values of the initial relative density, $\rho_0$. This result corresponds with previous findings by Odeku and Itiola (1998), Odeku (2005) and Adetunji *et al* (2006).

**Table 5.10**: Values of applied Pressure (P), zero pressure ($V_0$), Volume ($V_P$), degree of volume reduction (C) and P/C for chlorpheniramine maleate formulations

| Binder | Concentration | P | $V_0$ | $V_p$ | C | P/C |
|---|---|---|---|---|---|---|
| | (%w/w) | (MNm$^{-2}$) | (cm$^3$) | (cm$^3$) | | |
| | 0.0 | 56.62 | 0.712 | 0.396 | 0.444 | 127.574 |
| | | 84.93 | 0.712 | 0.387 | 0.456 | 186.062 |
| | | 113.23 | 0.712 | 0.381 | 0.465 | 243.564 |
| | | 141.54 | 0.712 | 0.376 | 0.472 | 299.930 |
| | | 169.85 | 0.712 | 0.368 | 0.483 | 351.550 |
| | | 198.16 | 0.712 | 0.363 | 0.490 | 404.269 |
| | | 224.47 | 0.712 | 0.354 | 0.503 | 446.432 |
| *Entandophragma angolense* gum | 2.5 | 56.62 | 0.823 | 0.379 | 0.539 | 104.95 |
| | | 84.93 | 0.823 | 0.373 | 0.547 | 155.33 |
| | | 113.23 | 0.823 | 0.371 | 0.549 | 206.17 |
| | | 141.54 | 0.823 | 0.354 | 0.570 | 248.37 |
| | | 169.85 | 0.823 | 0.352 | 0.572 | 296.79 |
| | | 198.16 | 0.823 | 0.347 | 0.578 | 342.62 |
| | | 224.47 | 0.823 | 0.345 | 0.581 | 386.48 |
| | 5.0 | 56.62 | 0.831 | 0.377 | 0.535 | 105.80 |
| | | 84.93 | 0.831 | 0.374 | 0.539 | 157.62 |
| | | 113.23 | 0.831 | 0.368 | 0.546 | 207.30 |
| | | 141.54 | 0.831 | 0.361 | 0.555 | 255.09 |
| | | 169.85 | 0.831 | 0.355 | 0.562 | 302.08 |
| | | 198.16 | 0.831 | 0.352 | 0.566 | 350.13 |
| | | 224.47 | 0.831 | 0.343 | 0.577 | 388.99 |

**Table 5.10** continued:

| Binder | Concentration (%w/w) | P (MNm$^{-2}$) | V$_0$ (cm$^3$) | V$_p$ (cm$^3$) | C | P/C |
|---|---|---|---|---|---|---|
| *Entandophragma angolense* gum | 7.5 | 56.62 | 0.819 | 0.369 | 0.544 | 104.10 |
| | | 84.93 | 0.819 | 0.363 | 0.551 | 154.06 |
| | | 113.23 | 0.819 | 0.360 | 0.555 | 204.02 |
| | | 141.54 | 0.819 | 0.352 | 0.565 | 250.57 |
| | | 169.85 | 0.819 | 0.349 | 0.569 | 298.71 |
| | | 198.16 | 0.819 | 0.344 | 0.575 | 344.76 |
| | | 224.47 | 0.819 | 0.342 | 0.577 | 388.86 |
| | 10.0 | 56.62 | 0.800 | 0.367 | 0.541 | 104.61 |
| | | 84.93 | 0.800 | 0.358 | 0.553 | 153.72 |
| | | 113.23 | 0.800 | 0.354 | 0.558 | 203.10 |
| | | 141.54 | 0.800 | 0.351 | 0.561 | 252.19 |
| | | 169.85 | 0.800 | 0.348 | 0.565 | 300.62 |
| | | 198.16 | 0.800 | 0.343 | 0.571 | 346.89 |
| | | 224.47 | 0.800 | 0.342 | 0.573 | 392.09 |
| Hydroxypropylcellulose | 2.5 | 56.62 | 0.826 | 0.382 | 0.444 | 127.52 |
| | | 84.93 | 0.826 | 0.376 | 0.450 | 188.73 |
| | | 113.23 | 0.826 | 0.372 | 0.454 | 249.41 |
| | | 141.54 | 0.826 | 0.342 | 0.484 | 292.44 |
| | | 169.85 | 0.826 | 0.337 | 0.489 | 347.34 |
| | | 198.16 | 0.826 | 0.331 | 0.495 | 400.32 |
| | | 224.47 | 0.826 | 0.324 | 0.502 | 447.15 |

**Table 5.10** continued:

| Binder | Concentration (%w/w) | P (MNm$^{-2}$) | V$_0$ (cm$^3$) | V$_p$ (cm$^3$) | C | P/C |
|---|---|---|---|---|---|---|
| Hydroxypropylcellulose | 5.0 | 56.62 | 0.837 | 0.379 | 0.458 | 123.62 |
| | | 84.93 | 0.837 | 0.372 | 0.465 | 182.65 |
| | | 113.23 | 0.837 | 0.368 | 0.469 | 241.43 |
| | | 141.54 | 0.837 | 0.362 | 0.475 | 297.98 |
| | | 169.85 | 0.837 | 0.359 | 0.478 | 355.33 |
| | | 198.16 | 0.837 | 0.355 | 0.482 | 411.12 |
| | | 224.47 | 0.837 | 0.351 | 0.486 | 461.87 |
| | 7.5 | 56.62 | 0.843 | 0.371 | 0.472 | 119.96 |
| | | 84.93 | 0.843 | 0.369 | 0.474 | 179.18 |
| | | 113.23 | 0.843 | 0.361 | 0.482 | 234.92 |
| | | 141.54 | 0.843 | 0.357 | 0.486 | 291.23 |
| | | 169.85 | 0.843 | 0.355 | 0.488 | 348.05 |
| | | 198.16 | 0.843 | 0.350 | 0.493 | 401.95 |
| | | 224.47 | 0.843 | 0.342 | 0.501 | 448.04 |
| | 10.0 | 56.62 | 0.859 | 0.369 | 0.490 | 115.55 |
| | | 84.93 | 0.859 | 0.362 | 0.497 | 170.89 |
| | | 113.23 | 0.859 | 0.360 | 0.499 | 226.91 |
| | | 141.54 | 0.859 | 0.359 | 0.500 | 283.08 |
| | | 169.85 | 0.859 | 0.354 | 0.505 | 336.34 |
| | | 198.16 | 0.859 | 0.351 | 0.508 | 390.08 |
| | | 224.47 | 0.859 | 0.346 | 0.513 | 437.56 |

**Table 5.10** continued:

| Binder | Binder Concentration (%w/w) | P (MNm$^{-2}$) | $V_0$ (cm$^3$) | $V_p$ (cm$^3$) | C | P/C |
|---|---|---|---|---|---|---|
| Gelatin | 2.5 | 56.62 | 0.821 | 0.375 | 0.543 | 104.23 |
| | | 84.93 | 0.821 | 0.373 | 0.546 | 155.64 |
| | | 113.23 | 0.821 | 0.370 | 0.549 | 206.12 |
| | | 141.54 | 0.821 | 0.362 | 0.559 | 253.17 |
| | | 169.85 | 0.821 | 0.356 | 0.566 | 299.89 |
| | | 198.16 | 0.821 | 0.348 | 0.576 | 343.95 |
| | | 224.47 | 0.821 | 0.343 | 0.582 | 385.54 |
| | 5.0 | 56.62 | 0.838 | 0.369 | 0.469 | 120.72 |
| | | 84.93 | 0.838 | 0.364 | 0.474 | 179.18 |
| | | 113.23 | 0.838 | 0.362 | 0.476 | 237.88 |
| | | 141.54 | 0.838 | 0.359 | 0.479 | 295.49 |
| | | 169.85 | 0.838 | 0.356 | 0.482 | 352.39 |
| | | 198.16 | 0.838 | 0.351 | 0.487 | 406.90 |
| | | 224.47 | 0.838 | 0.347 | 0.491 | 457.17 |
| | 7.5 | 56.62 | 0.804 | 0.364 | 0.547 | 103.46 |
| | | 84.93 | 0.804 | 0.359 | 0.553 | 153.45 |
| | | 113.23 | 0.804 | 0.357 | 0.556 | 203.66 |
| | | 141.54 | 0.804 | 0.356 | 0.557 | 254.01 |
| | | 169.85 | 0.804 | 0.349 | 0.566 | 300.13 |
| | | 198.16 | 0.804 | 0.347 | 0.568 | 348.62 |
| | | 224.47 | 0.804 | 0.343 | 0.573 | 391.48 |

**Table 5.10** continued:

| Binder | Binder Concentration (%w/w) | P (MNm$^{-2}$) | V$_0$ (cm$^3$) | V$_p$ (cm$^3$) | C | P/C |
|---|---|---|---|---|---|---|
| Gelatin | 10.0 | 56.62 | 0.798 | 0.363 | 0.545 | 103.87 |
| | | 84.93 | 0.798 | 0.354 | 0.556 | 152.64 |
| | | 113.23 | 0.798 | 0.351 | 0.560 | 202.14 |
| | | 141.54 | 0.798 | 0.349 | 0.563 | 251.56 |
| | | 169.85 | 0.798 | 0.347 | 0.565 | 300.53 |
| | | 198.16 | 0.798 | 0.345 | 0.568 | 349.08 |
| | | 224.47 | 0.798 | 0.344 | 0.569 | 394.55 |

**Table 5.11**: Values of applied Pressure (P), zero pressure ($V_0$), Volume ($V_P$), degree of volume reduction (C) and P/C for ibuprofen formulations

| Binder | Concentration (%w/w) | P (MNm$^{-2}$) | $V_0$ (cm$^3$) | $V_p$ (cm$^3$) | C | P/C |
|---|---|---|---|---|---|---|
| | 0.0 | 56.62 | 0.796 | 0.396 | 0.503 | 112.67 |
| | | 84.93 | 0.796 | 0.384 | 0.518 | 164.09 |
| | | 113.23 | 0.796 | 0.381 | 0.521 | 217.18 |
| | | 141.54 | 0.796 | 0.380 | 0.523 | 270.83 |
| | | 169.85 | 0.796 | 0.375 | 0.529 | 321.14 |
| | | 198.16 | 0.796 | 0.374 | 0.530 | 373.78 |
| | | 224.47 | 0.796 | 0.363 | 0.544 | 412.65 |
| *Entandophragma angolense* gum | 2.5 | 56.62 | 0.829 | 0.389 | 0.531 | 106.68 |
| | | 84.93 | 0.829 | 0.384 | 0.537 | 158.22 |
| | | 113.23 | 0.829 | 0.379 | 0.543 | 208.59 |
| | | 141.54 | 0.829 | 0.377 | 0.545 | 259.59 |
| | | 169.85 | 0.829 | 0.374 | 0.549 | 309.46 |
| | | 198.16 | 0.829 | 0.372 | 0.551 | 359.46 |
| | | 224.47 | 0.829 | 0.369 | 0.555 | 404.53 |
| | | 56.62 | 0.825 | 0.384 | 0.535 | 105.92 |
| | 5.0 | 84.93 | 0.825 | 0.381 | 0.538 | 157.81 |
| | | 113.23 | 0.825 | 0.376 | 0.544 | 208.05 |
| | | 141.54 | 0.825 | 0.371 | 0.550 | 257.20 |
| | | 169.85 | 0.825 | 0.370 | 0.552 | 307.97 |
| | | 198.16 | 0.825 | 0.366 | 0.556 | 356.17 |
| | | 224.47 | 0.825 | 0.362 | 0.561 | 399.97 |

**Table 5.11** continued:

| Binder | Concentration (%w/w) | P (MNm$^{-2}$) | V$_0$ (cm$^3$) | V$_p$ (cm$^3$) | C | P/C |
|---|---|---|---|---|---|---|
| *Entandophragma angolense* gum | 7.5 | 56.62 | 0.819 | 0.380 | 0.536 | 105.63 |
| | | 84.93 | 0.819 | 0.376 | 0.541 | 157.02 |
| | | 113.23 | 0.819 | 0.374 | 0.543 | 208.39 |
| | | 141.54 | 0.819 | 0.369 | 0.549 | 257.60 |
| | | 169.85 | 0.819 | 0.362 | 0.558 | 304.39 |
| | | 198.16 | 0.819 | 0.359 | 0.562 | 352.81 |
| | | 224.47 | 0.819 | 0.357 | 0.564 | 397.92 |
| | 10.0 | 56.62 | 0.805 | 0.377 | 0.532 | 106.49 |
| | | 84.93 | 0.805 | 0.372 | 0.538 | 157.90 |
| | | 113.23 | 0.805 | 0.369 | 0.542 | 209.06 |
| | | 141.54 | 0.805 | 0.365 | 0.547 | 258.95 |
| | | 169.85 | 0.805 | 0.359 | 0.554 | 306.57 |
| | | 198.16 | 0.805 | 0.354 | 0.560 | 353.70 |
| | | 224.47 | 0.805 | 0.349 | 0.566 | 396.27 |
| Hydroxypropylcellulose | 2.5 | 56.62 | 0.832 | 0.394 | 0.526 | 107.55 |
| | | 84.93 | 0.832 | 0.391 | 0.530 | 160.23 |
| | | 113.23 | 0.832 | 0.388 | 0.534 | 212.18 |
| | | 141.54 | 0.832 | 0.386 | 0.536 | 264.04 |
| | | 169.85 | 0.832 | 0.379 | 0.544 | 311.95 |
| | | 198.16 | 0.832 | 0.371 | 0.554 | 357.63 |
| | | 224.47 | 0.832 | 0.370 | 0.555 | 404.24 |

**Table 5.11** continued:

| Binder | Concentration (%w/w) | P (MNm$^{-2}$) | $V_0$ (cm$^3$) | $V_p$ (cm$^3$) | C | P/C |
|---|---|---|---|---|---|---|
| Hydroxypropylcellulose | 5.0 | 56.62 | 0.827 | 0.389 | 0.530 | 106.91 |
| | | 84.93 | 0.827 | 0.385 | 0.534 | 158.91 |
| | | 113.23 | 0.827 | 0.381 | 0.539 | 209.96 |
| | | 141.54 | 0.827 | 0.377 | 0.544 | 260.12 |
| | | 169.85 | 0.827 | 0.368 | 0.555 | 306.03 |
| | | 198.16 | 0.827 | 0.362 | 0.562 | 352.43 |
| | | 224.47 | 0.827 | 0.361 | 0.563 | 398.36 |
| | 7.5 | 56.62 | 0.822 | 0.387 | 0.529 | 106.99 |
| | | 84.93 | 0.822 | 0.384 | 0.533 | 159.39 |
| | | 113.23 | 0.822 | 0.381 | 0.536 | 211.05 |
| | | 141.54 | 0.822 | 0.375 | 0.544 | 260.28 |
| | | 169.85 | 0.822 | 0.365 | 0.556 | 305.51 |
| | | 198.16 | 0.822 | 0.361 | 0.561 | 353.34 |
| | | 224.47 | 0.822 | 0.359 | 0.563 | 398.52 |
| | 10.0 | 56.62 | 0.817 | 0.377 | 0.539 | 105.13 |
| | | 84.93 | 0.817 | 0.374 | 0.542 | 156.63 |
| | | 113.23 | 0.817 | 0.370 | 0.547 | 206.96 |
| | | 141.54 | 0.817 | 0.369 | 0.548 | 258.12 |
| | | 169.85 | 0.817 | 0.366 | 0.552 | 307.69 |
| | | 198.16 | 0.817 | 0.363 | 0.556 | 356.60 |
| | | 224.47 | 0.817 | 0.357 | 0.563 | 398.68 |

**Table 5.11** continued:

| Binder | Binder Concentration (%w/w) | P (MNm$^{-2}$) | V$_0$ (cm$^3$) | V$_p$ (cm$^3$) | C | P/C |
|---|---|---|---|---|---|---|
| Gelatin | 2.5 | 56.62 | 0.810 | 0.381 | 0.530 | 106.90 |
| | | 84.93 | 0.810 | 0.377 | 0.535 | 158.88 |
| | | 113.23 | 0.810 | 0.370 | 0.543 | 208.45 |
| | | 141.54 | 0.810 | 0.368 | 0.546 | 259.38 |
| | | 169.85 | 0.810 | 0.364 | 0.551 | 308.47 |
| | | 198.16 | 0.810 | 0.361 | 0.554 | 357.48 |
| | | 224.47 | 0.810 | 0.359 | 0.557 | 403.15 |
| | 5.0 | 56.62 | 0.812 | 0.379 | 0.433 | 130.76 |
| | | 84.93 | 0.812 | 0.371 | 0.441 | 192.59 |
| | | 113.23 | 0.812 | 0.367 | 0.445 | 254.45 |
| | | 141.54 | 0.812 | 0.361 | 0.451 | 313.84 |
| | | 169.85 | 0.812 | 0.359 | 0.453 | 374.94 |
| | | 198.16 | 0.812 | 0.357 | 0.455 | 435.52 |
| | | 224.47 | 0.812 | 0.353 | 0.459 | 489.04 |
| | 7.5 | 56.62 | 0.796 | 0.373 | 0.531 | 106.55 |
| | | 84.93 | 0.796 | 0.368 | 0.538 | 157.95 |
| | | 113.23 | 0.796 | 0.366 | 0.540 | 209.61 |
| | | 141.54 | 0.796 | 0.365 | 0.541 | 261.41 |
| | | 169.85 | 0.796 | 0.358 | 0.550 | 308.68 |
| | | 198.16 | 0.796 | 0.354 | 0.555 | 356.87 |
| | | 224.47 | 0.796 | 0.352 | 0.558 | 402.43 |

**Table 5.11** continued:

| Binder | Binder Concentration (%w/w) | P (MNm$^{-2}$) | V$_0$ (cm$^3$) | V$_p$ (cm$^3$) | C | P/C |
|--------|---------|---------|---------|---------|---------|---------|
| Gelatin | 10.0 | 56.62 | 0.784 | 0.372 | 0.526 | 107.74 |
| | | 84.93 | 0.784 | 0.369 | 0.529 | 160.45 |
| | | 113.23 | 0.784 | 0.366 | 0.533 | 212.37 |
| | | 141.54 | 0.784 | 0.361 | 0.540 | 262.33 |
| | | 169.85 | 0.784 | 0.359 | 0.542 | 313.32 |
| | | 198.16 | 0.784 | 0.353 | 0.550 | 360.46 |
| | | 224.47 | 0.784 | 0.350 | 0.554 | 405.49 |
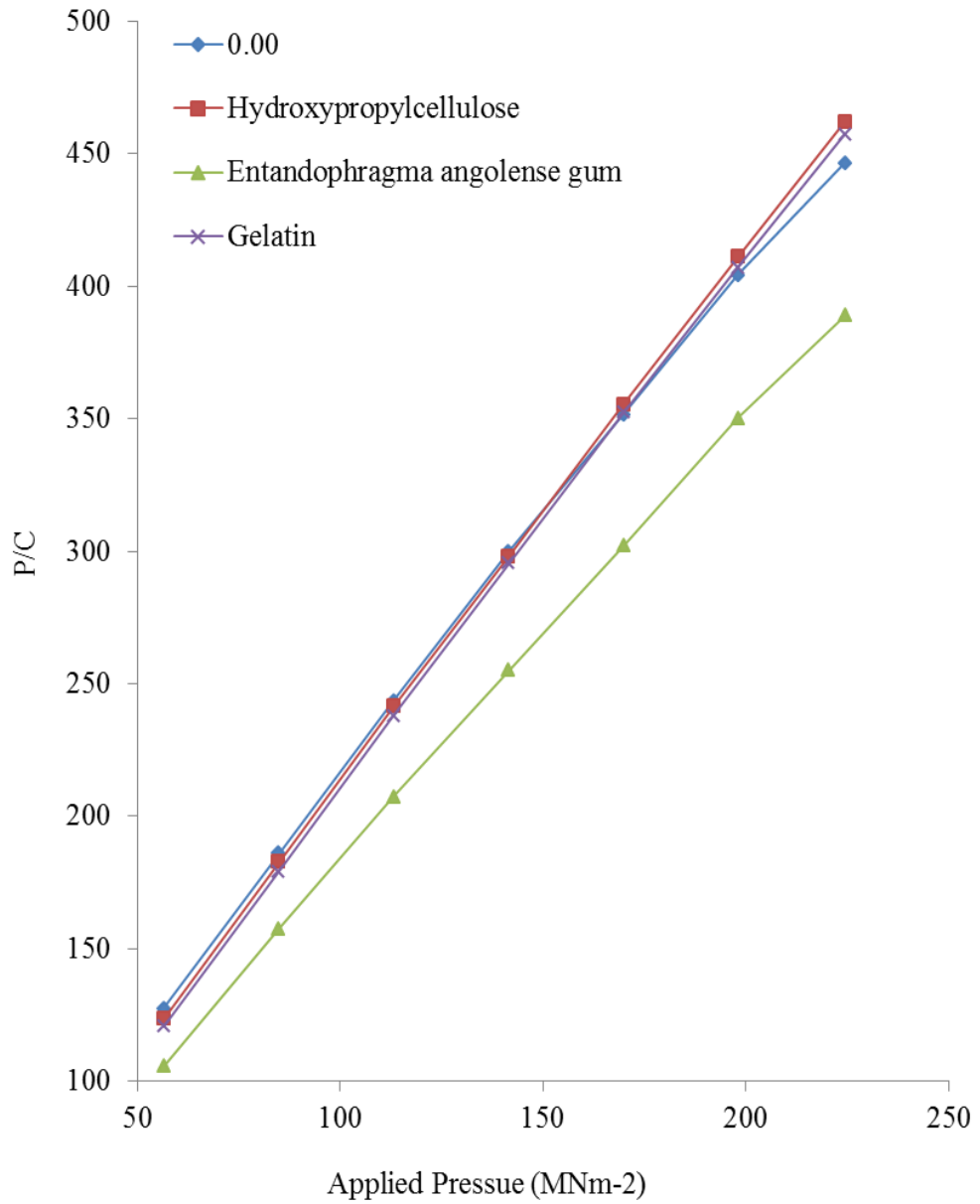
**Fig 5.8**: Kawakita plots for chlorpheniramine maleate formulations containing 5 %w/w polymer prepared for wet granulation
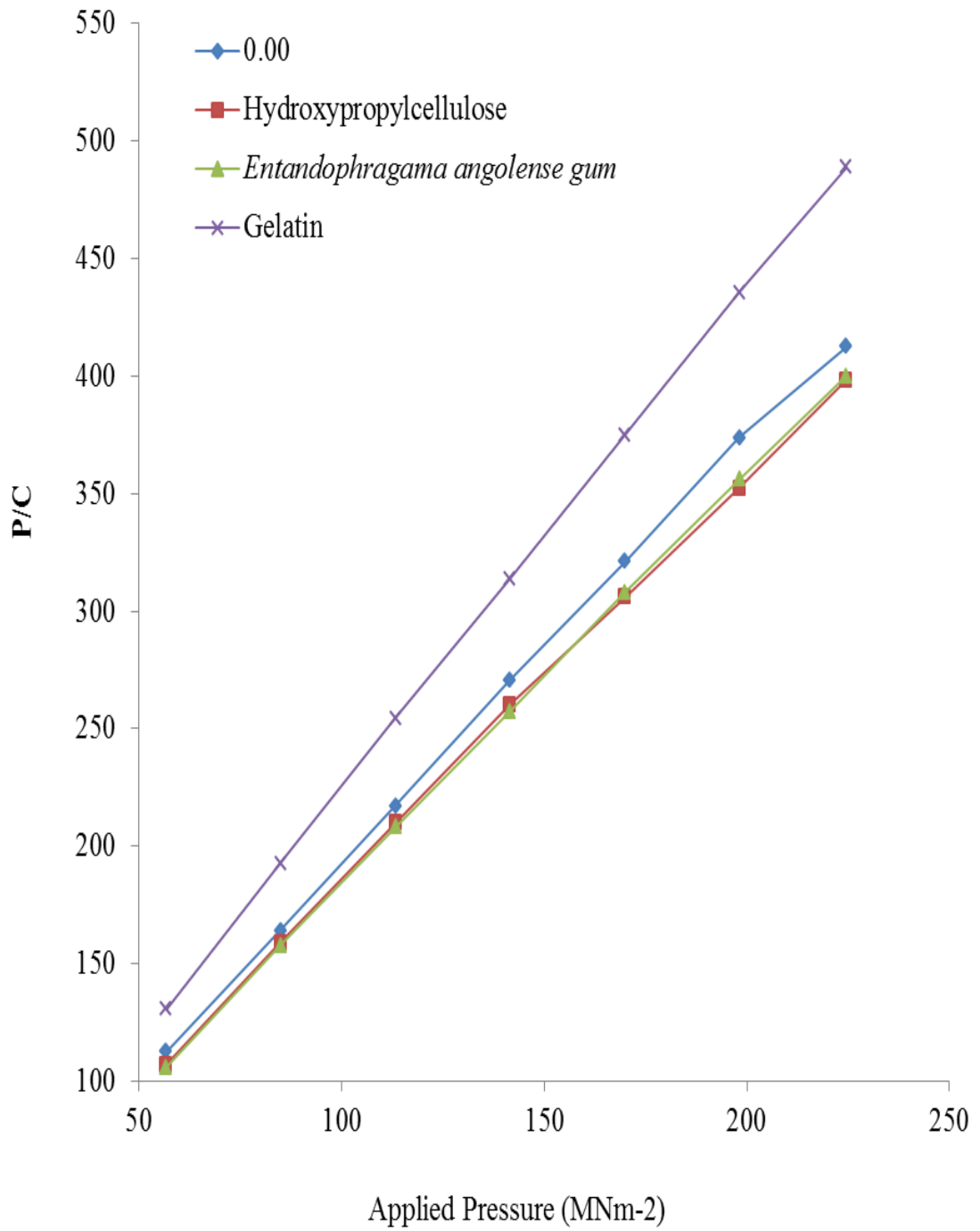
**Fig 5.9**: Kawakita plots for Ibuprofen formulations containing 5.0 %w/w polymer prepared for wet granulation

**Table 5.12**: Parameters derived from Kawakita plots for chlorpheniramine maleate formulations

| Binder | Concentration (%w/w) | $P_K$ | $\rho_I$ |
|---|---|---|---|
| | 0.0 | 3.711 | 0.472 |
| *Entandophragma angolense* gum | 2.5 | 3.524 | 0.496 |
| | 5.0 | 3.517 | 0.491 |
| | 7.5 | 3.496 | 0.482 |
| | 10.0 | 3.477 | 0.479 |
| Gelatin | 2.5 | 3.615 | 0.489 |
| | 5.0 | 3.607 | 0.487 |
| | 7.5 | 3.528 | 0.485 |
| | 10.0 | 3.511 | 0.484 |
| Hydroxypropylcellulose | 2.5 | 3.519 | 0.488 |
| | 5.0 | 3.511 | 0.481 |
| | 7.5 | 3.481 | 0.476 |
| | 10.0 | 3.467 | 0.462 |

**Table 5.13**: Parameters derived from Kawakita plots for ibuprofen formulations

| Binder | Concentration (%w/w) | $P_K$ | $\rho_I$ |
|---|---|---|---|
| | 0.0 | 3.811 | 0.474 |
| *Entandophragma angolense* gum | 2.5 | 3.613 | 0.516 |
| | 5.0 | 3.607 | 0.501 |
| | 7.5 | 3.514 | 0.494 |
| | 10.0 | 3.511 | 0.490 |
| Gelatin | 2.5 | 3.714 | 0.497 |
| | 5.0 | 3.633 | 0.495 |
| | 7.5 | 3.572 | 0.491 |
| | 10.0 | 3.549 | 0.482 |
| Hydroxypropylcellulose` | 2.5 | 3.603 | 0.521 |
| | 5.0 | 3.593 | 0.506 |
| | 7.5 | 3.587 | 0.495 |
| | 10.0 | 3.542 | 0.493 |

**5.4        Mechanical Properties of the Tablets**

**5.4.1        Tensile Strength**

The tensile strength results obtained from the diametral compression test on the tablets with hole ($T_0$) and without hole (T) at the centre are presented in Table 5.14. The results were found to fit the general equation; Log T (or $T_0$) = $A\rho_r$ + B. A linear relationship was obtained between the logarithm of tensile strength and relative density with correlation coefficient r> 0.997. The constants A and B in the equation depended on the type and concentration of binder used and on whether the tablet had a hole or not. Similar results have been reported by Itiola and Pilpel (1991). This is probably due to enhancement of the different types of forces acting between the constituent particles which include the interparticulate forces of attraction or van der Waals' forces, electrostatic forces, mechanical interlocking and other forces that operate between the particles as they are brought into closer contact. Generally, the degree of bonding directly depends on the area of contact between the particles.

The values of T and $T_0$ generally increased with increase in binder concentration, while formulations containing Ibuprofen were observed to have higher T and $T_0$ values. Other workers have also reported similar observations (Odeku and Itiola, 1998; Adetunji *et al*, 2006). Tablets formulated by wet granulation technique had higher T and $T_0$ values. The heat produced during compression would cause melting of the asperities which on cooling would solidify to form strong solid bonds between the particles (Kurup and Pilpel, 1979; Adeleye *et al*, 2011). Binders are soft and plasto-elastic and would therefore undergo plastic and elastic deformation under high compression pressures and would be forced into the interparticulate spaces, thereby increasing the area of contact between the particles and forming more solid bonds (Itiola, 1994). The amount of bonding would depend on the amount of binding agent present (Kurup and Pilpel, 1979; Itiola, 1994). The ranking of T was Hydroxypropylcellulose > *Entandophragma angolense* > Gelatin. The tensile strength of a tablet is known to be a function of the area of contact between its particles and the strength of bonds produced between them (Carstensen, 1980; Malmataris and Pilpel, 1984). The greater the degree of bonding, the greater is the tensile strength (Itiola, 1991, 1994; Itiola and Pilpel, 1994 and Odeku and Itiola, 1998).

The equations for the best fitting line and values of correlation coefficient for the formulations are presented in Table 4.15. Representative plots of log of tensile strength against relative density for tablets containing 5.0% w/w gum are presented in Figs 4.10 and 4.11. It can be seen that at all relative densities, the tensile strength of the tablets with a hole was less than that of same without a hole, the hole acting as a stress concentrator (Itiola, 1994).

**Table 5.14**: Values of Tensile strength for different formulations at different relative densities

| Formulation Type | Binder (% w/w) | Concentration | Tablets without hole (T) | | Tablets |
|---|---|---|---|---|---|
| | | | Relative Density ($\rho_r$) | Tensile Strength (MNm$^{-2}$) | Relative Density ($\rho_r$) |
| CPM | 0.0 | | 0.842 | 1.127 | 0.829 |
| | | | 0.851 | 1.183 | 0.836 |
| | | | 0.862 | 1.294 | 0.839 |
| | | | 0.876 | 1.318 | 0.845 |
| | | | 0.879 | 1.574 | 0.857 |
| CPM/ENTA (WG) | 2.5 | | 0.866 | 1.195 | 0.853 |
| | | | 0.875 | 1.282 | 0.858 |
| | | | 0.886 | 1.441 | 0.865 |
| | | | 0.887 | 1.736 | 0.876 |
| | | | 0.889 | 2.144 | 0.879 |
| | 5.0 | | 0.854 | 1.242 | 0.837 |
| | | | 0.857 | 1.284 | 0.848 |
| | | | 0.881 | 1.473 | 0.864 |
| | | | 0.898 | 1.817 | 0.886 |
| | | | 0.912 | 2.229 | 0.895 |
| | 7.5 | | 0.875 | 1.269 | 0.862 |
| | | | 0.881 | 1.291 | 0.865 |
| | | | 0.892 | 1.686 | 0.879 |
| | | | 0.899 | 1.823 | 0.898 |
| | | | 0.917 | 2.301 | 0.912 |
| | 10.0 | | 0.888 | 1.279 | 0.871 |
| | | | 0.924 | 1.294 | 0.907 |
| | | | 0.927 | 1.506 | 0.915 |

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| | | | | | | 0.933 | 1.922 | 0.923 |
| | | | | | | 0.947 | 2.261 | 0.928 |

**Table 5.14** continued:

| Formulation Type | Binder Concentration (% w/w) | | Tablets without hole (T) | | Tablets with hole ($T_0$) | |
|---|---|---|---|---|---|---|
| | | | Relative Density ($\rho_r$) | Tensile Strength (MN m$^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength (MN m$^{-2}$) |
| CPM/ENTA (DC) | 2.5 | | 0.851 | 1.186 | | |
| | | | | | 0.838 | 0.798 |
| | | | 0.872 | 1.277 | 0.855 | 0.832 |
| | | | 0.876 | 1.397 | 0.859 | 0.877 |
| | | | 0.880 | 1.721 | 0.863 | 0.892 |
| | | | 0.922 | 1.844 | 0.905 | 0.937 |
| | 5.0 | | 0.861 | 1.257 | 0.844 | 0.802 |
| | | | 0.870 | 1.279 | 0.855 | 0.814 |
| | | | 0.874 | 1.444 | 0.857 | 0.844 |
| | | | 0.883 | 1.726 | 0.868 | 0.948 |
| | | | 0.887 | 1.862 | 0.874 | 0.976 |
| | 7.5 | | 0.874 | 1.249 | 0.861 | 0.855 |
| | | | 0.880 | 1.283 | 0.867 | 0.869 |
| | | | 0.884 | 1.451 | 0.871 | 0.876 |
| | | | 0.893 | 1.576 | 0.883 | 0.916 |
| | | | 0.927 | 1.883 | 0.892 | 1.104 |

|  |  | 10.0 | 0.893 | 1.221 | 0.880 | 0.924 |
|  |  |  | 0.894 | 1.236 | 0.877 | 0.939 |
|  |  |  | 0.899 | 1.448 | 0.882 | 0.956 |
|  |  |  | 0.961 | 1.894 | 0.944 | 1.022 |
|  |  |  | 0.972 | 2.128 | 0.959 | 1.447 |

**Table 5.14** continued:

| Formulation Type | Binder Concentration (% w/w) | Tablets without hole (T) | | Tablets with hole ($T_0$) | |
|---|---|---|---|---|---|
|  |  | Relative Density ($\rho_r$) | Tensile Strength (MN m$^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength (MN m$^{-2}$) |
| CPM/HPC (WG) | 2.5 | 0.846 | 1.238 | 0.833 | 0.974 |
|  |  | 0.857 | 1.333 | 0.840 | 0.983 |
|  |  | 0.893 | 1.484 | 0.876 | 1.001 |
|  |  | 0.899 | 1.779 | 0.882 | 1.103 |
|  |  | 0.924 | 2.187 | 0.907 | 1.121 |
|  | 5.0 | 0.873 | 1.285 | 0.856 | 0.946 |
|  |  | 0.882 | 1.327 | 0.867 | 0.957 |
|  |  | 0.895 | 1.516 | 0.878 | 1.203 |
|  |  | 0.909 | 1.860 | 0.894 | 1.221 |
|  |  | 0.913 | 2.272 | 0.900 | 1.463 |
|  |  |  | 1.312 | 0.864 | 0.968 |

| | Binder Conc. | Relative Density ($\rho_r$) | Tensile Strength | Relative Density ($\rho_r$) | Tensile Strength |
|---|---|---|---|---|---|
| | 7.5 | 0.877 | | | |
| | | 0.878 | 1.334 | 0.865 | 1.016 |
| | | 0.899 | 1.529 | 0.886 | 1.453 |
| | | 0.942 | 1.866 | 0.929 | 1.461 |
| | | 0.957 | 2.344 | 0.940 | 1.469 |
| | 10.0 | 0.891 | 1.322 | 0.874 | 0.998 |
| | | 0.926 | 1.337 | 0.909 | 1.149 |
| | | 0.941 | 1.549 | 0.928 | 1.286 |
| | | 0.943 | 1.965 | 0.930 | 1.427 |
| | | 0.967 | 2.384 | 0.950 | 1.484 |

**Table 5.14** continued:

| Formulation Type | Binder Concentration (% w/w) | Tablets without hole (T) | | Tablets with hole ($T_0$) | |
|---|---|---|---|---|---|
| | | Relative Density ($\rho_r$) | Tensile Strength (MN m$^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength (MN m$^{-2}$) |
| CPM/HPC (DC) | 2.5 | 0.842 | 1.137 | 0.829 | 0.804 |
| | | 0.856 | 1.232 | 0.839 | 0.813 |
| | | 0.861 | 1.383 | 0.844 | 0.842 |
| | | 0.873 | 1.678 | 0.856 | 0.913 |
| | | 0.894 | 2.086 | 0.877 | 0.957 |
| | 5.0 | 0.861 | 1.184 | 0.844 | 0.821 |

| | | | | |
|---|---|---|---|---|
| | 0.872 | 1.226 | 0.857 | 0.849 |
| | 0.889 | 1.415 | 0.872 | 0.888 |
| | 0.897 | 1.759 | 0.882 | 0.832 |
| | 0.898 | 2.171 | 0.885 | 0.984 |
| 7.5 | 0.862 | 1.241 | 0.849 | 0.784 |
| | 0.868 | 1.386 | 0.855 | 0.806 |
| | 0.893 | 1.628 | 0.880 | 0.851 |
| | 0.921 | 2.265 | 0.908 | 0.989 |
| | 0.924 | 2.243 | 0.907 | 1.246 |
| 10.0 | 0.864 | 1.265 | 0.847 | 0.892 |
| | 0.892 | 1.331 | 0.875 | 0.907 |
| | 0.898 | 1.479 | 0.885 | 1.219 |
| | 0.944 | 2.274 | 0.931 | 1.335 |
| | 0.974 | 2.283 | 0.945 | 1.481 |

**Table 5.14** continued:

| Formulation Type | Binder Concentration (% w/w) | Tablets without hole (T) | | Tablets with hole ($T_0$) | |
|---|---|---|---|---|---|
| | | Relative Density ($\rho_r$) | Tensile Strength ($MNm^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength ($MNm^{-2}$) |
| CPM/GEL (WG) | 2.5 | 0.867 | 1.157 | 0.854 | 0.635 |
| | | 0.869 | 1.239 | 0.852 | 0.692 |
| | | 0.893 | 1.398 | 0.876 | 0.751 |
| | | 0.897 | 1.693 | 0.880 | 0.746 |
| | | 0.903 | 2.101 | 0.886 | 0.754 |
| | | | 1.204 | 0.858 | 0.757 |

| | | | | | |
|---|---|---|---|---|---|
| | 5.0 | 0.875 | | | |
| | | 0.883 | 1.246 | 0.868 | 0.824 |
| | | 0.885 | 1.435 | 0.868 | 0.873 |
| | | 0.897 | 1.779 | 0.882 | 0.887 |
| | | 0.931 | 2.191 | 0.918 | 0.931 |
| | | | | | |
| | 7.5 | 0.879 | 1.231 | 0.866 | 0.809 |
| | | 0.882 | 1.253 | 0.869 | 0.831 |
| | | 0.911 | 1.448 | 0.898 | 0.926 |
| | | 0.944 | 1.785 | 0.931 | 1.123 |
| | | 0.951 | 2.263 | 0.934 | 1.241 |
| | 10.0 | 0.892 | 1.241 | 0.875 | 0.894 |
| | | 0.893 | 1.251 | 0.876 | 0.904 |
| | | 0.897 | 1.463 | 0.884 | 1.116 |
| | | 0.938 | 1.879 | 0.925 | 1.357 |
| | | 0.941 | 2.298 | 0.924 | 1.276 |

**Table 5.14** continued:

| Formulation Type | Binder Concentration (% w/w) | Tablets without hole (T) | | Tablets with hole ($T_0$) | |
|---|---|---|---|---|---|
| | | Relative Density ($\rho_r$) | Tensile Strength ($MNm^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength ($MNm^{-2}$) |
| CPM/GEL (DC) | 2.5 | 0.857 | 1.056 | 0.844 | 0.642 |
| | | 0.859 | 1.138 | 0.842 | 0.672 |
| | | 0.862 | 1.297 | 0.845 | 0.781 |
| | | 0.874 | 1.592 | 0.857 | 0.876 |
| | | 0.899 | 1.788 | 0.882 | 0.884 |

| Formulation Type | Binder Concentration (% w/w) | Tablets without hole (T) | | Tablets with hole (T₀) | |
|---|---|---|---|---|---|
| | | Relative Density ($\rho_r$) | Tensile Strength ($MNm^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength ($MNm^{-2}$) |
| | 5.0 | 0.861 | 1.103 | 0.844 | 0.689 |
| | | 0.862 | 1.145 | 0.847 | 0.731 |
| | | 0.879 | 1.334 | 0.862 | 0.760 |
| | | 0.892 | 1.678 | 0.877 | 0.864 |
| | | 0.895 | 2.109 | 0.882 | 1.076 |
| | 7.5 | 0.863 | 1.135 | 0.850 | 0.716 |
| | | 0.864 | 1.152 | 0.851 | 0.838 |
| | | 0.876 | 1.347 | 0.863 | 0.839 |
| | | 0.892 | 1.684 | 0.879 | 0.970 |
| | | 0.936 | 2.162 | 0.919 | 1.118 |
| | 10.0 | 0.862 | 1.147 | 0.845 | 0.824 |
| | | 0.868 | 1.155 | 0.851 | 0.834 |
| | | 0.897 | 1.362 | 0.884 | 0.946 |
| | | 0.911 | 1.778 | 0.898 | 0.971 |
| | | 0.942 | 2.107 | 0.925 | 1.041 |

**Table 5.14** continued:

| Formulation Type | Binder Concentration (% w/w) | Tablets without hole (T) | | Tablets with hole (T₀) | |
|---|---|---|---|---|---|
| | | Relative Density ($\rho_r$) | Tensile Strength ($MNm^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength ($MNm^{-2}$) |
| IBUP | 0.0 | 0.856 | 1.139 | 0.843 | 0.887 |
| | | 0.868 | 1.143 | 0.851 | 0.896 |
| | | 0.874 | 1.301 | 0.868 | 1.138 |
| | | 0.887 | 1.369 | 0.880 | 1.281 |

| Formulation type | Binder Concentration (% w/w) | Relative Density ($\rho_r$) | Tensile Strength ($MNm^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength ($MNm^{-2}$) |
|---|---|---|---|---|---|
| | | 0.921 | 1.612 | 0.941 | 1.412 |
| IBUP/ENTA (WG) | 2.5 | 0.868 | 1.228 | 0.855 | 0.894 |
| | | 0.877 | 1.324 | 0.860 | 0.912 |
| | | 0.885 | 1.483 | 0.868 | 0.953 |
| | | 0.886 | 1.778 | 0.869 | 0.965 |
| | | 0.889 | 1.986 | 0.872 | 1.573 |
| | | 0.873 | 1.275 | 0.856 | 0.866 |
| | 5.0 | 0.885 | 1.317 | 0.870 | 0.893 |
| | | 0.892 | 1.506 | 0.875 | 0.982 |
| | | 0.911 | 2.251 | 0.896 | 1.003 |
| | | 0.926 | 2.262 | 0.913 | 1.506 |
| | | 0.882 | 1.302 | 0.869 | 0.888 |
| | 7.5 | 0.878 | 1.324 | 0.865 | 0.959 |
| | | 0.887 | 1.519 | 0.874 | 0996 |
| | | 0.892 | 1.856 | 0.879 | 1.651 |
| | | 0.939 | 2.334 | 0.922 | 1.699 |
| | 10.0 | 0.899 | 1.821 | 0.882 | 0.927 |
| | | 0.911 | 2.336 | 0.894 | 0.983 |
| | | 0.921 | 2.448 | 0.908 | 1.125 |
| | | 0.927 | 2.664 | 0.914 | 1.403 |
| | | 0.968 | 2.883 | 0.924 | 1.516 |

**Table 5.14** continued:

| Formulation type | Binder Concentration (% w/w) | Tablets without hole (T) | | Tablets with hole (T$_0$) | |
|---|---|---|---|---|---|
| | | Relative Density ($\rho_r$) | Tensile Strength ($MNm^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength ($MNm^{-2}$) |
| IBUP/ENTA (DC) | 2.5 | 0.857 | 1.164 | 0.844 | 0.817 |
| | | 0.869 | 1.319 | 0.852 | 0.851 |
| | | 0.871 | 1.439 | 0.854 | 0.896 |

| | | | | | |
|---|---|---|---|---|---|
| | | 0.875 | 1.763 | 0.858 | 0.911 |
| | | 0.881 | 2.133 | 0.864 | 0.956 |
| | 5.0 | 0.869 | 1.291 | 0.852 | 0.831 |
| | | 0.871 | 1.312 | 0.856 | 0.863 |
| | | 0.874 | 1.442 | 0.857 | 0.932 |
| | | 0.877 | 1.786 | 0.862 | 0.967 |
| | | 0.918 | 2.204 | 0.905 | 0.995 |
| | 7.5 | 0.870 | 1.238 | 0.857 | 0.874 |
| | | 0.879 | 1.316 | 0.866 | 0.888 |
| | | 0.882 | 1.484 | 0.869 | 0.895 |
| | | 0.916 | 1.509 | 0.903 | 0.935 |
| | | 0.927 | 1.516 | 0.910 | 1.123 |
| | 10.0 | 0.898 | 1.263 | 0.881 | 0.943 |
| | | 0.899 | 1.272 | 0.882 | 0.958 |
| | | 0.914 | 1.322 | 0.891 | 1.575 |
| | | 0.928 | 1.336 | 0.915 | 1.581 |
| | | 0.937 | 1.548 | 0.920 | 1.590 |

**Table 5.14** continued:

| Formulation type | Binder Concentration (% w/w) | Tablets without hole (T) | | Tablets with hole (T$_0$) | |
|---|---|---|---|---|---|
| | | Relative Density ($\rho_r$) | Tensile Strength (MNm$^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength (MNm$^{-2}$) |
| IBUP/HPC (WG) | 2.5 | 0.876 | 1.271 | 0.863 | 0.993 |
| | | 0.895 | 1.375 | 0.878 | 1.002 |

| | Binder Concentration (% w/w) | Relative Density ($\rho_r$) | Tensile Strength (MNm$^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength (MNm$^{-2}$) |
|---|---|---|---|---|---|
| | | 0.896 | 1.526 | 0.879 | 1.021 |
| | | 0.897 | 1.821 | 0.880 | 1.122 |
| | | 0.899 | 2.229 | 0.882 | 1.146 |
| | 5.0 | 0.861 | 1.318 | 0.844 | 0.965 |
| | | 0.898 | 2.365 | 0.883 | 0.976 |
| | | 0.903 | 2.549 | 0.886 | 1.222 |
| | | 0.907 | 2.833 | 0.892 | 1.24 |
| | | 0.911 | 2.845 | 0.898 | 1.482 |
| | 7.5 | 0.889 | 1.345 | 0.876 | 0.987 |
| | | 0.927 | 2.587 | 0.914 | 1.035 |
| | | 0.933 | 2.562 | 0.920 | 1.472 |
| | | 0.946 | 2.899 | 0.933 | 1.487 |
| | | 0.951 | 2.377 | 0.934 | 1.488 |
| | 10.0 | 0.924 | 1.364 | 0.907 | 1.017 |
| | | 0.933 | 1.379 | 0.916 | 1.168 |
| | | 0.972 | 1.591 | 0.959 | 1.305 |
| | | 0.981 | 2.007 | 0.968 | 1.446 |
| | | 0.986 | 2.426 | 0.969 | 1.736 |

| Formulation Type | Binder Concentration (% w/w) | Tablets without hole (T) | | Tablets with hole (T$_0$) | |
|---|---|---|---|---|---|
| | | Relative Density ($\rho_r$) | Tensile Strength (MNm$^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength (MNm$^{-2}$) |
| IBUP/HPC (DC) | 2.5 | 0.835 | 1.219 | 0.822 | 1.001 |
| | | 0.864 | 1.339 | 0.847 | 1.017 |

| | Binder Concentration (%w/w) | Relative Density ($\rho_r$) | Tensile Strength (MNm$^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength (MNm$^{-2}$) |
|---|---|---|---|---|---|
| | | 0.876 | 1.413 | 0.859 | 1.028 |
| | | 0.888 | 1.765 | 0.871 | 1.135 |
| | | 0.891 | 2.113 | 0.874 | 1.148 |
| | 5.0 | 0.856 | 1.247 | 0.839 | 0.973 |
| | | 0.875 | 1.362 | 0.860 | 0.984 |
| | | 0.883 | 1.477 | 0.866 | 1.233 |
| | | 0.892 | 1.792 | 0.877 | 1.248 |
| | | 0.893 | 2.262 | 0.880 | 1.491 |
| | 7.5 | 0.863 | 1.282 | 0.850 | 0.995 |
| | | 0.877 | 1.265 | 0.864 | 1.043 |
| | | 0.891 | 1.455 | 0.878 | 1.487 |
| | | 0.921 | 2.772 | 0.908 | 1.488 |
| | | 0.933 | 2.792 | 0.916 | 1.496 |
| | 10.0 | 0.876 | 1.307 | 0.859 | 1.025 |
| | | 0.891 | 1.373 | 0.874 | 1.476 |
| | | 0.937 | 2.575 | 0.924 | 1.573 |
| | | 0.951 | 2.810 | 0.938 | 1.594 |
| | | 0.957 | 2.814 | 0.940 | 1.628 |

**Table 5.14** continued:


**Table 5.14** continued:

| Formulation Type | Binder Concentration (%w/w) | Tablets without hole (T) | | Tablets with hole (T$_0$) | |
|---|---|---|---|---|---|
| | | Relative Density ($\rho_r$) | Tensile Strength (MNm$^{-2}$) | Relative Density ($\rho_r$) | Tensile Strength (MNm$^{-2}$) |

| Formulation Type | Binder Concentration (%w/w) | Relative Density | Tensile Strength | Relative Density | Tensile Strength |
|---|---|---|---|---|---|
| IBUP/Gelatin (WG) | 2.5 | 0.873 | 1.157 | 0.860 | 0.993 |
| | | 0.876 | 1.274 | 0.859 | 1.124 |
| | | 0.889 | 1.425 | 0.872 | 1.208 |
| | | 0.892 | 1.624 | 0.875 | 1.227 |
| | | 0.899 | 1.886 | 0.882 | 1.344 |
| | 5.0 | 0.884 | 1.217 | 0.867 | 0.965 |
| | | 0.892 | 1.259 | 0.877 | 0.976 |
| | | 0.898 | 1.448 | 0.881 | 1.222 |
| | | 0.899 | 1.559 | 0.884 | 1.24 |
| | | 0.927 | 2.198 | 0.914 | 1.482 |
| | 7.5 | 0.864 | 1.444 | 0.851 | 0.987 |
| | | 0.898 | 1.566 | 0.885 | 1.035 |
| | | 0.938 | 1.921 | 0.925 | 1.472 |
| | | 0.942 | 1.948 | 0.929 | 1.487 |
| | | 0.955 | 2.276 | 0.938 | 1.492 |
| | | 0.917 | 1.848 | 0.900 | 1.017 |
| | 10.0 | 0.943 | 1.878 | 0.926 | 1.168 |
| | | 0.958 | 1.894 | 0.945 | 1.305 |
| | | 0.974 | 1.906 | 0.961 | 1.446 |
| | | 0.981 | 2.325 | 0.964 | 1.503 |

**Table 5.14** continued:

| Formulation Type | Binder Concentration (%w/w) | Tablets without hole (T) | | Tablets with hole ($T_0$) | |
|---|---|---|---|---|---|
| | | Relative Density | Tensile Strength | Relative Density | Tensile Strength |

| | | $(\rho_r)$ | $(MNm^{-2})$ | $(\rho_r)$ | $(MNm^{-2})$ |
|---|---|---|---|---|---|
| IBUP/Gelatin (DC) | 2.5 | 0.866 | 1.19 | 0.853 | 0.654 |
| | | 0.875 | 1.281 | 0.858 | 0.711 |
| | | 0.886 | 1.442 | 0.869 | 0.773 |
| | | 0.887 | 1.735 | 0.870 | 0.765 |
| | | 0.889 | 2.143 | 0.872 | 0.773 |
| | 5.0 | 0.854 | 1.237 | 0.837 | 0.776 |
| | | 0.857 | 1.279 | 0.842 | 0.843 |
| | | 0.881 | 1.368 | 0.864 | 0.892 |
| | | 0.898 | 1.412 | 0.883 | 0.906 |
| | | 0.912 | 2.224 | 0.899 | 0.952 |
| | 7.5 | 0.875 | 1.264 | 0.862 | 0.828 |
| | | 0.881 | 1.286 | 0.868 | 0.857 |
| | | 0.892 | 1.381 | 0.879 | 0.945 |
| | | 0.905 | 1.818 | 0.892 | 1.142 |
| | | 0.917 | 2.296 | 0.900 | 1.264 |
| | 10.0 | 0.888 | 1.483 | 0.871 | 0.913 |
| | | 0.924 | 1.493 | 0.907 | 0.923 |
| | | 0.927 | 1.505 | 0.914 | 1.135 |
| | | 0.933 | 1.921 | 0.920 | 1.376 |
| | | 0.941 | 2.347 | 0.921 | 1.295 |

**Table 5.15:** Equations for the best fitting lines and correlation coefficients for log tensile strength for different formulations

| Formulation Type | Binder concentration (%w/w) | Equation for the best fitting line | Correlation Coefficient |
|---|---|---|---|

| | | | |
|---|---|---|---|
| | 0.0 | $\log T = 6.234 \rho_r - 4.114$ | 0.896 |
| | | $\log T_0 = 5.234 \rho_r - 3.197$ | 0.978 |
| CPM/ENTA (WG) | 2.5 | $\log T = 5.553 \rho_r - 2.233$ | 0.994 |
| | | $\log T_0 = 4.122 \rho_r - 2.344$ | 0.997 |
| | 5.0 | $\log T = 5.543 \rho_r - 4.112$ | 0.995 |
| | | $\log T_0 = 4.416 \rho_r - 3.312$ | 0.996 |
| | 7.5 | $\log T = 4.176 \rho_r - 3.687$ | 0.998 |
| | | $\log T_0 = 4.078 \rho_r - 3.776$ | 0.994 |
| | 10.0 | $\log T = 5.674 \rho_r - 4.240$ | 0.995 |
| | | $\log T_0 = 5.443 \rho_r - 4.117$ | 0.994 |
| CPM/ENTA (DC) | 2.5 | $\log T = 4.778 \rho_r - 3.987$ | 0.996 |
| | | $\log T_0 = 4.642 \rho_r - 4.125$ | 0.989 |
| | 5.0 | $\log T = 6.014 \rho_r - 5.245$ | 0.997 |
| | | $\log T_0 = 5.467 \rho_r - 4.546$ | 0.996 |
| | 7.5 | $\log T = 3.784 \rho_r - 3.1225$ | 0.989 |
| | | $\log T_0 = 4.256 \rho_r - 3.815$ | 0.997 |
| | 10.0 | $\log T = 4.678 \rho_r - 3.867$ | 0.995 |
| | | $\log T_0 = 5.335 \rho_r - 4.946$ | 0.979 |

**Table 5.15** continued:

| Formulation Type | Binder concentration (%w/w) | Equation for the best fitting line | Correlation Coefficient |
|---|---|---|---|

| | | | |
|---|---|---|---|
| CPM/HPC (WG) | 2.5 | Log T=5.396 $\rho_r$ -5.143 | 0.996 |
| | | Log $T_0$=4.134 $\rho_r$ -3.567 | 0.989 |
| | 5.0 | Log T=3.786 $\rho_r$ -2.357 | 0.997 |
| | | Log $T_0$=4.245 $\rho_r$ -3.567 | 0.996 |
| | 7.5 | Log T=3.609 $\rho_r$ -3.112 | 0.989 |
| | | Log $T_0$=4.256 $\rho_r$ -3.678 | 0.997 |
| | 10.0 | Log T=4.907 $\rho_r$ -4.132 | 0.998 |
| | | Log $T_0$=5.112 $\rho_r$ -4.138 | 0.995 |
| | | | |
| CPM/HPC (DC) | 2.5 | Log T=4.992 $\rho_r$ -4.225 | 0.997 |
| | | Log $T_0$=5.893 $\rho_r$ -4.355 | 0.989 |
| | 5.0 | Log T=4.167 $\rho_r$ -4.056 | 0.979 |
| | | Log $T_0$=5.342 $\rho_r$ -3.564 | 0.987 |
| | 7.5 | Log T=4.361 $\rho_r$ -3.564 | 0.997 |
| | | Log $T_0$=5.134 $\rho_r$ -4.675 | 0.996 |
| | 10.0 | Log T=4.674 $\rho_r$ -4.554 | 0.998 |
| | | Log $T_0$=5.674 $\rho_r$ -5.117 | 0.995 |

**Table 5.15** continued:

| Formulation Type | Binder concentration (%w/w) | Equation for the best fitting line | Correlation Coefficient |
|---|---|---|---|

| Formulation Type | Binder concentration (%w/w) | Equation for the best fitting line | Correlation Coefficient |
|---|---|---|---|
| CPM/GEL (WG) | 2.5 | $\text{Log } T = 3.442\, \rho_r - 3.105$ | 0.997 |
| | | $\text{Log } T_0 = 2.456\, \rho_r - 2.107$ | 0.989 |
| | 5.0 | $\text{Log } T = 6.114\, \rho_r - 5.334$ | 0.986 |
| | | $\text{Log } T_0 = 5.134\, \rho_r - 4.342$ | 0.989 |
| | 7.5 | $\text{Log } T = 6.418\, \rho_r - 4.556$ | 0.993 |
| | | $\text{Log } T_0 = 5.123\, \rho_r - 4.222$ | 0.992 |
| | 10.0 | $\text{Log } T = 6.223\, \rho_r - 5.446$ | 0.989 |
| | | $\text{Log } T_0 = 5.244\, \rho_r - 4.226$ | 0.994 |
| CPM/GEL (DC) | 2.5 | $\text{Log } T = 5.456\, \rho_r - 4.123$ | 0.995 |
| | | $\text{Log } T_0 = 4.334\, \rho_r - 3.876$ | 0.979 |
| | 5.0 | $\text{Log } T = 4.224\, \rho_r - 3.515$ | 0.994 |
| | | $\text{Log } T_0 = 2.786\, \rho_r - 2.435$ | 0.991 |
| | 7.5 | $\text{Log } T = 3.445\, \rho_r - 3.165$ | 0.993 |
| | | $\text{Log } T_0 = 2.897\, \rho_r - 2.763$ | 0.997 |
| | 10.0 | $\text{Log } T = 3.335\, \rho_r - 3.145$ | 0.987 |
| | | $\text{Log } T_0 = 2.987\, \rho_r - 2.143$ | 0.996 |

**Table 5.15** continued:

| Formulation Type | Binder concentration (%w/w) | Equation for the best fitting line | Correlation Coefficient |
|---|---|---|---|

| Formulation Type | Binder concentration (%w/w) | Equation for the best fitting line | Correlation Coefficient |
|---|---|---|---|
| IBUP/ENTA (WG) | 2.5 | Log T=3.187 $\rho_r$ -2.886 | 0.989 |
| | | Log $T_0$=4.108 $\rho_r$ -3.926 | 0.995 |
| | 5.0 | Log T=5.145 $\rho_r$ -4.987 | 0.998 |
| | | Log $T_0$=2.786 $\rho_r$ -2.334 | 0.989 |
| | 7.5 | Log T=4.074 $\rho_r$ -3.867 | 0.982 |
| | | Log $T_0$=3.865 $\rho_r$ -3.176 | 0.987 |
| | 10.0 | Log T=4.563 $\rho_r$ -3.655 | 0.996 |
| | | Log $T_0$=2.345 $\rho_r$ -2.342 | 0.994 |
| IBUP/ENTA (DC) | 2.5 | Log T=3.564 $\rho_r$ -3.443 | 0.993 |
| | | Log $T_0$=2.097 $\rho_r$ -1.996 | 0.994 |
| | 5.0 | Log T=4.993 $\rho_r$ -4.654 | 0.991 |
| | | Log $T_0$=2.995 $\rho_r$ -2.674 | 0.996 |
| | 7.5 | Log T=1.997 $\rho_r$ -1.453 | 0.988 |
| | | Log $T_0$=3.908 $\rho_r$ -3.332 | 0.989 |
| | 10.0 | Log T=3.443 $\rho_r$ -3.335 | 0.992 |
| | | Log $T_0$=1.876D-1.765 | 0.986 |

**Table 5.15** continued:

| Formulation Type | Binder concentration (%w/w) | Equation for the best fitting line | Correlation Coefficient |
|---|---|---|---|

| Formulation Type | Binder concentration (%w/w) | Equation for the best fitting line | Correlation Coefficient |
|---|---|---|---|
| IBUP/HPC (WG) | 2.5 | $\text{Log T} = 4.135 \, \rho_r - 3.876$ | 0.986 |
| | | $\text{Log T}_0 = 3.225 \, \rho_r - 3.105$ | 0.996 |
| | 5.0 | $\text{Log T} = 6.829 \, \rho_r - 5.234$ | 0.989 |
| | | $\text{Log T}_0 = 5.364 \, \rho_r - 4.887$ | 0.997 |
| | 7.5 | $\text{Log T} = 5.224 \, \rho_r - 4.995$ | 0.996 |
| | | $\text{Log T}_0 = 4.335 \, \rho_r - 3.875$ | 0.987 |
| | 10.0 | $\text{Log T} = 3.886 \, \rho_r - 2.773$ | 0.989 |
| | | $\text{Log T}_0 = 2.677 \, \rho_r - 2.435$ | 0.984 |
| IBUP/HPC (DC) | 2.5 | $\text{Log T} = 4.993 \, \rho_r - 4.201$ | 0.994 |
| | | $\text{Log T}_0 = 5.132 \, \rho_r - 4.776$ | 0.989 |
| | 5.0 | $\text{Log T} = 4.967 \, \rho_r - 4.187$ | 0.991 |
| | | $\text{Log T}_0 = 3.675 \, \rho_r - 3.223$ | 0.986 |
| | 7.5 | $\text{Log T} = 2.987 \, \rho_r - 2.321$ | 0.995 |
| | | $\text{Log T}_0 = 1.894 \, \rho_r - 1.664$ | 0.989 |
| | 10.0 | $\text{Log T} = 2.876 \, \rho_r - 2.154$ | 0.988 |
| | | $\text{Log T}_0 = 3.452 \, \rho_r - 3.126$ | 0.989 |

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**Table 5.15** continued:

| Formulation Type | Binder concentration (%w/w) | Equation for the best fitting line | Correlation Coefficient |
|---|---|---|---|

| | | | |
|---|---|---|---|
| IBUP/GEL (WG) | 2.5 | $\text{Log } T = 3.328 \, \rho_r - 3.178$ | 0.995 |
| | | $\text{Log } T_0 = 2.884 \, \rho_r - 2.725$ | 0.988 |
| | 5.0 | $\text{Log } T = 2.116 \, \rho_r - 1.956$ | 0.989 |
| | | $\text{Log } T_0 = 3.225 \, \rho_r - 2.976$ | 0.993 |
| | 7.5 | $\text{Log } T = 2.996 \, \rho_r - 2.306$ | 0.996 |
| | | $\text{Log } T_0 = 2.807 \, \rho_r - 2.652$ | 0.990 |
| | 10.0 | $\text{Log } T = 4.537 \, \rho_r - 3.943$ | 0.990 |
| | | $\text{Log } T_0 = 5.103 \, \rho_r - 4.976$ | 0.997 |
| | | | |
| IBUP/GEL (DC) | 2.5 | $\text{Log } T = 5.113 \, \rho_r - 4.652$ | 0.996 |
| | | $\text{Log } T_0 = 4.332 \, \rho_r - 4.305$ | 0.989 |
| | 5.0 | $\text{Log } T = 3.994 \, \rho_r - 3.632$ | 0.995 |
| | | $\text{Log } T_0 = 4.821 \, \rho_r - 3.823$ | 0.985 |
| | 7.5 | $\text{Log } T = 3.512 \, \rho_r - 2.876$ | 0.995 |
| | | $\text{Log } T_0 = 2.877 \, \rho_r - 2.674$ | 0.991 |
| | 10.0 | $\text{Log } T = 5.653 \, \rho_r - 5.227$ | 0.995 |
| | | $\text{Log } T_0 = 4.987 \, \rho_r - 4.543$ | 0.979 |
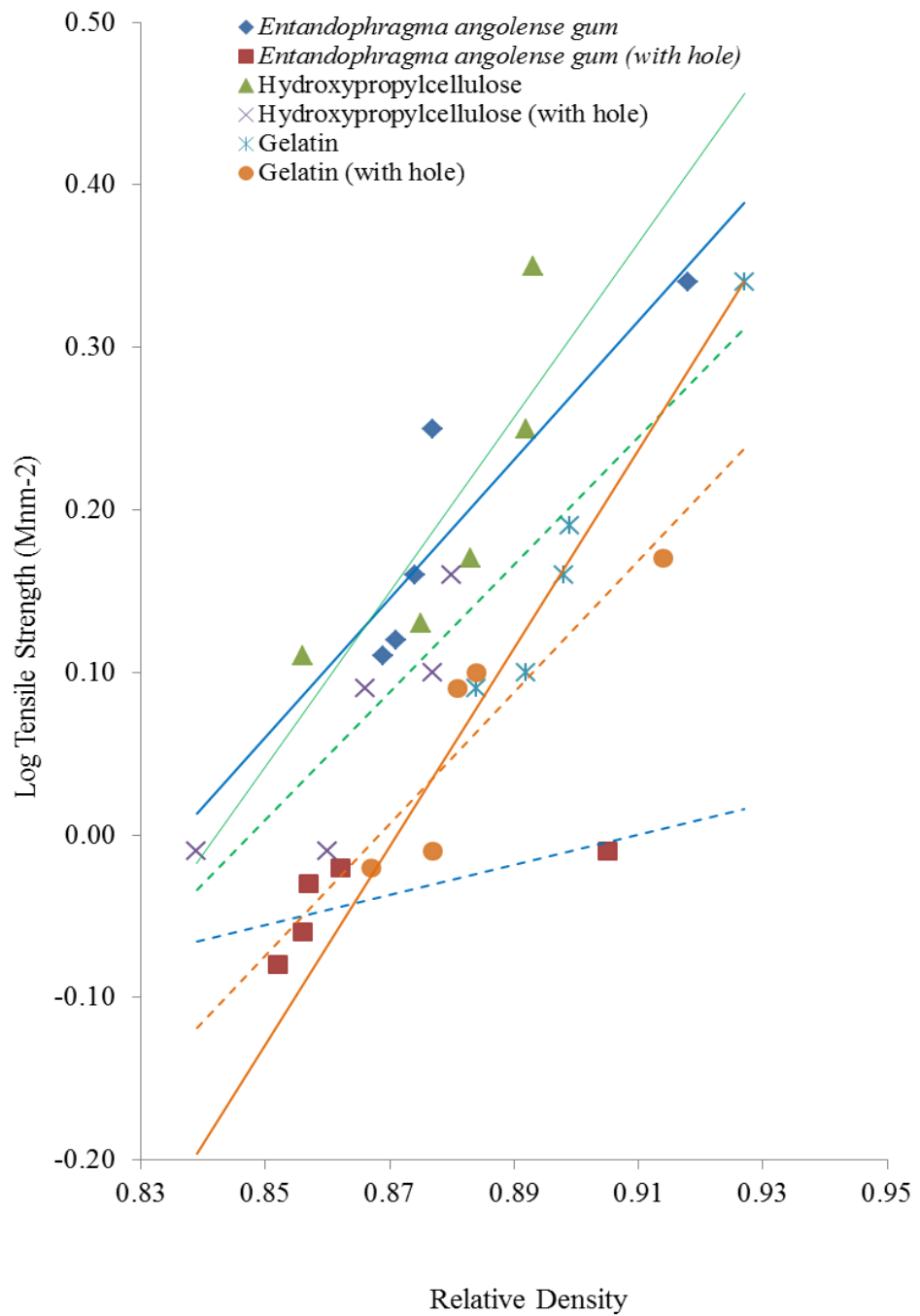
**Fig 5.10**: Log Tensile Strength versus relative density for chlorpheniramine maleate tablets containing 5 %w/w binder formulated by wet granulation

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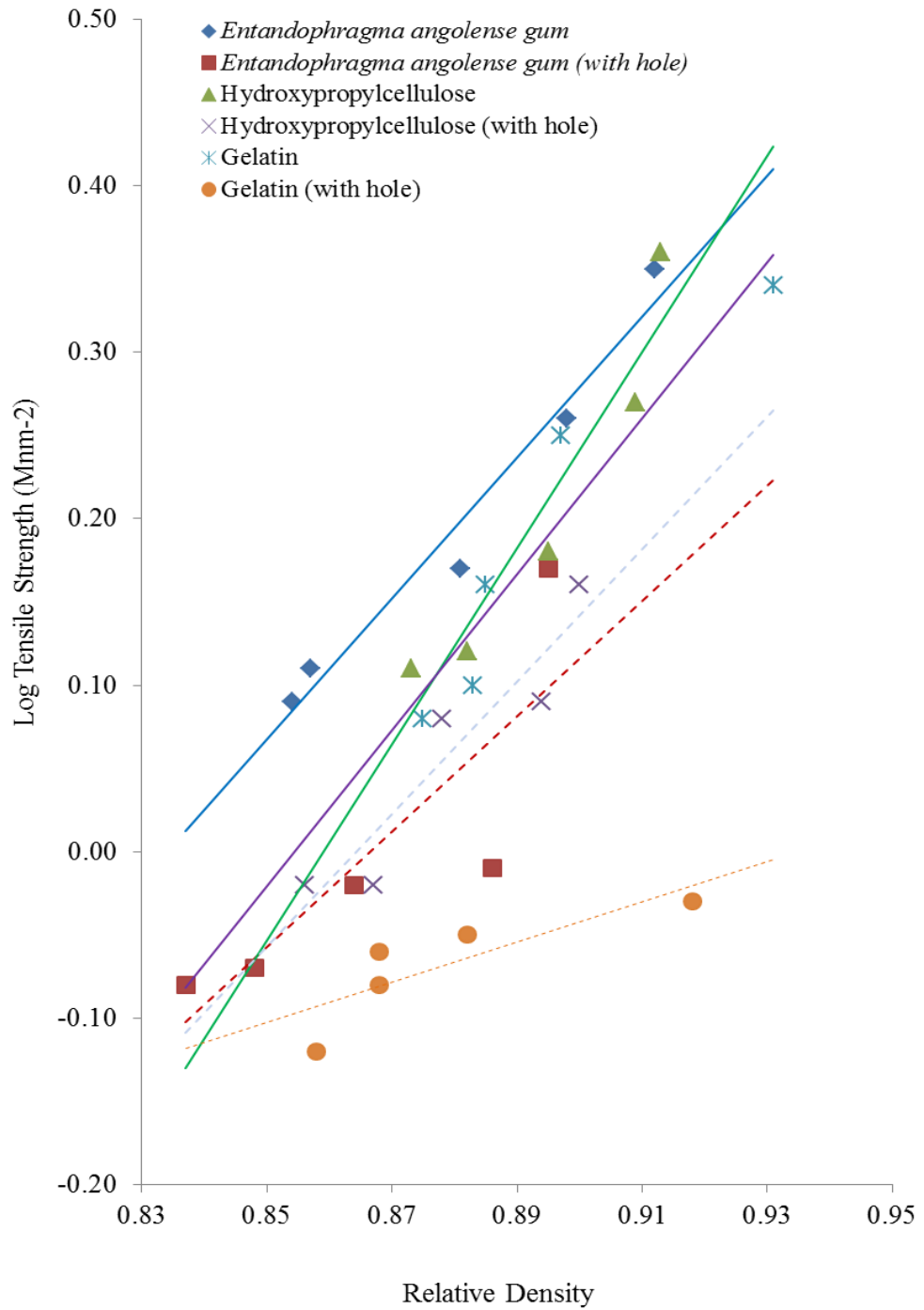
**Fig 5.11**: Log Tensile Strength versus relative density for Ibuprofen tablets containing 5 %w/w binder formulated by direct compression

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As mentioned earlier on, Odeku and Itiola (1998) established that $P_k$ provides a measure of the total amount of plastic deformation occurring during compression. Formulations containing *Entandophragma angolense* gum and hydroxypropylcellulose which had lower $P_k$ values than those containing gelatin showed higher mechanical strength as indicated by higher T values, thus further supporting this assertion.

## 5.4.2 Brittle Fracture Index

The Brittle Fracture Index (BFI) for the different formulations of Chlorpheniramine maleate and Ibuprofen are presented in Table 4.16. The BFI values for the formulation increased generally with increase in relative density. This suggests that the brittle properties of the materials were accentuated at high relative densities where harder tablets were formed. Tablets that were formulated by wet granulation produced harder tablets and this is probably responsible for higher BFI values than directly compressed tablets. Representative plots of BFI versus relative density are presented in Figs 4.12 and 4.13. Values of T, $T_0$, and BFI at relative density of 0.90, which is representative of commercial tablets, are presented in Table 4.17. Tablets containing *Entandophragma angolense* gum as binder had lowerr BFI values than those containing hydroxypropylcellulose as binder, thus indicating that Hydroxypropylcellulose would reduce capping tendencies in tablets more than *Entandophragma angolense* gum.

**Table 5.16:** Values of Brittle Fracture Index (BFI) for different formulations

| Formulation type | Binder concentration (%w/w) | Relative Density ($\rho_r$) | BFI |
|---|---|---|---|
| CPM/ENTA  (WG) | 2.5 | 0.825 | 0.109 |
| | | 0.850 | 0.118 |
| | | 0.875 | 0.159 |
| | | 0.900 | 0.169 |
| | | 0.925 | 0.231 |
| | | 0.950 | 0.247 |
| | | 0.975 | 0.263 |
| | 5.0 | 0.825 | 0.116 |
| | | 0.850 | 0.122 |
| | | 0.875 | 0.181 |
| | | 0.900 | 0.217 |
| | | 0.925 | 0.258 |
| | | 0.950 | 0.269 |
| | | 0.975 | 0.286 |
| | 7.5 | 0.825 | 0.143 |
| | | 0.850 | 0.176 |
| | | 0.875 | 0.236 |
| | | 0.900 | 0.243 |
| | | 0.925 | 0.268 |
| | | 0.950 | 0.293 |
| | | 0.975 | 0.318 |
| | 10.0 | 0.825 | 0.204 |
| | | 0.850 | 0.219 |
| | | 0.875 | 0.261 |
| | | 0.900 | 0.277 |
| | | 0.925 | 0.317 |
| | | 0.950 | 0.329 |
| | | 0.975 | 0.331 |

**Table 5.16** continued:

| Formulation type | Binder concentration (%w/w) | Relative Density ($\rho_r$) | BFI |
|---|---|---|---|
| CPM/ENTA (DC) | 2.5 | 0.825 | 0.102 |
| | | 0.850 | 0.109 |
| | | 0.875 | 0.148 |
| | | 0.900 | 0.158 |
| | | 0.925 | 0.222 |
| | | 0.950 | 0.238 |
| | | 0.975 | 0.254 |
| | 5.0 | 0.825 | 0.107 |
| | | 0.850 | 0.113 |
| | | 0.875 | 0.172 |
| | | 0.900 | 0.208 |
| | | 0.925 | 0.247 |
| | | 0.950 | 0.262 |
| | | 0.975 | 0.279 |
| | 7.5 | 0.825 | 0.136 |
| | | 0.850 | 0.169 |
| | | 0.875 | 0.229 |
| | | 0.900 | 0.236 |
| | | 0.925 | 0.261 |
| | | 0.950 | 0.286 |
| | | 0.975 | 0.311 |
| | 10.0 | 0.825 | 0.193 |
| | | 0.850 | 0.217 |
| | | 0.875 | 0.252 |
| | | 0.900 | 0.268 |
| | | 0.925 | 0.308 |
| | | 0.950 | 0.318 |
| | | 0.975 | 0.326 |

**Table 5.16** continued:

| Formulation type | Binder concentration (% w/w) | Relative Density ($\rho_r$) | BFI |
|---|---|---|---|
| CPM/GEL (WG) | 2.5 | 0.825 | 0.124 |
| | | 0.850 | 0.131 |
| | | 0.875 | 0.172 |
| | | 0.900 | 0.182 |
| | | 0.925 | 0.244 |
| | | 0.950 | 0.260 |
| | | 0.975 | 0.276 |
| | 5.0 | 0.825 | 0.131 |
| | | 0.850 | 0.137 |
| | | 0.875 | 0.196 |
| | | 0.900 | 0.232 |
| | | 0.925 | 0.273 |
| | | 0.950 | 0.284 |
| | | 0.975 | 0.301 |
| | 7.5 | 0.825 | 0.158 |
| | | 0.850 | 0.191 |
| | | 0.875 | 0.251 |
| | | 0.900 | 0.258 |
| | | 0.925 | 0.283 |
| | | 0.950 | 0.306 |
| | | 0.975 | 0.331 |
| | 10.0 | 0.825 | 0.217 |
| | | 0.850 | 0.232 |
| | | 0.875 | 0.274 |
| | | 0.900 | 0.290 |
| | | 0.925 | 0.330 |
| | | 0.950 | 0.342 |
| | | 0.975 | 0.344 |

**Table 5.16** continued:

| Formulation type | Binder concentration (%w/w) | Relative Density ($\rho_r$) | BFI |
|---|---|---|---|
| CPM/ GEL (DC) | 2.5 | 0.825 | 0.117 |
| | | 0.850 | 0.122 |
| | | 0.875 | 0.163 |
| | | 0.900 | 0.173 |
| | | 0.925 | 0.235 |
| | | 0.950 | 0.251 |
| | | 0.975 | 0.267 |
| | 5.0 | 0.825 | 0.122 |
| | | 0.850 | 0.130 |
| | | 0.875 | 0.189 |
| | | 0.900 | 0.225 |
| | | 0.925 | 0.266 |
| | | 0.950 | 0.277 |
| | | 0.975 | 0.294 |
| | 7.5 | 0.825 | 0.151 |
| | | 0.850 | 0.184 |
| | | 0.875 | 0.244 |
| | | 0.900 | 0.251 |
| | | 0.925 | 0.276 |
| | | 0.950 | 0.297 |
| | | 0.975 | 0.322 |
| | 10.0 | 0.825 | 0.208 |
| | | 0.850 | 0.223 |
| | | 0.875 | 0.265 |
| | | 0.900 | 0.281 |
| | | 0.925 | 0.321 |
| | | 0.950 | 0.333 |
| | | 0.975 | 0.335 |

**Table 5.16** continued:

| Formulation type | Binder concentration (%w/w) | Relative Density ($\rho_r$) | BFI |
|---|---|---|---|
| CPM/HPC (WG) | 2.5 | 0.825 | 0.091 |
| | | 0.850 | 0.106 |
| | | 0.875 | 0.141 |
| | | 0.900 | 0.165 |
| | | 0.925 | 0.189 |
| | | 0.950 | 0.214 |
| | | 0.975 | 0.228 |
| | 5.0 | 0.825 | 0.112 |
| | | 0.850 | 0.119 |
| | | 0.875 | 0.168 |
| | | 0.900 | 0.198 |
| | | 0.925 | 0.221 |
| | | 0.950 | 0.239 |
| | | 0.975 | 0.249 |
| | 7.5 | 0.825 | 0.121 |
| | | 0.850 | 0.153 |
| | | 0.875 | 0.204 |
| | | 0.900 | 0.215 |
| | | 0.925 | 0.231 |
| | | 0.950 | 0.242 |
| | | 0.975 | 0.264 |
| | 10.0 | 0.825 | 0.188 |
| | | 0.850 | 0.197 |
| | | 0.875 | 0.242 |
| | | 0.900 | 0.253 |
| | | 0.925 | 0.297 |
| | | 0.950 | 0.321 |
| | | 0.975 | 0.324 |

**Table 5.16** continued:

| Formulation type | Binder concentration (%w/w) | Relative Density ($\rho_r$) | BFI |
|---|---|---|---|
| CPM/ HPC (DC) | 2.5 | 0.825 | 0.084 |
| | | 0.850 | 0.097 |
| | | 0.875 | 0.130 |
| | | 0.900 | 0.154 |
| | | 0.925 | 0.180 |
| | | 0.950 | 0.205 |
| | | 0.975 | 0.219 |
| | 5.0 | 0.825 | 0.103 |
| | | 0.850 | 0.110 |
| | | 0.875 | 0.159 |
| | | 0.900 | 0.189 |
| | | 0.925 | 0.210 |
| | | 0.950 | 0.232 |
| | | 0.975 | 0.242 |
| | 7.5 | 0.825 | 0.114 |
| | | 0.850 | 0.146 |
| | | 0.875 | 0.197 |
| | | 0.900 | 0.208 |
| | | 0.925 | 0.224 |
| | | 0.950 | 0.235 |
| | | 0.975 | 0.257 |
| | 10.0 | 0.825 | 0.177 |
| | | 0.850 | 0.188 |
| | | 0.875 | 0.233 |
| | | 0.900 | 0.244 |
| | | 0.925 | 0.288 |
| | | 0.950 | 0.310 |
| | | 0.975 | 0.313 |

**Table 5.16** continued:

| Formulation type | Binder concentration (%w/w) | Relative Density ( $\rho_r$ ) | BFI |
|---|---|---|---|
| IBUP/ENTA  (WG) | 2.5 | 0.825 | 0.127 |
| | | 0.850 | 0.134 |
| | | 0.875 | 0.142 |
| | | 0.900 | 0.173 |
| | | 0.925 | 0.181 |
| | | 0.950 | 0.189 |
| | | 0.975 | 0.193 |
| | 5.0 | 0.825 | 0.149 |
| | | 0.850 | 0.174 |
| | | 0.875 | 0.233 |
| | | 0.900 | 0.241 |
| | | 0.925 | 0.261 |
| | | 0.950 | 0.277 |
| | | 0.975 | 0.315 |
| | 7.5 | 0.825 | 0.151 |
| | | 0.850 | 0.183 |
| | | 0.875 | 0.242 |
| | | 0.900 | 0.262 |
| | | 0.925 | 0.273 |
| | | 0.950 | 0.298 |
| | | 0.975 | 0.347 |
| | 10.0 | 0.825 | 0.198 |
| | | 0.850 | 0.213 |
| | | 0.875 | 0.256 |
| | | 0.900 | 0.271 |
| | | 0.925 | 0.299 |
| | | 0.950 | 0.321 |
| | | 0.975 | 0.363 |

**Table 5.16** continued:

| Formulation Type | Binder Concentration (%w/w) | Relative Density ($\rho_r$) | BFI |
|---|---|---|---|
| IBUP /ENTA (DC) | 2.5 | 0.825 | 0.120 |
| | | 0.850 | 0.125 |
| | | 0.875 | 0.133 |
| | | 0.900 | 0.164 |
| | | 0.925 | 0.172 |
| | | 0.950 | 0.180 |
| | | 0.975 | 0.184 |
| | 5.0 | 0.825 | 0.140 |
| | | 0.850 | 0.167 |
| | | 0.875 | 0.226 |
| | | 0.900 | 0.234 |
| | | 0.925 | 0.254 |
| | | 0.950 | 0.270 |
| | | 0.975 | 0.308 |
| | 7.5 | 0.825 | 0.144 |
| | | 0.850 | 0.176 |
| | | 0.875 | 0.235 |
| | | 0.900 | 0.255 |
| | | 0.925 | 0.266 |
| | | 0.950 | 0.289 |
| | | 0.975 | 0.338 |
| | 10.0 | 0.825 | 0.189 |
| | | 0.850 | 0.204 |
| | | 0.875 | 0.247 |
| | | 0.900 | 0.262 |
| | | 0.925 | 0.290 |
| | | 0.950 | 0.312 |
| | | 0.975 | 0.354 |

**Table 5.16** continued:

| Formulation Type | Binder Concentration (%w/w) | Relative Density ($\rho_r$) | BFI |
|---|---|---|---|
| IBUP/HPC (WG) | 2.5 | 0.825 | 0.142 |
| | | 0.850 | 0.147 |
| | | 0.875 | 0.155 |
| | | 0.900 | 0.186 |
| | | 0.925 | 0.194 |
| | | 0.950 | 0.202 |
| | | 0.975 | 0.206 |
| | 5.0 | 0.825 | 0.164 |
| | | 0.850 | 0.189 |
| | | 0.875 | 0.248 |
| | | 0.900 | 0.256 |
| | | 0.925 | 0.276 |
| | | 0.950 | 0.292 |
| | | 0.975 | 0.330 |
| | 7.5 | 0.825 | 0.166 |
| | | 0.850 | 0.198 |
| | | 0.875 | 0.257 |
| | | 0.900 | 0.277 |
| | | 0.925 | 0.288 |
| | | 0.950 | 0.311 |
| | | 0.975 | 0.360 |
| | 10.0 | 0.825 | 0.211 |
| | | 0.850 | 0.226 |
| | | 0.875 | 0.269 |
| | | 0.900 | 0.284 |
| | | 0.925 | 0.312 |
| | | 0.950 | 0.334 |
| | | 0.975 | 0.376 |

**Table 5.16** continued:

| Formulation Type | Binder Concentration (%w/w) | Relative Density ($\rho_r$) | BFI |
|---|---|---|---|
| IBUP/HPC (DC) | 2.5 | 0.825 | 0.135 |
| | | 0.850 | 0.138 |
| | | 0.875 | 0.146 |
| | | 0.900 | 0.177 |
| | | 0.925 | 0.185 |
| | | 0.950 | 0.193 |
| | | 0.975 | 0.197 |
| | 5.0 | 0.825 | 0.155 |
| | | 0.850 | 0.182 |
| | | 0.875 | 0.241 |
| | | 0.900 | 0.249 |
| | | 0.925 | 0.269 |
| | | 0.950 | 0.285 |
| | | 0.975 | 0.323 |
| | 7.5 | 0.825 | 0.159 |
| | | 0.850 | 0.191 |
| | | 0.875 | 0.250 |
| | | 0.900 | 0.270 |
| | | 0.925 | 0.281 |
| | | 0.950 | 0.302 |
| | | 0.975 | 0.351 |
| | 10.0 | 0.825 | 0.202 |
| | | 0.850 | 0.217 |
| | | 0.875 | 0.260 |
| | | 0.900 | 0.275 |
| | | 0.925 | 0.303 |
| | | 0.950 | 0.325 |
| | | 0.975 | 0.367 |

**Table 5.16** continued:

| Formulation Type | Binder Concentration (%w/w) | Relative Density ($\rho_r$) | BFI |
|---|---|---|---|
| IBUP/HPC (WG) | 2.5 | 0.825 | 0.097 |
| | | 0.850 | 0.121 |
| | | 0.875 | 0.151 |
| | | 0.900 | 0.153 |
| | | 0.925 | 0.187 |
| | | 0.950 | 0.196 |
| | | 0.975 | 0.294 |
| | 5.0 | 0.825 | 0.161 |
| | | 0.850 | 0.168 |
| | | 0.875 | 0.173 |
| | | 0.900 | 0.174 |
| | | 0.925 | 0.207 |
| | | 0.950 | 0.239 |
| | | 0.975 | 0.303 |
| | 7.5 | 0.825 | 0.169 |
| | | 0.850 | 0.171 |
| | | 0.875 | 0.209 |
| | | 0.900 | 0.214 |
| | | 0.925 | 0.221 |
| | | 0.950 | 0.241 |
| | | 0.975 | 0.317 |
| | 10.0 | 0.825 | 0.176 |
| | | 0.850 | 0.181 |
| | | 0.875 | 0.221 |
| | | 0.900 | 0.228 |
| | | 0.925 | 0.231 |
| | | 0.950 | 0.249 |
| | | 0.975 | 0.312 |

**Table 5.16** continued:

| Formulation Type | Binder Concentration (%w/w) | Relative Density ($\rho_r$) | BFI |
|---|---|---|---|
| IBUP/HPC (DC) | 2.5 | 0.825 | 0.090 |
| | | 0.850 | 0.112 |
| | | 0.875 | 0.140 |
| | | 0.900 | 0.142 |
| | | 0.925 | 0.178 |
| | | 0.950 | 0.187 |
| | | 0.975 | 0.285 |
| | 5.0 | 0.825 | 0.152 |
| | | 0.850 | 0.159 |
| | | 0.875 | 0.164 |
| | | 0.900 | 0.165 |
| | | 0.925 | 0.196 |
| | | 0.950 | 0.232 |
| | | 0.975 | 0.296 |
| | 7.5 | 0.825 | 0.162 |
| | | 0.850 | 0.164 |
| | | 0.875 | 0.202 |
| | | 0.900 | 0.207 |
| | | 0.925 | 0.214 |
| | | 0.950 | 0.234 |
| | | 0.975 | 0.310 |
| | 10.0 | 0.825 | 0.165 |
| | | 0.850 | 0.172 |
| | | 0.875 | 0.212 |
| | | 0.900 | 0.219 |
| | | 0.925 | 0.222 |
| | | 0.950 | 0.238 |
| | | 0.975 | 0.301 |
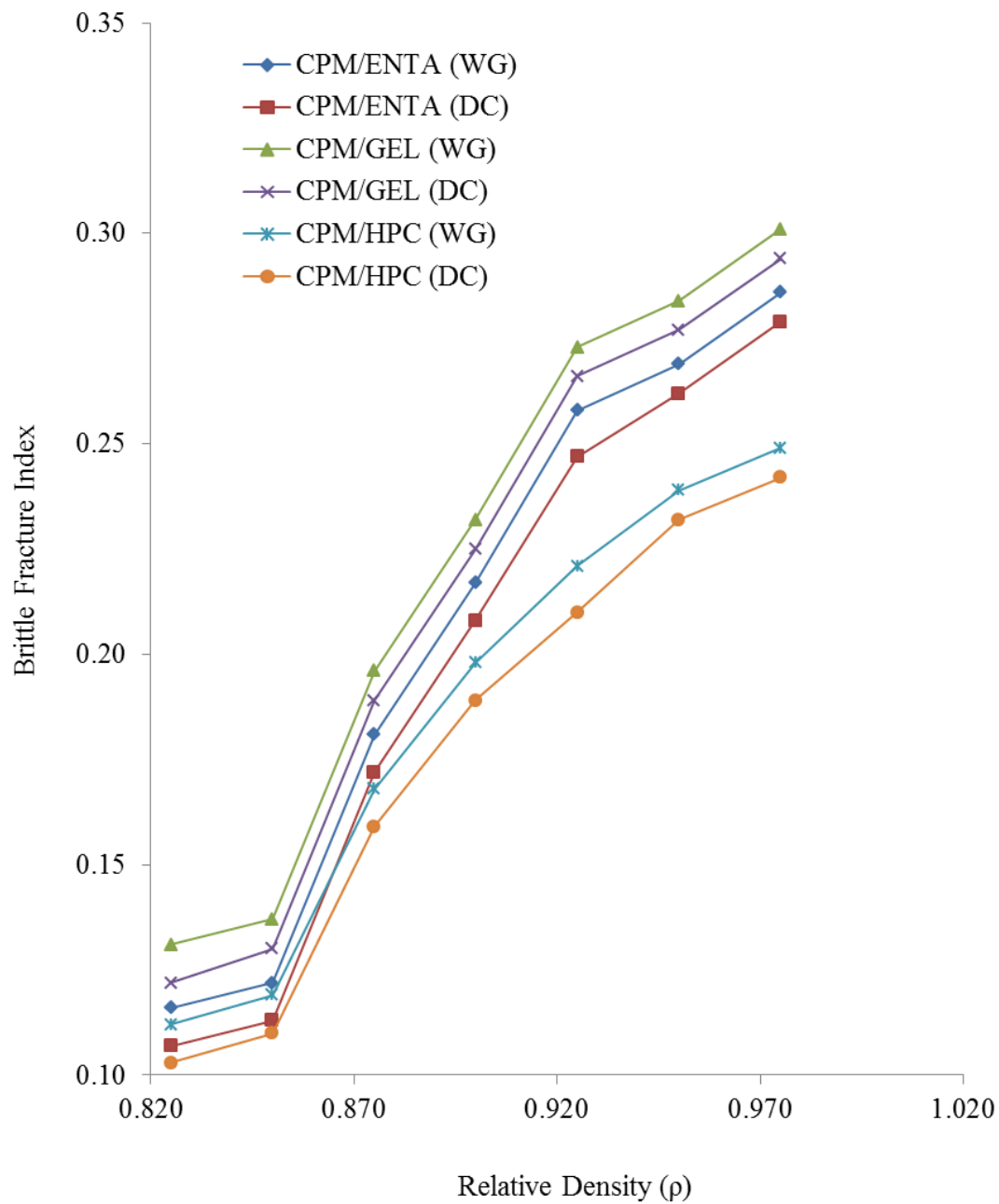
**Fig 5.12:** Plot of Brittle Fracture Index versus Relative Density for chlorpheniramine maleate tablets containing 5.0%w/w polymer as binder
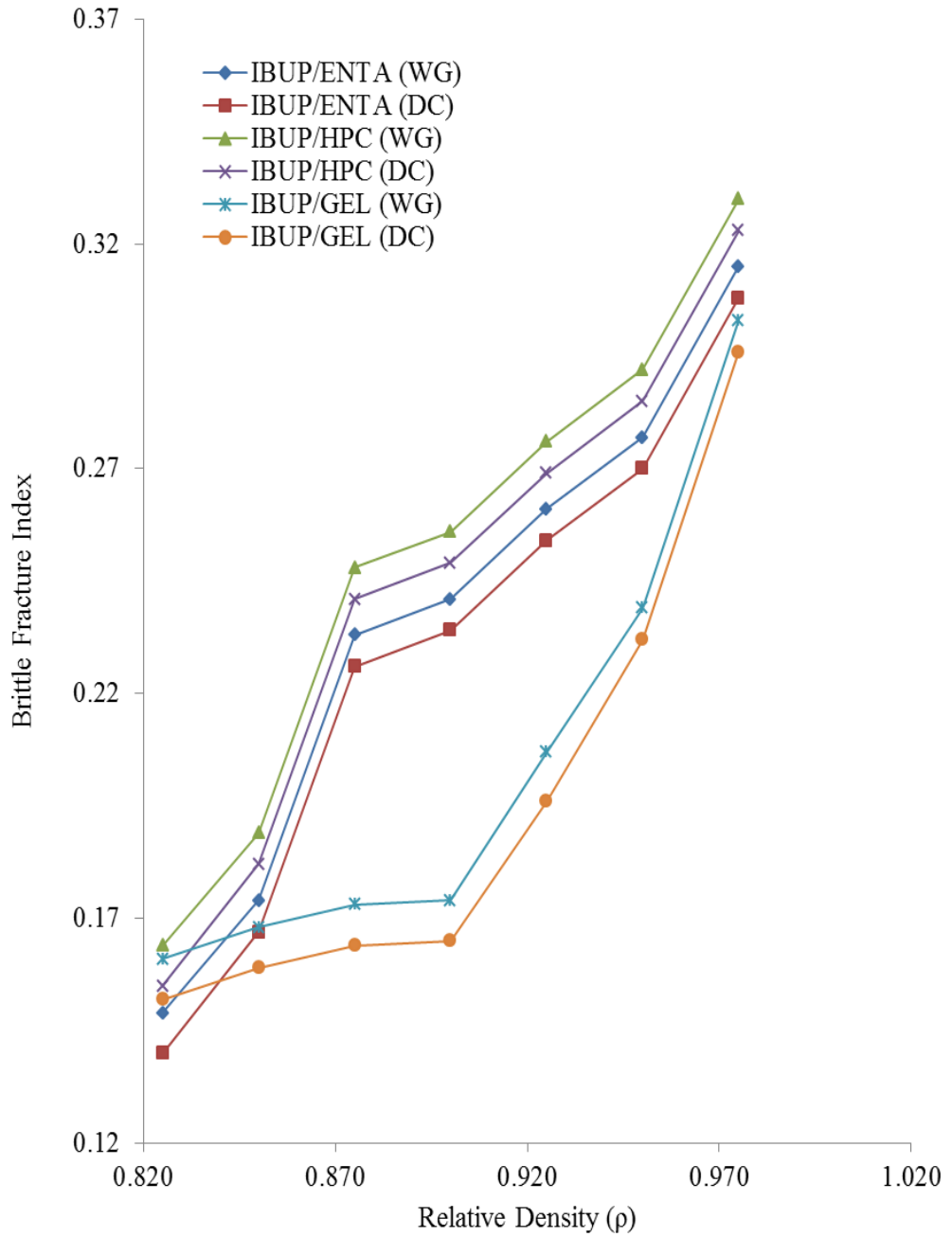
**Fig 5.13:** Plot of Brittle Fracture Index versus Relative Density for ibuprofen tablets containing 5.0%w/w polymer as binder

**Table 5.17:** Tensile Strength (MNm$^{-2}$) and Brittle Fracture Index (BFI) values for different formulations at relative density, $\rho_r = 0.90$

| Formulation | Binder Concentration (%w/w) | T (MNm$^{-2}$) | T$_0$ (MNm$^{-2}$) | BFI |
|---|---|---|---|---|
| CPM/ENTA (WG) | 2.5 | 2.155 | 1.792 | 0.169 |
| | 5.0 | 2.211 | 1.803 | 0.217 |
| | 7.5 | 2.248 | 1.812 | 0.243 |
| | 10.0 | 2.257 | 1.842 | 0.277 |
| CPM/ENTA (DC) | 2.5 | 1.817 | 0.899 | 0.158 |
| | 5.0 | 1.871 | 1.128 | 0.208 |
| | 7.5 | 1.879 | 1.134 | 0.236 |
| | 10.0 | 1.883 | 1.137 | 0.268 |
| CPM/GEL (WG) | 2.5 | 1.783 | 1.103 | 0.182 |
| | 5.0 | 1.851 | 1.453 | 0.232 |
| | 7.5 | 1.860 | 1.461 | 0.258 |
| | 10.0 | 1.642 | 1.336 | 0.290 |
| CPM/GEL (DC) | 2.5 | 2.102 | 1.127 | 0.173 |
| | 5.0 | 2.176 | 1.206 | 0.225 |
| | 7.5 | 2.213 | 1.218 | 0.251 |
| | 10.0 | 2.247 | 1.239 | 0.281 |
| CPM/HPC (WG) | 2.5 | 2.092 | 0.912 | 0.165 |
| | 5.0 | 2.128 | 0.929 | 0.198 |
| | 7.5 | 1.376 | 1.021 | 0.215 |
| | 10.0 | 1.452 | 1.123 | 0.253 |
| CPM/HPC (DC) | 2.5 | 1.788 | 0.908 | 0.154 |
| | 5.0 | 2.128 | 1.093 | 0.189 |
| | 7.5 | 2.132 | 1.103 | 0.208 |
| | 10.0 | 2.427 | 1.117 | 0.244 |

**Table 5.17** continued:

| Formulation | Binder Concentration (%w/w) | T (MNm$^{-2}$) | T$_0$ (MNm$^{-2}$) | BFI |
|---|---|---|---|---|
| IBUP/ENTA (WG) | 2.5 | 1.993 | 1.598 | 0.173 |
|  | 5.0 | 2.126 | 1.601 | 0.241 |
|  | 7.5 | 2.197 | 1.607 | 0.262 |
|  | 10.0 | 2.221 | 1.120 | 0.271 |
| IBUP/ENTA (DC) | 2.5 | 2.186 | 0.974 | 0.164 |
|  | 5.0 | 2.195 | 0.983 | 0.234 |
|  | 7.5 | 1.501 | 0.987 | 0.255 |
|  | 10.0 | 1.527 | 1.579 | 0.262 |
| IBUP/GEL (WG) | 2.5 | 2.229 | 1.153 | 0.186 |
|  | 5.0 | 2.371 | 1.489 | 0.256 |
|  | 7.5 | 2.543 | 1.528 | 0.277 |
|  | 10.0 | 2.551 | 1.011 | 0.284 |
| IBUP/GEL (DC) | 2.5 | 2.124 | 1.165 | 0.177 |
|  | 5.0 | 2.277 | 1.471 | 0.249 |
|  | 7.5 | 2.301 | 1.481 | 0.270 |
|  | 10.0 | 2.413 | 1.490 | 0.275 |
| IBUP/HPC (WG) | 2.5 | 1.886 | 1.356 | 0.153 |
|  | 5.0 | 2.003 | 1.450 | 0.174 |
|  | 7.5 | 1.916 | 1.462 | 0.214 |
|  | 10.0 | 1.822 | 1.017 | 0.228 |
| IBUP/HPC (DC) | 2.5 | 2.147 | 0.832 | 0.142 |
|  | 5.0 | 2.167 | 0.952 | 0.165 |
|  | 7.5 | 2.170 | 1.264 | 0.207 |
|  | 10.0 | 2.335 | 1.332 | 0.219 |

### 5.4.3 Friability

Friability tests are used to determine the extent to which tablets can withstand mechanical stress when subjected to various abrasive motions during production and subsequent use. The values of friability are presented in Table 5.18. Representative plots of friability versus relative density for tablets containing 5 %w/w of the polymers as binders are shown in Fig 5.14. The friability decreased with an increase in relative density and concentration of the binders. The ranking for friability was Hydroxypropylcellulose < *Entandophragma angolense* < Gelatin. The friability values of the tablets at a relative density of 0.90, which is representative of commercial tablets, are shown in Table 5.19. Conventional compressed tablets that lose less than 1% of their weight during the friability test are generally considered acceptable (Itiola, 1994). Directly compressed tablets were more friable than tablets formulated by wet granulation technique. Also, ibuprofen tablets had higher tensile strength and lower percentage friability values than chlorpheniramine maleate tablets.

**Table 5.18:** Values of Friability (%) for chlorpheniramine maleate and Ibuprofen tablets at different relative densities

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | % Friability |
|---|---|---|---|
| CPM/ENTA (WG) | 2.5 | 0.822 | 2.43±0.02 |
| | | 0.847 | 2.36±0.02 |
| | | 0.872 | 2.47±0.03 |
| | | 0.897 | 2.41±0.06 |
| | | 0.922 | 2.32±0.05 |
| | | 0.947 | 2.22±0.04 |
| | | 0.972 | 2.76±0.02 |
| | 5.0 | 0.823 | 2.13±0.01 |
| | | 0.849 | 2.18±0.03 |
| | | 0.871 | 2.33±0.01 |
| | | 0.886 | 2.11±0.01 |
| | | 0.951 | 2.09±0.03 |
| | | 0.966 | 2.13±0.05 |
| | | 0.979 | 2.22±0.02 |
| | 7.5 | 0.833 | 1.83±0.09 |
| | | 0.858 | 1.76±0.03 |
| | | 0.883 | 1.83±0.05 |
| | | 0.908 | 1.88±0.04 |
| | | 0.933 | 1.22±0.04 |
| | | 0.958 | 1.05±0.05 |
| | | 0.983 | 1.12±0.03 |
| | 10.0 | 0.828 | 0.67±0.02 |
| | | 0.853 | 0.76±0.04 |
| | | 0.878 | 0.73±0.05 |
| | | 0.933 | 0.64±0.05 |
| | | 0.938 | 0.53±0.04 |
| | | 0.963 | 0.44±0.11 |
| | | 0.988 | 0.43±0.07 |

**Table 5.18** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | % Friability |
|---|---|---|---|
| CPM/ENTA (DC) | 2.5 | 0.816 | 2.82±0.11 |
| | | 0.841 | 2.78±0.05 |
| | | 0.866 | 2.86±0.06 |
| | | 0.891 | 2.88±0.06 |
| | | 0.916 | 2.76±0.12 |
| | | 0.941 | 2.75±0.07 |
| | | 0.966 | 2.86±0.03 |
| | 5.0 | 0.817 | 2.23±0.02 |
| | | 0.843 | 2.25±0.02 |
| | | 0.865 | 2.18±0.03 |
| | | 0.880 | 2.19±0.07 |
| | | 0.945 | 2.16±0.02 |
| | | 0.960 | 1.99±0.02 |
| | | 0.973 | 2.03±0.05 |
| | 7.5 | 0.827 | 1.23±0.04 |
| | | 0.852 | 1.14±0.03 |
| | | 0.877 | 1.35±0.04 |
| | | 0.902 | 1.22±0.02 |
| | | 0.927 | 1.35±0.02 |
| | | 0.952 | 1.21±0.01 |
| | | 0.977 | 1.16±0.02 |
| | 10.0 | 0.822 | 1.01±0.05 |
| | | 0.847 | 0.98±0.03 |
| | | 0.872 | 0.87±0.03 |
| | | 0.927 | 1.00±0.02 |
| | | 0.932 | 0.87±0.02 |
| | | 0.957 | 0.93±0.04 |
| | | 0.982 | 0.86±0.05 |

**Table 5.18** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | % Friability |
|---|---|---|---|
| CPM/HPC (WG) | 2.5 | 0.829 | 1.87±0.02 |
| | | 0.854 | 1.86±0.02 |
| | | 0.879 | 1.76±0.04 |
| | | 0.904 | 1.65±0.02 |
| | | 0.929 | 1.74±0.02 |
| | | 0.954 | 1.86±0.03 |
| | | 0.979 | 1.23±0.03 |
| | 5.0 | 0.830 | 1.22±0.04 |
| | | 0.856 | 1.24±0.04 |
| | | 0.878 | 1.22±0.02 |
| | | 0.893 | 1.24±0.04 |
| | | 0.958 | 1.25±0.01 |
| | | 0.973 | 1.18±0.02 |
| | | 0.986 | 1.13±0.03 |
| | 7.5 | 0.840 | 1.15±0.02 |
| | | 0.865 | 1.05±0.02 |
| | | 0.890 | 1.05±0.03 |
| | | 0.915 | 0.92±0.04 |
| | | 0.940 | 0.87±0.02 |
| | | 0.965 | 0.65±0.03 |
| | | 0.990 | 0.87±0.02 |
| | 10.0 | 0.835 | 0.78±0.02 |
| | | 0.860 | 0.64±0.03 |
| | | 0.885 | 0.61±0.04 |
| | | 0.940 | 0.53±0.02 |
| | | 0.945 | 0.49±0.02 |
| | | 0.970 | 0.49±0.01 |
| | | 0.995 | 0.43±0.01 |

**Table 5.18** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Friability (%) |
|---|---|---|---|
| CPM/HPC (DC) | 2.5 | 0.824 | 1.95±0.01 |
| | | 0.849 | 1.95±0.02 |
| | | 0.874 | 1.94±0.02 |
| | | 0.899 | 1.86±0.02 |
| | | 0.924 | 1.84±0.01 |
| | | 0.949 | 1.86±0.03 |
| | | 0.974 | 1.77±0.04 |
| | 5.0 | 0.825 | 1.65±0.02 |
| | | 0.851 | 1.61±0.03 |
| | | 0.873 | 1.62±0.02 |
| | | 0.888 | 1.64±0.04 |
| | | 0.953 | 1.65±0.05 |
| | | 0.968 | 1.78±0.04 |
| | | 0.981 | 1.83±0.04 |
| | 7.5 | 0.835 | 1.45±0.05 |
| | | 0.860 | 1.23±0.02 |
| | | 0.885 | 1.32±0.02 |
| | | 0.910 | 1.04±0.03 |
| | | 0.935 | 1.11±0.02 |
| | | 0.960 | 0.97±0.04 |
| | | 0.985 | 0.94±0.02 |
| | 10.0 | 0.830 | 0.65±0.02 |
| | | 0.855 | 0.56±0.03 |
| | | 0.880 | 0.81±0.02 |
| | | 0.935 | 0.85±0.04 |
| | | 0.940 | 0.69±0.02 |
| | | 0.965 | 0.67±0.02 |
| | | 0.990 | 0.68±0.02 |

**Table 5.18** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Friability (%) |
|---|---|---|---|
| CPM/GEL (WG) | 2.5 | 0.804 | 2.68±0.02 |
| | | 0.829 | 2.61±0.03 |
| | | 0.854 | 2.67±0.02 |
| | | 0.879 | 2.59±0.02 |
| | | 0.904 | 2.48±0.03 |
| | | 0.929 | 2.42±0.03 |
| | | 0.954 | 2.53±0.04 |
| | 5.0 | 0.805 | 2.23±0.03 |
| | | 0.831 | 2.26±0.06 |
| | | 0.853 | 2.46±0.06 |
| | | 0.868 | 2.31±0.02. |
| | | 0.933 | 2.32±0.04 |
| | | 0.948 | 2.48±0.04 |
| | | 0.961 | 2.41±0.02 |
| | 7.5 | 0.815 | 1.93±0.03 |
| | | 0.840 | 1.74±0.03 |
| | | 0.865 | 1.75±0.06 |
| | | 0.890 | 1.81±0.03 |
| | | 0.915 | 1.63±0.02 |
| | | 0.940 | 1.16±0.01 |
| | | 0.965 | 1.19±0.04 |
| | 10.0 | 0.810 | 1.09±0.05 |
| | | 0.835 | 0.87±0.03 |
| | | 0.860 | 0.88±0.02 |
| | | 0.915 | 0.75±0.04 |
| | | 0.920 | 0.67±0.04 |
| | | 0.945 | 0.66±0.03 |
| | | 0.970 | 0.66±0.02 |

**Table 5.18** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Friability (%) |
|---|---|---|---|
| CPM/GEL (DC) | 2.5 | 0.798 | 2.74±0.03 |
| | | 0.823 | 2.61±0.02 |
| | | 0.848 | 2.47±0.07 |
| | | 0.873 | 2.48±0.03 |
| | | 0.898 | 2.41±0.05 |
| | | 0.923 | 2.38±0.06 |
| | | 0.948 | 2.40±0.02 |
| | 5.0 | 0.799 | 2.23±0.01 |
| | | 0.825 | 2.26±0.04 |
| | | 0.847 | 2.46±0.11 |
| | | 0.862 | 2.36±0.14 |
| | | 0.927 | 2.29±0.03 |
| | | 0.942 | 2.38±0.06 |
| | | 0.955 | 2.31±0.04 |
| | 7.5 | 0.809 | 1.93±0.06 |
| | | 0.834 | 1.71±0.01 |
| | | 0.859 | 1.75±0.09 |
| | | 0.884 | 1.78±0.11 |
| | | 0.909 | 1.57±0.05 |
| | | 0.934 | 1.16±0.07 |
| | | 0.959 | 1.19±0.05 |
| | 10.0 | 0.804 | 1.09±0.02 |
| | | 0.829 | 0.87±0.17 |
| | | 0.854 | 0.88±0.06 |
| | | 0.909 | 0.75±0.02 |
| | | 0.914 | 0.67±0.04 |
| | | 0.939 | 0.66±0.05 |
| | | 0.964 | 0.66±0.06 |

**Table 5.18** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Friability (%) |
|---|---|---|---|
| IBUP/ENTA (WG) | 2.5 | 0.868 | 2.68±0.05 |
|  |  | 0.877 | 2.61±1.02 |
|  |  | 0.885 | 2.67±0.05 |
|  |  | 0.886 | 2.59±1.04 |
|  |  | 0.889 | 2.48±0.06 |
|  |  | 0.899 | 2.42±0.04 |
|  |  | 0.912 | 2.53±0.06 |
|  | 5.0 | 0.873 | 2.23±0.05 |
|  |  | 0.885 | 2.26±0.15 |
|  |  | 0.892 | 2.46±0.03 |
|  |  | 0.911 | 2.31±0.04 |
|  |  | 0.926 | 2.32±0.02 |
|  |  | 0.933 | 2.48±0.03 |
|  |  | 0.952 | 2.41±0.02 |
|  | 7.5 | 0.882 | 1.93±0.04 |
|  |  | 0.878 | 1.74±0.05 |
|  |  | 0.887 | 1.75±0.04 |
|  |  | 0.892 | 1.81±0.05 |
|  |  | 0.939 | 1.63±0.12 |
|  |  | 0.967 | 1.16±0.02 |
|  |  | 0.981 | 1.19±0.02 |
|  | 10.0 | 0.899 | 0.93±0.03 |
|  |  | 0.911 | 0.88±0.04 |
|  |  | 0.921 | 0.87±0.03 |
|  |  | 0.927 | 0.75±0.12 |
|  |  | 0.968 | 0.67±0.06 |
|  |  | 0.983 | 0.67±0.03 |
|  |  | 0.991 | 0.66±0.18 |

**Table 5.18** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Friability (%) |
|---|---|---|---|
| IBUP/ENTA (DC) | 2.5 | 0.860 | 2.77±0.13 |
| | | 0.872 | 2.63±0.18 |
| | | 0.874 | 2.65±0.19 |
| | | 0.878 | 2.62±0.11 |
| | | 0.884 | 2.51±0.07 |
| | | 0.894 | 2.53±0.18 |
| | | 0.904 | 2.67±0.06 |
| | 5.0 | 0.872 | 2.37±0.12 |
| | | 0.874 | 2.23±0.05 |
| | | 0.877 | 2.31±0.11 |
| | | 0.880 | 2.31±0.03 |
| | | 0.921 | 2.34±0.05 |
| | | 0.924 | 2.31±0.06 |
| | | 0.933 | 2.15±0.05 |
| | 7.5 | 0.873 | 1.65±0.04 |
| | | 0.882 | 1.66±0.05 |
| | | 0.885 | 1.67±0.12 |
| | | 0.919 | 1.63±0.11 |
| | | 0.930 | 1.57±0.06 |
| | | 0.954 | 1.46±0.04 |
| | | 0.966 | 1.36±0.03 |
| | 10.0 | 0.901 | 1.10±0.18 |
| | | 0.902 | 0.93±0.05 |
| | | 0.907 | 0.89±0.04 |
| | | 0.931 | 0.88±0.11 |
| | | 0.940 | 0.67±0.12 |
| | | 0.950 | 0.56±0.05 |
| | | 0.955 | 0.68±0.17 |

**Table 5.18** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Friability (%) |
|---|---|---|---|
| IBUP/HPC (WG) | 2.5 | 0.876 | 1.98±1.12 |
| | | 0.895 | 1.97±0.18 |
| | | 0.896 | 1.87±0.14 |
| | | 0.897 | 1.86±0.16 |
| | | 0.899 | 1.89±0.11 |
| | | 0.914 | 1.92±0.09 |
| | | 0.926 | 1.83±0.16 |
| | 5.0 | 0.861 | 1.76±0.12 |
| | | 0.898 | 1.76±0.11 |
| | | 0.903 | 1.65±0.14 |
| | | 0.907 | 1.81±1.12 |
| | | 0.911 | 1.65±1.10 |
| | | 0.912 | 1.46±1.11 |
| | | 0.936 | 1.57±0.13 |
| | 7.5 | 0.889 | 0.97±0.11 |
| | | 0.927 | 0.88±0.13 |
| | | 0.933 | 0.88±0.09 |
| | | 0.946 | 0.85±1.14 |
| | | 0.951 | 0.65±0.15 |
| | | 0.974 | 0.64±0.16 |
| | | 0.987 | 0.43±0.17 |
| | 10.0 | 0.924 | 0.53±1.13 |
| | | 0.933 | 0.47±1.05 |
| | | 0.972 | 0.53±0.06 |
| | | 0.981 | 0.43±0.03 |
| | | 0.986 | 0.37±1.12 |
| | | 0.988 | 0.38±0.14 |
| | | 0.989 | 0.34±0.12 |

**Table 5.18** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ( $\rho_r$ ) | Friability (%) |
|---|---|---|---|
| IBUP/HPC (DC) | 2.5 | 0.835 | 2.34±0.07 |
| | | 0.864 | 2.26±0.04 |
| | | 0.876 | 2.17±0.05 |
| | | 0.888 | 2.28±0.06 |
| | | 0.891 | 1.89±1.09 |
| | | 0.894 | 2.11±0.05 |
| | | 0.899 | 2.13±0.06 |
| | 5.0 | 0.856 | 2.09±1.14 |
| | | 0.875 | 2.11±1.07 |
| | | 0.883 | 1.98±1.14 |
| | | 0.892 | 1.82±0.04 |
| | | 0.893 | 1.87±0.05 |
| | | 0.896 | 1.88±0.03 |
| | | 0.908 | 1.83±0.09 |
| | 7.5 | 0.867 | 1.32±1.05 |
| | | 0.881 | 1.33±1.16 |
| | | 0.895 | 1.43±1.05 |
| | | 0.925 | 1.28±1.05 |
| | | 0.937 | 1.11±0.05 |
| | | 0.969 | 1.21±0.07 |
| | | 0.977 | 1.13±1.15 |
| | 10.0 | 0.871 | 1.12±1.06 |
| | | 0.885 | 0.95±0.05 |
| | | 0.899 | 0.86±1.13 |
| | | 0.929 | 0.56±0.06 |
| | | 0.941 | 0.65±0.05 |
| | | 0.973 | 0.55±1.13 |
| | | 0.982 | 0.52±1.09 |

**Table 5.18** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Friability (%) |
|---|---|---|---|
| IBUP/GEL (WG) | 2.5 | 0.862 | 2.44±0.09 |
| | | 0.871 | 2.43±0.08 |
| | | 0.879 | 2.51±0.13 |
| | | 0.880 | 2.39±0.16 |
| | | 0.883 | 2.24±0.17 |
| | | 0.893 | 2.21±0.09 |
| | | 0.906 | 2.19±0.05 |
| | 5.0 | 0.867 | 2.11±0.19 |
| | | 0.879 | 2.10±0.07 |
| | | 0.886 | 2.03±0.18 |
| | | 0.905 | 2.07±0.06 |
| | | 0.920 | 2.01±0.05 |
| | | 0.927 | 2.04±0.06 |
| | | 0.946 | 2.10±0.12 |
| | 7.5 | 0.876 | 1.53±0.11 |
| | | 0.872 | 1.47±0.14 |
| | | 0.881 | 1.43±0.06 |
| | | 0.886 | 1.36±0.08 |
| | | 0.933 | 1.29±0.15 |
| | | 0.961 | 1.22±0.05 |
| | | 0.975 | 1.21±0.04 |
| | 10.0 | 0.893 | 1.23±0.13 |
| | | 0.905 | 1.11±0.17 |
| | | 0.915 | 1.12±0.20 |
| | | 0.921 | 0.87±0.05 |
| | | 0.962 | 0.62±0.17 |
| | | 0.977 | 0.58±0.23 |
| | | 0.985 | 0.49±0.15 |

**Table 5.18** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Friability (%) |
|---|---|---|---|
| IBUP/GEL (DC) | 2.5 | 0.857 | 3.02±0.06 |
| | | 0.866 | 2.65±0.05 |
| | | 0.874 | 2.63±0.05 |
| | | 0.875 | 2.58±0.13 |
| | | 0.878 | 2.52±0.09 |
| | | 0.888 | 2.55±1.04 |
| | | 0.901 | 2.54±1.03 |
| | 5.0 | 0.862 | 2.43±1.12 |
| | | 0.874 | 2.38±1.11 |
| | | 0.881 | 2.45±0.09 |
| | | 0.900 | 2.48±0.16 |
| | | 0.915 | 2.44±1.15 |
| | | 0.922 | 2.37±0.05 |
| | | 0.941 | 2.21±1.15 |
| | 7.5 | 0.871 | 1.86±1.05 |
| | | 0.867 | 1.87±0.06 |
| | | 0.876 | 1.64±0.24 |
| | | 0.881 | 1.65±0.05 |
| | | 0.928 | 1.65±1.14 |
| | | 0.956 | 1.67±1.06 |
| | | 0.970 | 1.54±1.05 |
| | 10.0 | 0.888 | 1.10±0.06 |
| | | 0.900 | 0.74±0.05 |
| | | 0.910 | 0.63±1.04 |
| | | 0.916 | 0.57±1.11 |
| | | 0.957 | 0.42±0.15 |
| | | 0.972 | 0.49±0.10 |
| | | 0.980 | 0.55±0.07 |

**Table 5.19**: Friability (%) values for different formulations at relative density, $\rho_r = 0.90$

| Formulation | Binder Concentration(%w/w) | Friability (%) |
|---|---|---|
| CPM/ENTA(WG) | 2.5 | 2.41 |
| | 5.0 | 2.11 |
| | 7.5 | 1.88 |
| | 10.0 | 0.64 |
| CPM/ENTA(DC) | 2.5 | 2.88 |
| | 5.0 | 2.19 |
| | 7.5 | 1.22 |
| | 10.0 | 1.00 |
| CPM/HPC(WG) | 2.5 | 1.65 |
| | 5.0 | 1.24 |
| | 7.5 | 0.92 |
| | 10.0 | 0.53 |
| CPM/HPC(DC) | 2.5 | 1.86 |
| | 5.0 | 1.64 |
| | 7.5 | 1.04 |
| | 10.0 | 0.85 |
| CPM/GEL(WG) | 2.5 | 2.59 |
| | 5.0 | 2.31 |
| | 7.5 | 1.81 |
| | 10.0 | 0.75 |
| CPM/GEL(DC) | 2.5 | 2.48 |
| | 5.0 | 2.36 |
| | 7.5 | 1.78 |
| | 10.0 | 0.75 |

**Table 5.19** continued:

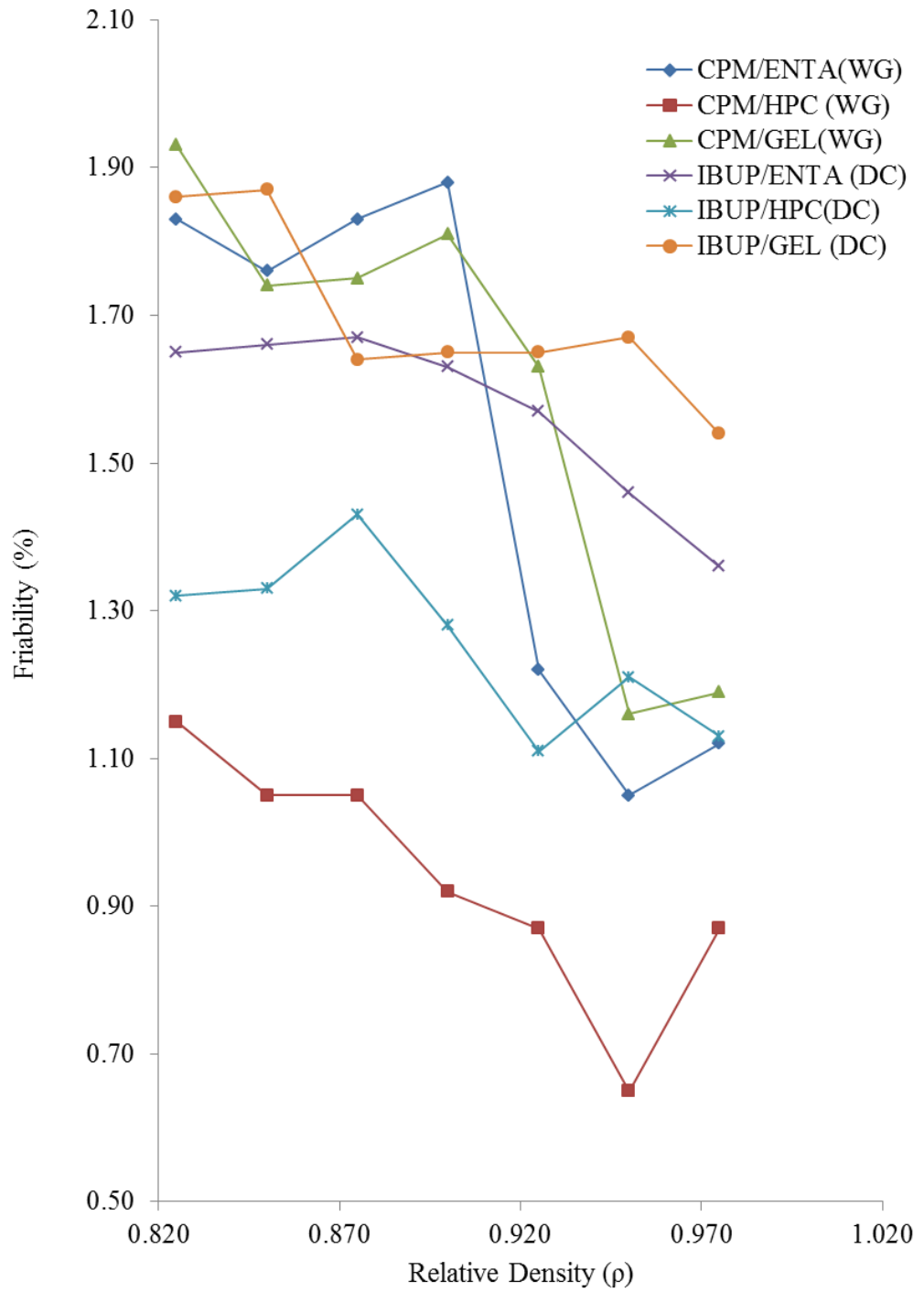| Formulation | Binder Concentration (%w/w) | Friability (%) |
| --- | --- | --- |
| IBUP/ENTA(WG) | 2.5 | 2.59 |
| | 5.0 | 2.31 |
| | 7.5 | 1.81 |
| | 10.0 | 0.75 |
| IBUP/ENTA(DC) | 2.5 | 2.62 |
| | 5.0 | 2.31 |
| | 7.5 | 1.63 |
| | 10.0 | 0.88 |
| IBUP/HPC(WG) | 2.5 | 1.86 |
| | 5.0 | 1.81 |
| | 7.5 | 0.85 |
| | 10.0 | 0.43 |
| IBUP/HPC(DC) | 2.5 | 2.28 |
| | 5.0 | 1.82 |
| | 7.5 | 1.28 |
| | 10.0 | 0.56 |
| IBUP/GEL (WG) | 2.5 | 2.39 |
| | 5.0 | 2.07 |
| | 7.5 | 1.36 |
| | 10.0 | 0.87 |
| IBUP/GEL (DC) | 2.5 | 2.58 |
| | 5.0 | 2.48 |
| | 7.5 | 1.65 |
| | 10.0 | 0.57 |

**Fig 5.14:** Plot of Friability (%) versus Relative Density for tablets containing 7.5%w/w polymers as binder

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**5.5**      **Disintegration and Dissolution properties**

**5.5.1**      **Disintegration Properties**

The disintegration times of the different formulations at different relative densities are presented in Table 5.20. Representative plots of the disintegration time of the tablets containing 5 %w/w of the binders against relative density are presented in Figs 5.15 and 5.16. For all the formulations, disintegration time was found to increase with increase in relative density. Tablets containing chlorpheniramine maleate disintegrated faster than those containing ibuprofen. The fragmentation of granules on compression in a die leads to an increase in the specific surface area. At higher relative densities, the fragments reform into compacts by the process of cold bonding and an increase in plastic deformation and densification leads to further bonding. This will retard liquid penetration into the interstitial void spaces of the tablets that would have led to disruption of the tablets, thus disintegration time of the tablets is increased (Esezobo and Ambujam, 1982).

At relative density, $\rho_r$, of 0.90, disintegration time generally increased with increase in concentration of the binder (Table 4.21). Tablets that were formulated by wet granulation had higher disintegration values, especially at high concentrations than tablets formulated by direct compression technique. The ranking of the disintegration time was Hydroxypropylcellulose > *Entandophragma angolense* gum > Gelatin. Some authors (Stenlake, 1981; Wells and Walker, 1983; Adolfsson and Nystron, 1996) have reported that the ease with which fluid penetrates the tablet appears to control the disintegration process.

**Table 5.20**: Values of disintegration time (min) for different formulations

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration time (mins) |
|---|---|---|---|
| CPM/ENTA (WG) | 2.5 | 0.866 | 1.78 |
| | | 0.875 | 1.86 |
| | | 0.886 | 1.93 |
| | | 0.887 | 2.11 |
| | | 0.889 | 2.34 |
| | | 0.893 | 2.35 |
| | | 0.897 | 3.88 |
| | 5.0 | 0.854 | 1.84 |
| | | 0.857 | 1.96 |
| | | 0.881 | 2.08 |
| | | 0.898 | 2.97 |
| | | 0.912 | 3.44 |
| | | 0.935 | 3.74 |
| | | 0.946 | 3.92 |
| | 7.5 | 0.875 | 4.18 |
| | | 0.881 | 5.34 |
| | | 0.892 | 5.51 |
| | | 0.905 | 5.90 |
| | | 0.917 | 6.43 |
| | | 0.948 | 6.72 |
| | | 0.965 | 6.88 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration time (mins) |
|---|---|---|---|
| CPM/ENTA (WG) | 10.0 | 0.888 | 7.56 |
| | | 0.924 | 8.93 |
| | | 0.927 | 10.76 |
| | | 0.933 | 11.43 |
| | | 0.941 | 12.28 |
| | | 0.952 | 13.12 |
| | | 0.987 | 13.26 |
| CPM/ENTA (DC) | 2.5 | 0.851 | 1.45 |
| | | 0.872 | 1.63 |
| | | 0.876 | 1.72 |
| | | 0.880 | 2.03 |
| | | 0.922 | 2.17 |
| | | 0.941 | 2.19 |
| | | 0.951 | 2.76 |
| | 5.0 | 0.861 | 1.72 |
| | | 0.870 | 1.84 |
| | | 0.874 | 1.99 |
| | | 0.883 | 2.45 |
| | | 0.887 | 3.18 |
| | | 0.947 | 3.23 |
| | | 0.953 | 3.56 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration time (mins) |
|---|---|---|---|
| CPM/ENTA (DC) | 7.5 | 0.874 | 3.96 |
| | | 0.880 | 4.84 |
| | | 0.884 | 5.37 |
| | | 0.887 | 5.62 |
| | | 0.889 | 5.94 |
| | | 0.956 | 6.28 |
| | | 0.962 | 6.57 |
| | 10.0 | 0.893 | 6.92 |
| | | 0.894 | 7.89 |
| | | 0.899 | 10.33 |
| | | 0.961 | 10.43 |
| | | 0.972 | 11.47 |
| | | 0.977 | 11.39 |
| | | 0.989 | 12.28 |
| CPM/HPC (WG) | 2.5 | 0.846 | 1.82 |
| | | 0.857 | 2.14 |
| | | 0.893 | 2.28 |
| | | 0.899 | 2.41 |
| | | 0.924 | 2.57 |
| | | 0.944 | 2.83 |
| | | 0.949 | 2.98 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration time (mins) |
|---|---|---|---|
| CPM/HPC (WG) | 5.0 | 0.873 | 2.07 |
| | | 0.882 | 2.21 |
| | | 0.895 | 2.65 |
| | | 0.909 | 3.18 |
| | | 0.913 | 3.55 |
| | | 0.947 | 3.87 |
| | | 0.953 | 4.09 |
| | 7.5 | 0.877 | 4.38 |
| | | 0.878 | 6.27 |
| | | 0.899 | 6.33 |
| | | 0.942 | 6.89 |
| | | 0.957 | 6.92 |
| | | 0.963 | 7.14 |
| | | 0.971 | 7.38 |
| | 10.0 | 0.891 | 7.72 |
| | | 0.926 | 9.18 |
| | | 0.941 | 10.96 |
| | | 0.943 | 11.83 |
| | | 0.967 | 12.78 |
| | | 0.972 | 13.37 |
| | | 0.987 | 14.13 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration time (mins) |
|---|---|---|---|
| CPM/HPC (DC) | 2.5 | 0.842 | 1.56 |
| | | 0.856 | 1.97 |
| | | 0.861 | 2.11 |
| | | 0.873 | 2.27 |
| | | 0.894 | 2.47 |
| | | 0.897 | 2.69 |
| | | 0.917 | 2.83 |
| | 5.0 | 0.861 | 2.11 |
| | | 0.872 | 2.19 |
| | | 0.889 | 2.52 |
| | | 0.897 | 2.97 |
| | | 0.898 | 3.43 |
| | | 0.913 | 3.97 |
| | | 0.929 | 4.12 |
| | 7.5 | 0.862 | 4.21 |
| | | 0.868 | 5.44 |
| | | 0.893 | 6.57 |
| | | 0.921 | 6.83 |
| | | 0.924 | 7.07 |
| | | 0.937 | 7.38 |
| | | 0.974 | 7.41 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration time (mins) |
|---|---|---|---|
| CPM/HPC (DC) | 10.0 | 0.864 | 7.66 |
| | | 0.892 | 8.11 |
| | | 0.898 | 9.67 |
| | | 0.944 | 10.92 |
| | | 0.962 | 11.43 |
| | | 0.966 | 12.25 |
| | | 0.979 | 12.97 |
| CPM/GEL (WG) | 2.5 | 0.867 | 1.44 |
| | | 0.869 | 1.58 |
| | | 0.893 | 1.69 |
| | | 0.897 | 2.11 |
| | | 0.903 | 2.23 |
| | | 0.955 | 2.44 |
| | | 0.967 | 2.57 |
| | 5.0 | 0.875 | 1.69 |
| | | 0.883 | 1.76 |
| | | 0.885 | 1.83 |
| | | 0.897 | 2.55 |
| | | 0.931 | 2.99 |
| | | 0.947 | 3.18 |
| | | 0.952 | 3.35 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration time (mins) |
|---|---|---|---|
| CPM/GEL (WG) | 7.5 | 0.879 | 2.98 |
|  |  | 0.882 | 3.57 |
|  |  | 0.911 | 4.28 |
|  |  | 0.944 | 5.53 |
|  |  | 0.951 | 5.62 |
|  |  | 0.962 | 5.79 |
|  |  | 0.969 | 6.28 |
|  |  |  |  |
|  | 10.0 | 0.892 | 5.33 |
|  |  | 0.893 | 7.68 |
|  |  | 0.897 | 10.73 |
|  |  | 0.938 | 10.91 |
|  |  | 0.941 | 11.29 |
|  |  | 0.953 | 11.44 |
|  |  | 0.989 | 12.09 |
|  |  |  |  |
| CPM/GEL (DC) | 2.5 | 0.857 | 1.38 |
|  |  | 0.859 | 1.62 |
|  |  | 0.862 | 1.64 |
|  |  | 0.874 | 1.93 |
|  |  | 0.899 | 2.38 |
|  |  | 0.912 | 2.47 |
|  |  | 0.923 | 2.69 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration time (mins) |
|---|---|---|---|
| CPM/GEL (DC) | 5.0 | 0.861 | 1.58 |
| | | 0.862 | 1.62 |
| | | 0.879 | 1.77 |
| | | 0.892 | 2.19 |
| | | 0.895 | 2.49 |
| | | 0.898 | 2.89 |
| | | 0.941 | 3.26 |
| | 7.5 | 0.863 | 2.87 |
| | | 0.864 | 3.56 |
| | | 0.876 | 4.27 |
| | | 0.892 | 5.17 |
| | | 0.936 | 5.44 |
| | | 0.941 | 5.69 |
| | | 0.944 | 6.43 |
| | 10.0 | 0.862 | 5.65 |
| | | 0.868 | 7.97 |
| | | 0.897 | 8.93 |
| | | 0.911 | 9.81 |
| | | 0.942 | 10.89 |
| | | 0.967 | 11.87 |
| | | 0.972 | 12.26 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration Time (mins) |
|---|---|---|---|
| IBUP/ENTA (WG) | 2.5 | 0.868 | 1.64 |
| | | 0.877 | 1.97 |
| | | 0.885 | 2.13 |
| | | 0.886 | 2.42 |
| | | 0.889 | 2.87 |
| | | 0.899 | 3.16 |
| | | 0.912 | 3.34 |
| | 5.0 | 0.873 | 1.77 |
| | | 0.885 | 2.23 |
| | | 0.892 | 3.68 |
| | | 0.911 | 3.97 |
| | | 0.926 | 4.34 |
| | | 0.933 | 4.56 |
| | | 0.952 | 5.17 |
| | 7.5 | 0.882 | 5.56 |
| | | 0.878 | 5.63 |
| | | 0.887 | 5.78 |
| | | 0.892 | 6.48 |
| | | 0.939 | 6.79 |
| | | 0.967 | 7.13 |
| | | 0.981 | 8.28 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration Time (mins) |
|---|---|---|---|
| IBUP/ENTA (WG) | 10.0 | 0.899 | 7.99 |
| | | 0.911 | 8.28 |
| | | 0.921 | 9.98 |
| | | 0.927 | 11.23 |
| | | 0.968 | 11.34 |
| | | 0.983 | 13.65 |
| | | 0.991 | 14.32 |
| | | | |
| IBUP/ENTA (DC) | 2.5 | 0.857 | 1.56 |
| | | 0.869 | 1.86 |
| | | 0.871 | 2.26 |
| | | 0.875 | 2.76 |
| | | 0.881 | 2.99 |
| | | 0.891 | 3.07 |
| | | 0.901 | 3.28 |
| | | | |
| | 5.0 | 0.869 | 2.11 |
| | | 0.871 | 2.27 |
| | | 0.874 | 3.59 |
| | | 0.877 | 3.76 |
| | | 0.918 | 4.26 |
| | | 0.921 | 4.62 |
| | | 0.930 | 4.87 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration Time (mins) |
|---|---|---|---|
| IBUP/ENTA (DC) | 7.5 | 0.870 | 6.02 |
| | | 0.879 | 6.13 |
| | | 0.882 | 6.23 |
| | | 0.916 | 6.58 |
| | | 0.927 | 6.69 |
| | | 0.951 | 7.24 |
| | | 0.963 | 7.79 |
| | 10.0 | 0.898 | 7.55 |
| | | 0.899 | 8.41 |
| | | 0.904 | 9.22 |
| | | 0.928 | 11.46 |
| | | 0.937 | 11.65 |
| | | 0.947 | 12.98 |
| | | 0.952 | 13.97 |
| IBUP/HPC (WG) | 2.5 | 0.876 | 1.55 |
| | | 0.895 | 1.63 |
| | | 0.896 | 2.98 |
| | | 0.897 | 3.41 |
| | | 0.899 | 3.57 |
| | | 0.914 | 3.87 |
| | | 0.926 | 4.17 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration Time (mins) |
|---|---|---|---|
| IBUP/HPC (WG) | 5.0 | 0.861 | 2.09 |
| | | 0.898 | 2.22 |
| | | 0.903 | 3.89 |
| | | 0.907 | 4.08 |
| | | 0.911 | 4.54 |
| | | 0.912 | 4.68 |
| | | 0.936 | 5.26 |
| | 7.5 | 0.889 | 6.58 |
| | | 0.927 | 6.98 |
| | | 0.933 | 7.13 |
| | | 0.946 | 7.25 |
| | | 0.951 | 7.66 |
| | | 0.974 | 8.17 |
| | | 0.987 | 8.55 |
| | 10.0 | 0.924 | 7.77 |
| | | 0.933 | 7.94 |
| | | 0.972 | 10.46 |
| | | 0.981 | 11.69 |
| | | 0.986 | 12.59 |
| | | 0.988 | 12.54 |
| | | 0.989 | 14.27 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ( $\rho_r$ ) | Disintegration Time (mins) |
|---|---|---|---|
| IBUP/HPC (DC) | 2.5 | 0.835 | 1.22 |
| | | 0.864 | 1.44 |
| | | 0.876 | 1.98 |
| | | 0.888 | 2.54 |
| | | 0.891 | 3.27 |
| | | 0.894 | 3.98 |
| | | 0.899 | 3.99 |
| | 5.0 | 0.856 | 2.17 |
| | | 0.875 | 2.32 |
| | | 0.883 | 3.77 |
| | | 0.892 | 3.97 |
| | | 0.893 | 4.28 |
| | | 0.896 | 4.57 |
| | | 0.908 | 4.98 |
| | 7.5 | 0.863 | 6.09 |
| | | 0.877 | 6.56 |
| | | 0.891 | 6.97 |
| | | 0.921 | 7.18 |
| | | 0.933 | 7.38 |
| | | 0.965 | 8.34 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration Time (mins) |
|---|---|---|---|
| IBUP/GEL  (WG) | 2.5 | 0.873 | 1.65 |
| | | 0.876 | 1.77 |
| | | 0.889 | 1.87 |
| | | 0.892 | 2.87 |
| | | 0.899 | 3.17 |
| | | 0.913 | 3.67 |
| | | 0.920 | 3.98 |
| | 5.0 | 0.884 | 2.13 |
| | | 0.892 | 2.34 |
| | | 0.898 | 3.17 |
| | | 0.899 | 4.16 |
| | | 0.927 | 4.89 |
| | | 0.936 | 5.21 |
| | | 0.951 | 6.75 |
| | 7.5 | 0.864 | 7.11 |
| | | 0.898 | 7.22 |
| | | 0.938 | 7.43 |
| | | 0.942 | 7.59 |
| | | 0.955 | 8.07 |
| | | 0.967 | 8.24 |
| | | 0.979 | 8.45 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration Time (mins) |
|---|---|---|---|
| IBUP/GEL (WG) | 10.0 | 0.917 | 8.45 |
| | | 0.943 | 8.56 |
| | | 0.958 | 10.86 |
| | | 0.974 | 12.78 |
| | | 0.981 | 13.11 |
| | | 0.986 | 13.67 |
| | | 0.988 | 14.11 |
| | | | |
| IBUP/GEL (DC) | 2.5 | 0.866 | 1.53 |
| | | 0.875 | 1.67 |
| | | 0.886 | 1.97 |
| | | 0.887 | 1.99 |
| | | 0.889 | 2.68 |
| | | 0.893 | 2.87 |
| | | 0.897 | 3.67 |
| | | | |
| | 5.0 | 0.854 | 2.45 |
| | | 0.857 | 2.89 |
| | | 0.881 | 2.97 |
| | | 0.898 | 3.78 |
| | | 0.912 | 4.35 |
| | | 0.935 | 5.67 |
| | | 0.946 | 6.17 |

**Table 5.20** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Disintegration Time (mins) |
|---|---|---|---|
| IBUP/GEL (DC) | 7.5 | 0.875 | 7.35 |
| | | 0.881 | 7.67 |
| | | 0.892 | 7.88 |
| | | 0.905 | 7.99 |
| | | 0.917 | 8.17 |
| | | 0.948 | 8.34 |
| | | 0.965 | 8.56 |
| | 10.0 | 0.888 | 7.98 |
| | | 0.924 | 8.45 |
| | | 0.927 | 9.87 |
| | | 0.933 | 13.17 |
| | | 0.941 | 13.51 |
| | | 0.952 | 13.67 |
| | | 0.987 | 13.91 |

**Table 5.21**: Values of disintegration times (mins) for chlorpheniramine maleate and ibuprofen tablets at a relative density, $\rho_r = 0.90$

| Formulation Type | Binder Concentration (%w/w) | Disintegration Time (mins) |
|---|---|---|
| CPM/ENTA (WG) | 2.5 | 2.92 |
| | 5.0 | 3.13 |
| | 7.5 | 5.63 |
| | 10.0 | 7.71 |
| | | |
| CPM/ENTA (DC) | 2.5 | 2.09 |
| | 5.0 | 3.21 |
| | 7.5 | 5.96 |
| | 10.0 | 7.39 |
| | | |
| CPM/HPC (WG) | 2.5 | 2.47 |
| | 5.0 | 2.76 |
| | 7.5 | 6.34 |
| | 10.0 | 8.37 |
| | | |
| CPM/HPC (DC) | 2.5 | 2.76 |
| | 5.0 | 3.51 |
| | 7.5 | 6.63 |
| | 10.0 | 9.71 |
| | | |
| CPM/GEL ( WG) | 2.5 | 2.17 |
| | 5.0 | 2.61 |
| | 7.5 | 3.66 |
| | 10.0 | 10.87 |
| | | |
| CPM/GEL (DC) | 2.5 | 2.41 |
| | 5.0 | 2.89 |
| | 7.5 | 5.27 |
| | 10.0 | 9.28 |

**Table 5.21** continued:

| Formulation Type | Binder Concentration (%w/w) | Disintegration Time (mins) |
|---|---|---|
| IBUP/ENTA (WG) | 2.5 | 3.16 |
|  | 5.0 | 3.70 |
|  | 7.5 | 6.50 |
|  | 10.0 | 7.99 |
| IBUP/ENTA (DC) | 2.5 | 3.11 |
|  | 5.0 | 3.69 |
|  | 7.5 | 6.31 |
|  | 10.0 | 7.61 |
| IBUP/HPC (WG) | 2.5 | 3.57 |
|  | 5.0 | 2.24 |
|  | 7.5 | 6.60 |
|  | 10.0 | 7.47 |
| IBUP/HPC (DC) | 2.5 | 3.97 |
|  | 5.0 | 4.59 |
|  | 7.5 | 6.99 |
|  | 10.0 | 7.72 |
| IBUP/GEL ( WG) | 2.5 | 3.17 |
|  | 5.0 | 4.16 |
|  | 7.5 | 7.30 |
|  | 10.0 | 8.22 |
| IBUP/GEL (DC) | 2.5 | 3.72 |
|  | 5.0 | 3.81 |
|  | 7.5 | 7.92 |
|  | 10.0 | 8.13 |
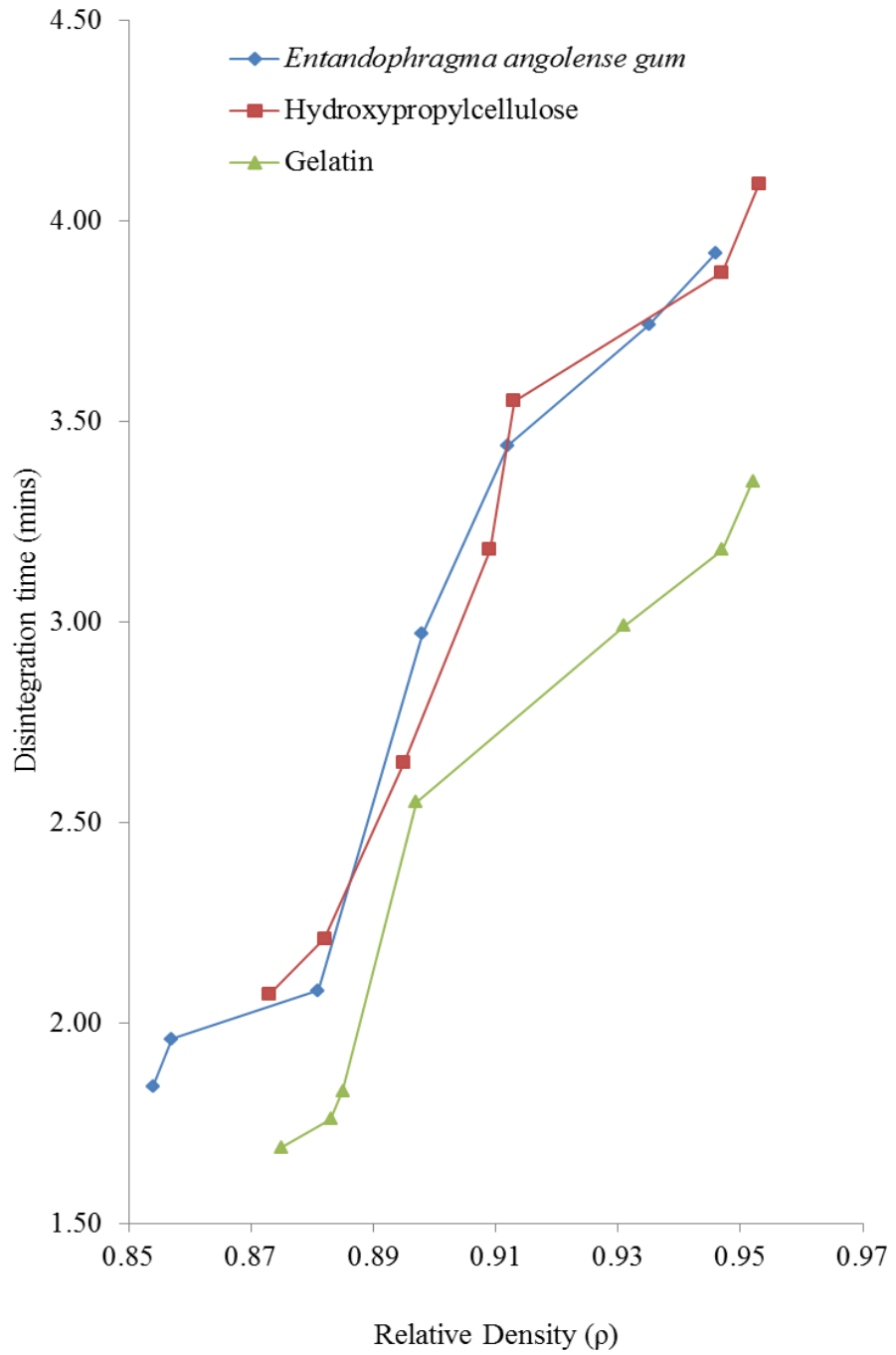
**Fig 5.15**: Disintegration time versus relative density for chlorpheniramine maleate tablets containing 5%w/w binder formulated by wet granulation
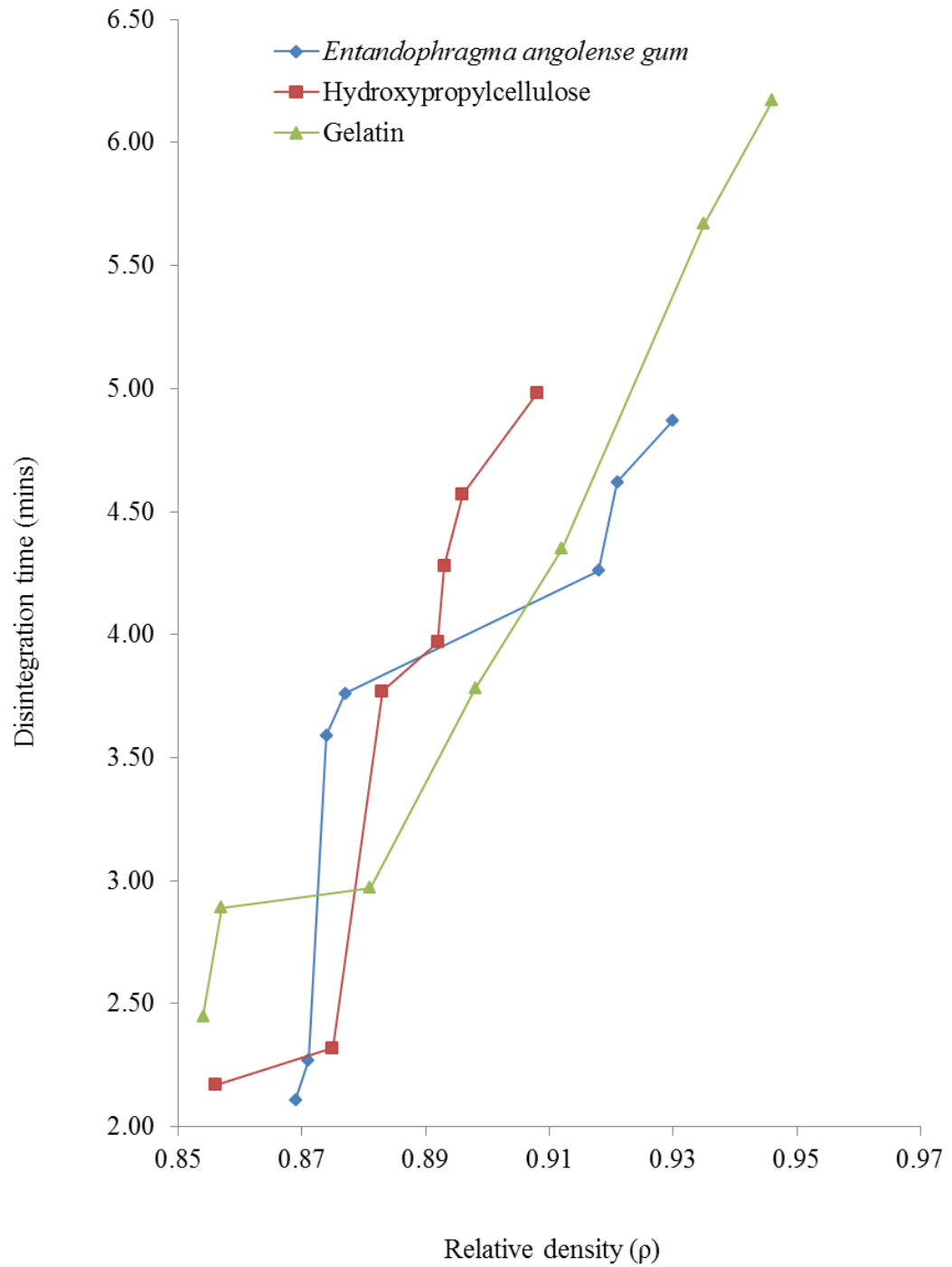
**Fig 5.16**: Disintegration time versus relative density for ibuprofen tablets containing 5%w/w binder formulated by direct compression

## 5.5.2 Dissolution Tests

The amount of chlorpheniramine maleate and ibuprofen released were plotted against time and representative plots for tablets containing 5 %w/w of the polymers as binders are presented in Figs 5.17 and 5.18.The results of the dissolution test on all the tablets are listed in Appendix I. The values of $t_{50}$ and $t_{80}$ (i.e. the times required for 50 % and 80 % of the drugs in the different formulations to be released) were calculated from the plots. Values of In [Cs/(Cs-Ct)] were plotted against t (Kitazawa *et al*, 1975) and the representative plots are shown in Figs 5.19 and 5.20 for tablets containing 5%w/w polymers as binders. In all cases, two linear regression lines with slopes $k_1$ and $k_2$ respectively intersecting at time $t_1$ were obtained. Table 5.22 shows the values of $t_{50}, t_{80}, t_1,$ $k_1$ and $k_2$ for all formulations at a selected relative density of 0.90, which is representative of commercial tablets. The plots showed $K_1$ to be lower than $K_2,$ implying that the dissolution rate of the drugs was faster after $t_1$. The ranking of $t_1$ values was Hydroxypropylcellulose > *Entandophragma angolense* gum > Gelatin for formulations containing chlorpheniramine maleate, while the ranking was Hydroxypropylcellulose > Gelatin > *Entandophragma angolense* gum for formulations containing ibuprofen. The change from $K_1$ to $K_2$ at time $t_1$ is attributable to a change in the surface area due to the break up of the tablets into fragments (Itiola and Pilpel, 1986). In all the formulations, the values of $t_1$ were greater for tablets formulated by wet granulation. It was also observed that $t_1$ values were generally higher than the disintegration time values, probably as a result of the greater agitation employed in the disintegration test than in dissolution tests (Kitazawa *et al*, 1975; Itiola and Pilpel, 1991). Disintegration and de-aggregation of tablets would therefore have significant influence on the dissolution rate by exposing higher surface area of particles to the dissolution medium. Thus, the changes in surface area, as already mentioned, was manifested in the explosive increase in the dissolution rate as proposed by Kitazawa *et al* (1975). The dissolution rate constant, $K_2$ can probably be ascribed to the dissolution phase following tablet disintegration and commencing at time $t_1$.
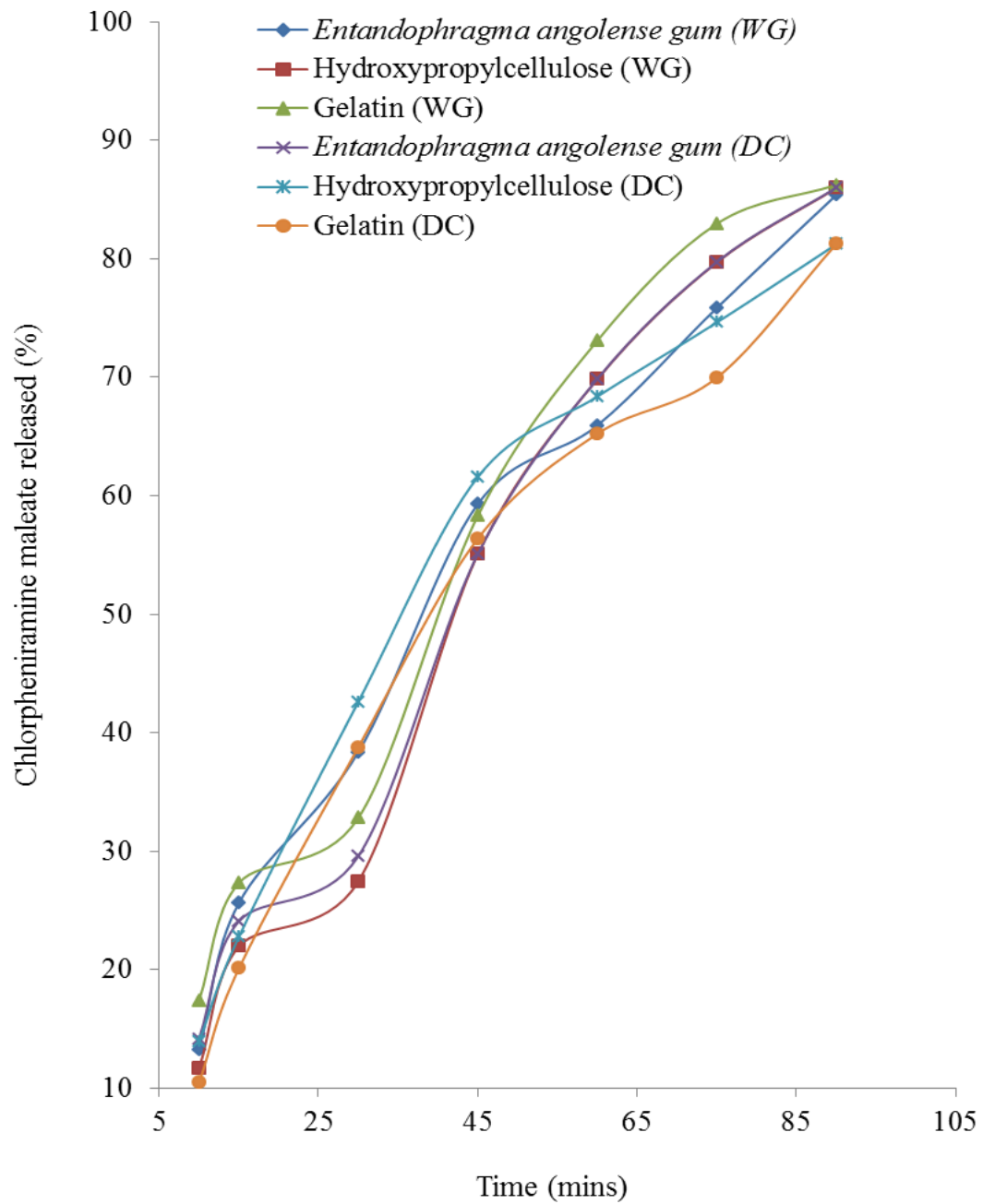
**Fig 5.17**: Dissolution profile of chlorpheniramine maleate tablets formulated by wet granulation (WG) and direct compression (DC) containing 5%w/w polymers
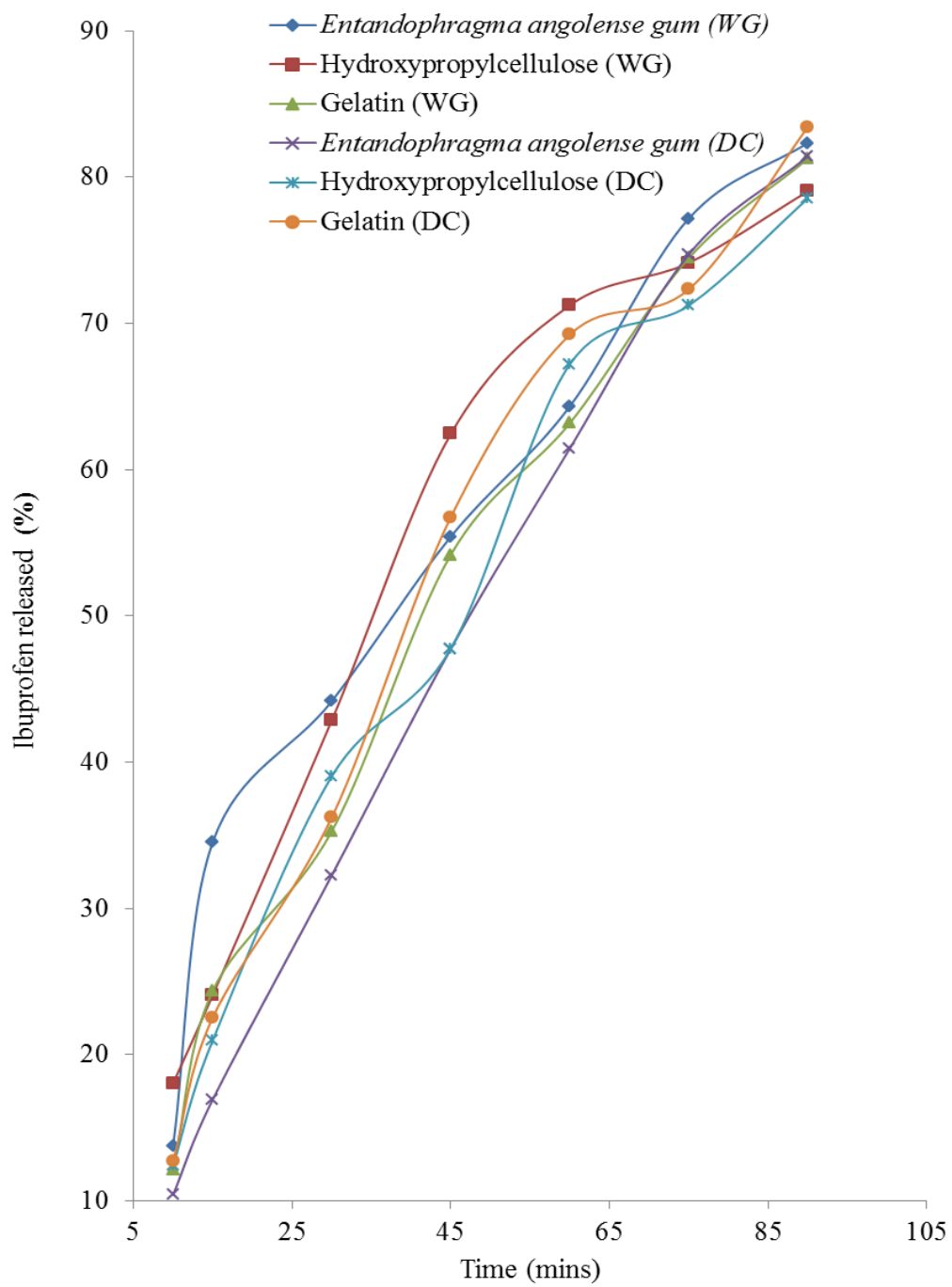
**Fig 5.18**: Dissolution profile of Ibuprofen tablets formulated by wet granulation (WG) and direct compression (DC) containing 5 %w/w polymers
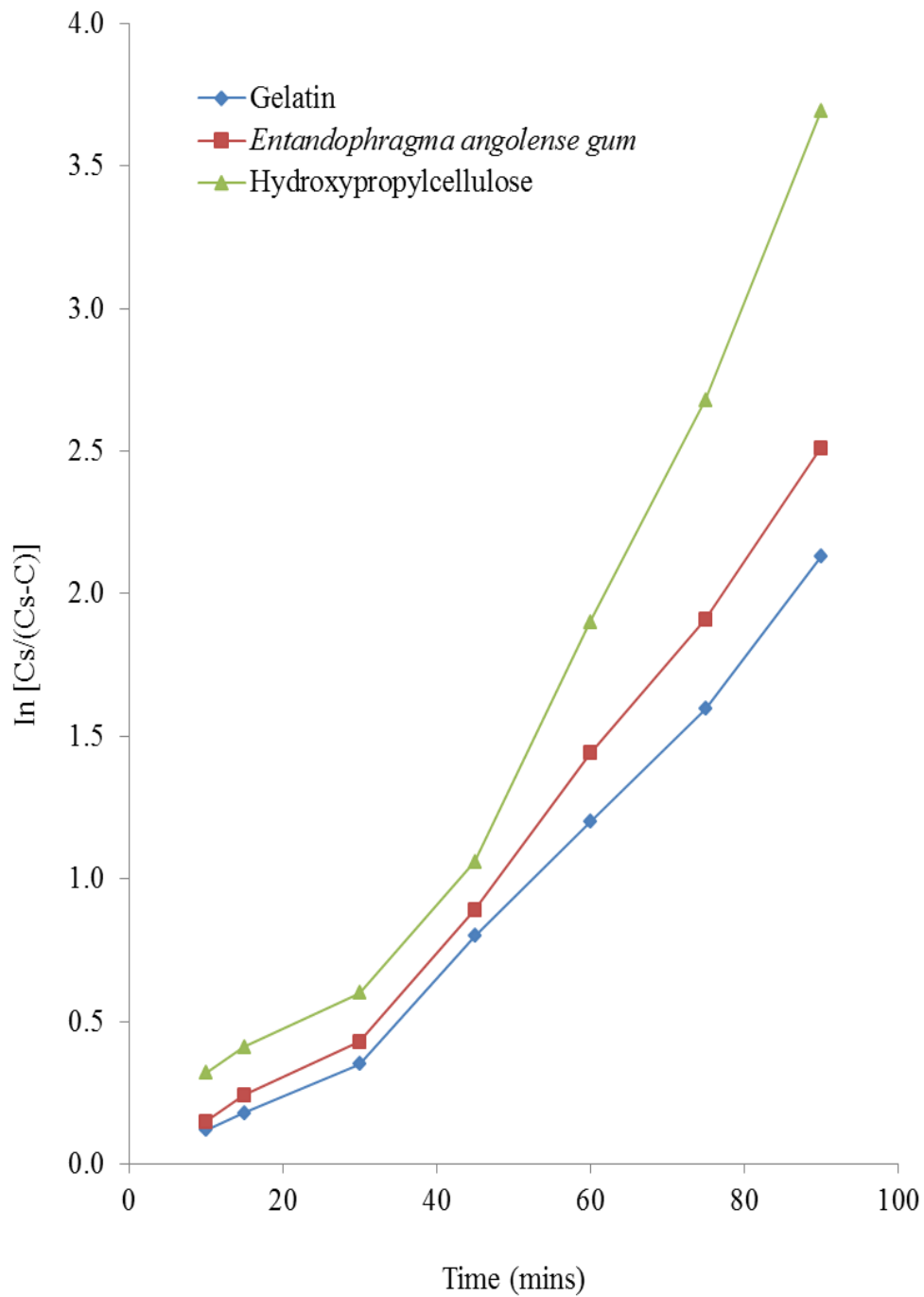
**Fig 5.19**: Plot of In[Cs/(Cs-C)] Vs Time for chlorpheniramine maleate tablets
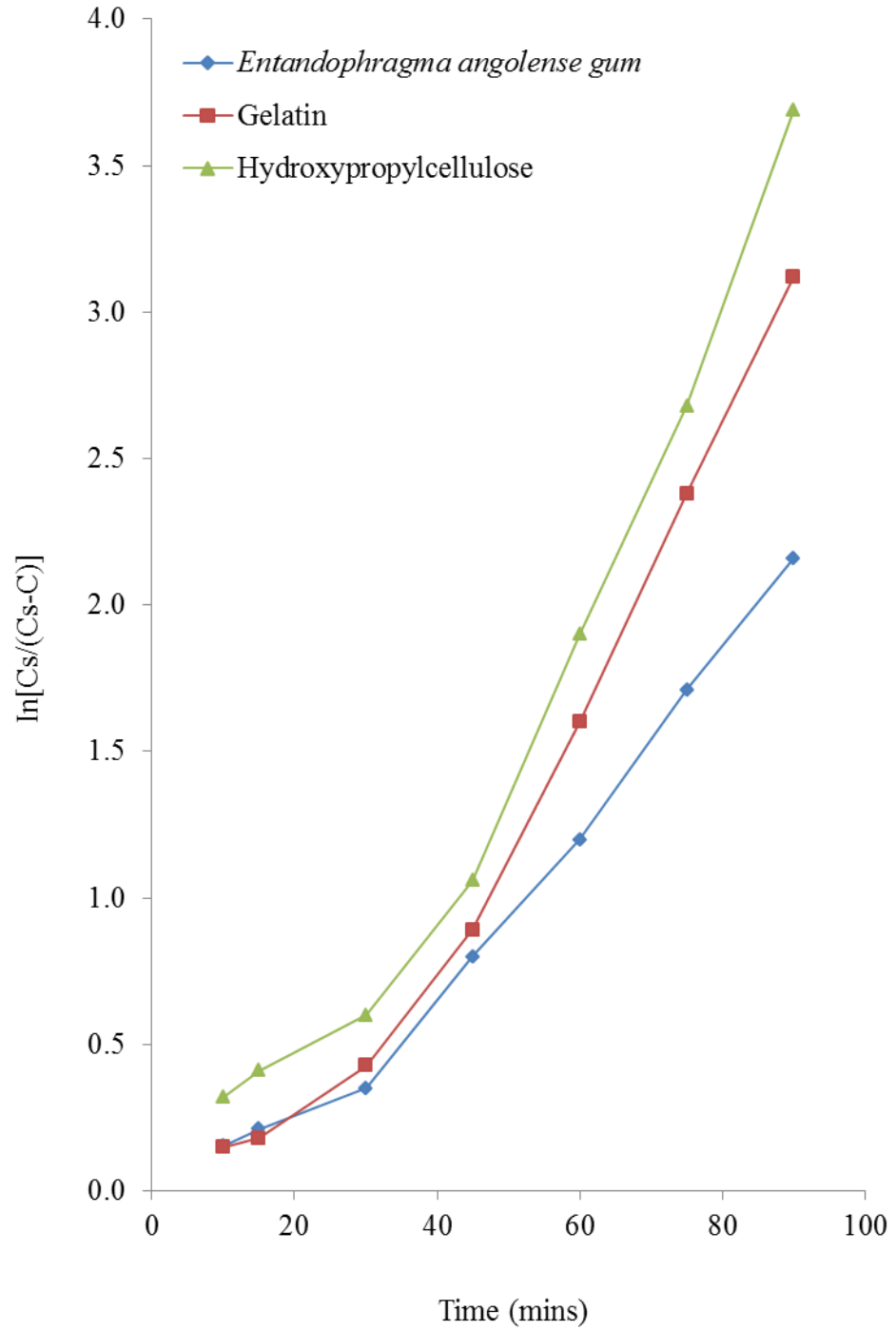containing 5%w/w polymers as binder.

**Fig 5.20**: Plot of In[Cs/(Cs-C)] Vs Time for Ibuprofen tablets containing 5%w/w polymers as binder.

**Table 5.22**: Parameters obtained from Kitazawa analysis for different formulations at relative density, $\rho_r$=0.90

| Formulation Type | Binder Concentration (%w/w) | $t_{50}$ (min) | $t_{80}$ (min) | $t_1$ (min) | $K_1$ | $K_2$ |
|---|---|---|---|---|---|---|
| CPM/ENTA(WG) | 2.5 | 38.0 | 79.0 | 41.21 | 0.0324 | 0.0517 |
| | 5.0 | 34.0 | 76.5 | 43.63 | 0.0201 | 0.0493 |
| | 7.5 | 33.5 | 75.0 | 45.42 | 0.0196 | 0.0375 |
| | 10.0 | 31.0 | 71.5 | 45.57 | 0.0181 | 0.0224 |
| CPM/ENTA(DC) | 2.5 | 35.0 | 64.0 | 41.17 | 0.0229 | 0.0491 |
| | 5.0 | 31.5 | 61.5 | 42.28 | 0.0176 | 0.0482 |
| | 7.5 | 29.0 | 60.5 | 43.71 | 0.0152 | 0.0466 |
| | 10.0 | 27.5 | 59.5 | 44.12 | 0.0143 | 0.0417 |
| CPM/HPC(WG) | 2.5 | 42.5 | 81.5 | 46.12 | 0.0181 | 0.0437 |
| | 5.0 | 38.5 | 75.0 | 46.38 | 0.0176 | 0.0424 |
| | 7.5 | 35.5 | 74.0 | 47.12 | 0.0172 | 0.0381 |
| | 10.0 | 32.5 | 71.5 | 48.01 | 0.0168 | 0.0376 |
| CPM/HPC (DC) | 2.5 | 38.5 | 76.0 | 43.17 | 0.0174 | 0.0414 |
| | 5.0 | 36.5 | 74.5 | 43.21 | 0.0171 | 0.0404 |
| | 7.5 | 34.0 | 71.0 | 44.08 | 0.0162 | 0.0401 |
| | 10.0 | 33.0 | 69.5 | 44.22 | 0.0160 | 0.0376 |
| CPM/GEL (WG) | 2.5 | 36.5 | 77.5 | 42.38 | 0.0178 | 0.0449 |
| | 5.0 | 35.0 | 76.0 | 43.52 | 0.0159 | 0.0365 |
| | 7.5 | 33.0 | 72.5 | 45.66 | 0.0142 | 0.0304 |
| | 10.0 | 31.5 | 70.0 | 46.72 | 0.0122 | 0.0277 |
| CPM/GEL (DC) | 2.5 | 27.5 | 63.0 | 41.12 | 0.0175 | 0.0424 |
| | 5.0 | 26.0 | 59.5 | 42.35 | 0.0138 | 0.0317 |
| | 7.5 | 25.5 | 57.5 | 43.13 | 0.0127 | 0.0294 |
| | 10.0 | 20.5 | 56.0 | 44.01 | 0.0124 | 0.0201 |

**Table 5.22** continued:

| Formulation Type | Binder Concentration (%w/w) | $t_{50}$(min) | $t_{80}$(min) | $t_1$(min) | $K_1$ | $K_2$ |
|---|---|---|---|---|---|---|
| IBUP/ENTA (WG) | 2.5 | 41.0 | 76.0 | 41.77 | 0.0427 | 0.0511 |
| | 5.0 | 39.0 | 74.0 | 43.68 | 0.0313 | 0.0399 |
| | 7.5 | 38.0 | 71.5 | 46.04 | 0.0176 | 0.0386 |
| | 10.0 | 36.5 | 70.0 | 46.17 | 0.0162 | 0.0301 |
| IBUP/ENTA (DC) | 2.5 | 40.0 | 75.0 | 43.25 | 0.0317 | 0.0416 |
| | 5.0 | 38.5 | 74.5 | 44.26 | 0.0283 | 0.0402 |
| | 7.5 | 36.0 | 69.5 | 44.23 | 0.0161 | 0.0382 |
| | 10.0 | 35.5 | 67.5 | 45.09 | 0.0155 | 0.0317 |
| IBUP/HPC (WG) | 2.5 | 41.5 | 72.0 | 44.01 | 0.0181 | 0.0441 |
| | 5.0 | 39.0 | 71.0 | 44.12 | 0.0173 | 0.0437 |
| | 7.5 | 34.5 | 68.5 | 46.38 | 0.0170 | 0.0396 |
| | 10.0 | 32.5 | 67.5 | 47.12 | 0.0162 | 0.0383 |
| IBUP/HPC (DC) | 2.5 | 42.5 | 67.5 | 39.22 | 0.0179 | 0.0414 |
| | 5.0 | 41.0 | 65.5 | 42.08 | 0.0174 | 0.0397 |
| | 7.5 | 40.5 | 64.5 | 43.11 | 0.0167 | 0.0388 |
| | 10.0 | 40.0 | 64.0 | 44.27 | 0.0161 | 0.0369 |
| IBUP/GEL (WG) | 2.5 | 41.5 | 72.0 | 43.17 | 0.0163 | 0.0371 |
| | 5.0 | 39.0 | 71.0 | 44.08 | 0.0161 | 0.0328 |
| | 7.5 | 34.5 | 68.5 | 44.73 | 0.0157 | 0.0317 |
| | 10.0 | 32.5 | 67.5 | 46.82 | 0.0138 | 0.0294 |
| IBUP/GEL (DC) | 2.5 | 40.0 | 70.5 | 43.08 | 0.0158 | 0.0412 |
| | 5.0 | 38.5 | 69.5 | 43.22 | 0.0147 | 0.0401 |
| | 7.5 | 32.0 | 68.0 | 44.18 | 0.0141 | 0.0322 |
| | 10.0 | 31.5 | 66.5 | 42.17 | 0.0126 | 0.0301 |

CHAPTER SIX

MUCOADHESIVE AND MATRIX PROPERTIES OF POLYMERS AND FACTORIAL EXPERIMENTAL DESIGN

## 6.1 Mucoadhesive Properties of Polymers

The results of the *ex-vivo* mucoadhesive studies on the different formulations carried out in 0.1M HCL and phosphate buffer are presented in Table 6.1. Table 6.2 shows the results of the *ex-vivo* mucoadhesive studies of the tablets at a relative density of 0.90, while the graphical representation is presented in Fig 6.1. Generally, the tablets attached longer to the intestinal mucosa in the 0.1M HCL medium when compared with the phosphate buffer medium, while the formulation method affected the mucoadhesive bond strength, with tablets formulated by wet granulation technique adhering longer to the intestinal mucosa than tablets formulated by direct compression. The ranking of the *ex-vivo* mucoadhesive studies was Hydroxypropylcellulose > *Entandophragma angolense* gum > Gelatin for the formulations.

The amount of polymer incorporated into the oral tablets was an important factor in defining the residence time of the tablets on the intestinal mucosa during the ex-vivo mucoadhesive studies. There was an increase in residence time as the concentration of the polymer was increased. The same linear relationship was observed by Ch'ng *et al* (1985), Harris *et al* (1989) and Alur *et al* (1999). A possible reason for an increase in the mucoadhesive bond strength with an increase in the content of the polymer might be due to enhanced water uptake by the polymer, which resulted in tablets swelling and mobilization of flexible chains (Alur *et al*, 1999).

The photomicrographs observed following application and removal of the tablets from the pig ileum during the *ex-vivo* mucoadhesive studies (Fig 6.2) show that there was no erosion of the mucosa after the tablets detached.

**Table 6.1:** Values of time of detachment (minutes) in 0.1M HCl and Phosphate buffer, for different formulations at different relative densities

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
|---|---|---|---|---|
| | | | 0.1M HCl | Phosphate Buffer |
| CPM | 0.0 | 0.825 | 8 | 6 |
| | | 0.850 | 11 | 9 |
| | | 0.875 | 15 | 14 |
| | | 0.900 | 17 | 15 |
| | | 0.950 | 19 | 18 |
| | | 0.975 | 19 | 17 |
| CPM/ENTA (WG) | 2.5 | 0.825 | 201 | 162 |
| | | 0.850 | 203 | 162 |
| | | 0.875 | 205 | 164 |
| | | 0.900 | 214 | 166 |
| | | 0.950 | 227 | 171 |
| | | 0.975 | 283 | 174 |
| | 5.0 | 0.825 | 212 | 168 |
| | | 0.850 | 247 | 173 |
| | | 0.875 | 268 | 179 |
| | | 0.900 | 285 | 187 |
| | | 0.950 | 284 | 190 |
| | | 0.975 | 279 | 190 |
| | 7.5 | 0.825 | 286 | 215 |
| | | 0.850 | 312 | 233 |
| | | 0.875 | 314 | 250 |
| | | 0.900 | 316 | 257 |
| | | 0.925 | 317 | 254 |
| | | 0.950 | 318 | 259 |
| | | 0.975 | 323 | 261 |

**Table 6.1:** continued

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
|---|---|---|---|---|
| | | | 0.1M HCl | Phosphate Buffer |
| CPM/ENTA (WG) | 10.0 | 0.825 | 304 | 277 |
| | | 0.850 | 304 | 279 |
| | | 0.875 | 304 | 281 |
| | | 0.900 | 305 | 282 |
| | | 0.925 | 314 | 286 |
| | | 0.950 | 322 | 291 |
| | | 0.975 | 327 | 297 |
| CPM/ENTA (DC) | 2.5 | 0.825 | 173 | 150 |
| | | 0.850 | 173 | 151 |
| | | 0.875 | 174 | 151 |
| | | 0.900 | 175 | 152 |
| | | 0.925 | 177 | 154 |
| | | 0.950 | 176 | 158 |
| | | 0.975 | 176 | 163 |
| | 5.0 | 0.825 | 185 | 157 |
| | | 0.850 | 187 | 161 |
| | | 0.875 | 187 | 161 |
| | | 0.900 | 187 | 163 |
| | | 0.925 | 191 | 168 |
| | | 0.950 | 195 | 167 |
| | | 0.975 | 198 | 169 |

**Table 6.1** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) 0.1M HCl | Phosphate Buffer |
|---|---|---|---|---|
| CPM/ENTA | 7.5 | 0.825 | 193 | 174 |
| (DC) | | 0.850 | 194 | 175 |
| | | 0.875 | 196 | 175 |
| | | 0.900 | 200 | 177 |
| | | 0.925 | 201 | 179 |
| | | 0.950 | 208 | 179 |
| | | 0.975 | 213 | 181 |
| | 10.0 | 0.825 | 233 | 209 |
| | | 0.850 | 233 | 210 |
| | | 0.875 | 237 | 213 |
| | | 0.900 | 241 | 217 |
| | | 0.925 | 245 | 221 |
| | | 0.950 | 246 | 227 |
| | | 0.975 | 248 | 229 |
| CPM/HPC (WG) | 2.5 | 0.825 | 203 | 172 |
| | | 0.850 | 204 | 169 |
| | | 0.875 | 204 | 170 |
| | | 0.900 | 207 | 172 |
| | | 0.925 | 209 | 174 |
| | | 0.950 | 211 | 175 |
| | | 0.975 | 217 | 179 |

**Table 6.1** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
|---|---|---|---|---|
| | | | 0.1M HCl | Phosphate Buffer |
| CPM/HPC (WG) | 5.0 | 0.825 | 220 | 186 |
| | | 0.850 | 221 | 189 |
| | | 0.875 | 221 | 189 |
| | | 0.900 | 224 | 193 |
| | | 0.925 | 226 | 195 |
| | | 0.950 | 228 | 195 |
| | | 0.975 | 228 | 197 |
| | 7.5 | 0.825 | 306 | 271 |
| | | 0.850 | 307 | 272 |
| | | 0.875 | 310 | 275 |
| | | 0.900 | 314 | 279 |
| | | 0.925 | 313 | 278 |
| | | 0.950 | 313 | 278 |
| | | 0.975 | 314 | 281 |
| | 10.0 | 0.825 | 319 | 288 |
| | | 0.850 | 320 | 290 |
| | | 0.875 | 321 | 287 |
| | | 0.900 | 322 | 291 |
| | | 0.925 | 329 | 294 |
| | | 0.950 | 336 | 291 |
| | | 0.975 | 338 | 293 |

**Table 6.1** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
|---|---|---|---|---|
| | | | 0.1M HCl | Phosphate Buffer |
| CPM/HPC (DC) | 2.5 | 0.825 | 187 | 174 |
| | | 0.850 | 188 | 181 |
| | | 0.875 | 192 | 178 |
| | | 0.900 | 200 | 177 |
| | | 0.925 | 201 | 175 |
| | | 0.950 | 201 | 176 |
| | | 0.975 | 202 | 177 |
| | 5.0 | 0.825 | 209 | 184 |
| | | 0.850 | 210 | 185 |
| | | 0.875 | 211 | 185 |
| | | 0.900 | 211 | 186 |
| | | 0.925 | 215 | 190 |
| | | 0.950 | 218 | 191 |
| | | 0.975 | 218 | 198 |
| | 7.5 | 0.825 | 286 | 259 |
| | | 0.850 | 288 | 261 |
| | | 0.875 | 287 | 262 |
| | | 0.900 | 287 | 262 |
| | | 0.925 | 287 | 262 |
| | | 0.950 | 293 | 268 |
| | | 0.975 | 296 | 271 |

**Table 6.1** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
|---|---|---|---|---|
| | | | 0.1M HCl | Phosphate Buffer |
| CPM/HPC (DC) | 10 | 0.825 | 304 | 279 |
| | | 0.850 | 308 | 283 |
| | | 0.875 | 310 | 285 |
| | | 0.900 | 313 | 286 |
| | | 0.925 | 314 | 287 |
| | | 0.950 | 315 | 288 |
| | | 0.975 | 317 | 290 |
| CPM/GEL (WG) | 2.5 | 0.825 | 147 | 141 |
| | | 0.850 | 148 | 147 |
| | | 0.875 | 148 | 139 |
| | | 0.900 | 152 | 143 |
| | | 0.925 | 155 | 144 |
| | | 0.950 | 159 | 144 |
| | | 0.975 | 159 | 147 |
| | 5.0 | 0.825 | 155 | 147 |
| | | 0.850 | 156 | 148 |
| | | 0.875 | 159 | 153 |
| | | 0.900 | 160 | 152 |
| | | 0.925 | 163 | 152 |
| | | 0.950 | 164 | 154 |
| | | 0.975 | 167 | 153 |

**Table 6.1** continued**:**

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
|---|---|---|---|---|
| | | | 0.1M HCl | Phosphate Buffer |
| CPM/GEL (WG) | 7.5 | 0.825 | 185 | 184 |
| | | 0.850 | 188 | 187 |
| | | 0.875 | 185 | 184 |
| | | 0.900 | 198 | 189 |
| | | 0.925 | 198 | 185 |
| | | 0.950 | 199 | 186 |
| | | 0.975 | 201 | 189 |
| | 10.0 | 0.825 | 271 | 263 |
| | | 0.850 | 273 | 265 |
| | | 0.875 | 277 | 266 |
| | | 0.900 | 277 | 268 |
| | | 0.925 | 280 | 271 |
| | | 0.950 | 281 | 270 |
| | | 0.975 | 286 | 278 |
| CPM/GEL (DC) | 2.5 | 0.825 | 115 | 102 |
| | | 0.850 | 118 | 103 |
| | | 0.875 | 118 | 104 |
| | | 0.900 | 124 | 109 |
| | | 0.925 | 126 | 109 |
| | | 0.950 | 127 | 110 |
| | | 0.975 | 128 | 115 |

**Table 6.1** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
|---|---|---|---|---|
| | | | 0.1M HCl | Phosphate Buffer |
| CPM/GEL (DC) | 5.0 | 0.825 | 154 | 139 |
| | | 0.850 | 164 | 141 |
| | | 0.875 | 158 | 143 |
| | | 0.900 | 164 | 149 |
| | | 0.925 | 166 | 151 |
| | | 0.950 | 162 | 149 |
| | | 0.975 | 165 | 152 |
| | 7.5 | 0.825 | 171 | 161 |
| | | 0.850 | 173 | 160 |
| | | 0.875 | 175 | 161 |
| | | 0.900 | 177 | 162 |
| | | 0.925 | 182 | 167 |
| | | 0.950 | 182 | 167 |
| | | 0.975 | 182 | 168 |
| | 10 | 0.825 | 262 | 247 |
| | | 0.850 | 258 | 243 |
| | | 0.875 | 259 | 246 |
| | | 0.900 | 254 | 241 |
| | | 0.925 | 256 | 243 |
| | | 0.950 | 259 | 246 |
| | | 0.975 | 256 | 241 |

**Table 6.1** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) 0.1M HCl | Phosphate Buffer |
|---|---|---|---|---|
| IBUP | 0.0 | 0.825 | 11 | 12 |
| | | 0.850 | 13 | 12 |
| | | 0.875 | 17 | 18 |
| | | 0.900 | 17 | 17 |
| | | 0.950 | 18 | 18 |
| | | 0.975 | 21 | 19 |
| IBUP/ENTA (WG) | 2.5 | 0.825 | 184 | 172 |
| | | 0.850 | 187 | 173 |
| | | 0.875 | 190 | 173 |
| | | 0.900 | 191 | 176 |
| | | 0.925 | 192 | 179 |
| | | 0.950 | 193 | 179 |
| | | 0.975 | 196 | 179 |
| | 5.0 | 0.825 | 195 | 190 |
| | | 0.850 | 196 | 188 |
| | | 0.875 | 200 | 189 |
| | | 0.900 | 202 | 191 |
| | | 0.925 | 204 | 193 |
| | | 0.950 | 205 | 197 |
| | | 0.975 | 207 | 199 |
| | 7.5 | 0.825 | 271 | 269 |
| | | 0.850 | 272 | 267 |
| | | 0.875 | 273 | 266 |
| | | 0.900 | 273 | 266 |
| | | 0.925 | 276 | 266 |
| | | 0.950 | 276 | 267 |
| | | 0.975 | 276 | 268 |

**Table 6.1:** continued

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
|---|---|---|---|---|
| | | | 0.1M HCl | Phosphate Buffer |
| IBUP/ENTA (WG) | 10.0 | 0.825 | 295 | 284 |
| | | 0.850 | 302 | 291 |
| | | 0.875 | 299 | 288 |
| | | 0.900 | 300 | 289 |
| | | 0.925 | 297 | 290 |
| | | 0.950 | 298 | 291 |
| | | 0.975 | 298 | 294 |
| IBUP/ENTA (DC) | 2.5 | 0.825 | 184 | 172 |
| | | 0.850 | 186 | 175 |
| | | 0.875 | 186 | 175 |
| | | 0.900 | 185 | 174 |
| | | 0.925 | 189 | 178 |
| | | 0.950 | 187 | 175 |
| | | 0.975 | 188 | 176 |
| | 5.0 | 0.825 | 196 | 185 |
| | | 0.850 | 200 | 189 |
| | | 0.875 | 204 | 193 |
| | | 0.900 | 197 | 186 |
| | | 0.925 | 202 | 190 |
| | | 0.950 | 203 | 191 |
| | | 0.975 | 198 | 186 |

**Table 6.1** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
| --- | --- | --- | --- | --- |
| | | | 0.1M HCl | Phosphate Buffer |
| IBUP/ENTA (DC) | 7.5 | 0.825 | 286 | 274 |
| | | 0.850 | 281 | 269 |
| | | 0.875 | 282 | 271 |
| | | 0.900 | 289 | 277 |
| | | 0.925 | 291 | 280 |
| | | 0.950 | 291 | 279 |
| | | 0.975 | 292 | 281 |
| | 10.0 | 0.825 | 296 | 284 |
| | | 0.850 | 295 | 283 |
| | | 0.875 | 294 | 282 |
| | | 0.900 | 291 | 280 |
| | | 0.925 | 292 | 281 |
| | | 0.950 | 292 | 280 |
| | | 0.975 | 292 | 281 |
| IBUP/HPC (WG) | 2.5 | 0.825 | 196 | 183 |
| | | 0.850 | 198 | 187 |
| | | 0.875 | 195 | 189 |
| | | 0.900 | 196 | 185 |
| | | 0.925 | 198 | 187 |
| | | 0.950 | 197 | 186 |
| | | 0.975 | 198 | 187 |

**Table 6.1** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) 0.1M HCl | Phosphate Buffer |
|---|---|---|---|---|
| IBUP/HPC (WG) | 5.0 | 0.825 | 225 | 219 |
| | | 0.850 | 234 | 221 |
| | | 0.875 | 236 | 223 |
| | | 0.900 | 230 | 217 |
| | | 0.925 | 225 | 219 |
| | | 0.950 | 222 | 216 |
| | | 0.975 | 221 | 215 |
| | 7.5 | 0.825 | 270 | 259 |
| | | 0.850 | 272 | 261 |
| | | 0.875 | 271 | 260 |
| | | 0.900 | 274 | 263 |
| | | 0.925 | 267 | 261 |
| | | 0.950 | 269 | 263 |
| | | 0.975 | 276 | 265 |
| | 10.0 | 0.825 | 303 | 297 |
| | | 0.850 | 320 | 309 |
| | | 0.875 | 315 | 304 |
| | | 0.900 | 313 | 302 |
| | | 0.925 | 303 | 297 |
| | | 0.950 | 310 | 299 |
| | | 0.975 | 308 | 302 |

**Table 6.1** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
|---|---|---|---|---|
| | | | 0.1M HCl | Phosphate Buffer |
| IBUP/HPC (DC) | 2.5 | 0.825 | 170 | 163 |
| | | 0.850 | 178 | 169 |
| | | 0.875 | 175 | 164 |
| | | 0.900 | 176 | 165 |
| | | 0.925 | 176 | 167 |
| | | 0.950 | 180 | 169 |
| | | 0.975 | 175 | 164 |
| | 5.0 | 0.825 | 213 | 206 |
| | | 0.850 | 222 | 211 |
| | | 0.875 | 216 | 209 |
| | | 0.900 | 218 | 207 |
| | | 0.925 | 217 | 210 |
| | | 0.950 | 218 | 209 |
| | | 0.975 | 218 | 209 |
| | 7.5 | 0.825 | 246 | 239 |
| | | 0.850 | 256 | 245 |
| | | 0.875 | 257 | 248 |
| | | 0.900 | 255 | 244 |
| | | 0.925 | 248 | 241 |
| | | 0.950 | 252 | 243 |
| | | 0.975 | 254 | 247 |

**Table 6.1** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
|---|---|---|---|---|
| | | | 0.1M HCl | Phosphate Buffer |
| IBUP/HPC (DC) | 10 | 0.825 | 255 | 247 |
| | | 0.850 | 256 | 247 |
| | | 0.875 | 258 | 249 |
| | | 0.900 | 262 | 251 |
| | | 0.925 | 267 | 251 |
| | | 0.950 | 268 | 251 |
| | | 0.975 | 269 | 254 |
| IBUP/GEL (WG) | 2.5 | 0.825 | 179 | 168 |
| | | 0.850 | 181 | 171 |
| | | 0.875 | 181 | 171 |
| | | 0.900 | 182 | 171 |
| | | 0.925 | 185 | 174 |
| | | 0.950 | 185 | 175 |
| | | 0.975 | 188 | 175 |
| | 5.0 | 0.825 | 187 | 179 |
| | | 0.850 | 188 | 180 |
| | | 0.875 | 189 | 181 |
| | | 0.900 | 194 | 183 |
| | | 0.925 | 194 | 184 |
| | | 0.950 | 198 | 185 |
| | | 0.975 | 198 | 186 |

**Table 6.1** continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
|---|---|---|---|---|
| | | | 0.1M HCl | Phosphate Buffer |
| IBUP/GEL (WG) | 7.5 | 0.825 | 205 | 193 |
| | | 0.850 | 205 | 194 |
| | | 0.875 | 207 | 194 |
| | | 0.900 | 207 | 196 |
| | | 0.925 | 208 | 197 |
| | | 0.950 | 208 | 197 |
| | | 0.975 | 208 | 197 |
| | 10.0 | 0.825 | 259 | 251 |
| | | 0.850 | 260 | 249 |
| | | 0.875 | 261 | 251 |
| | | 0.900 | 263 | 252 |
| | | 0.925 | 265 | 254 |
| | | 0.950 | 268 | 254 |
| | | 0.975 | 270 | 259 |
| IBUP/GEL (DC) | 2.5 | 0.825 | 171 | 161 |
| | | 0.850 | 172 | 164 |
| | | 0.875 | 173 | 165 |
| | | 0.900 | 174 | 166 |
| | | 0.925 | 178 | 167 |
| | | 0.950 | 179 | 163 |
| | | 0.975 | 179 | 169 |

**Table 6.1**continued:

| Formulation Type | Concentration (%w/w) | Relative Density ($\rho_r$) | Time of detachment (min) | |
|---|---|---|---|---|
| | | | 0.1M HCl | Phosphate Buffer |
| IBUP/GEL (DC) | 5.0 | 0.825 | 181 | 173 |
| | | 0.850 | 181 | 173 |
| | | 0.875 | 183 | 175 |
| | | 0.900 | 180 | 176 |
| | | 0.925 | 183 | 177 |
| | | 0.950 | 183 | 177 |
| | | 0.975 | 184 | 177 |
| | 7.5 | 0.825 | 181 | 175 |
| | | 0.850 | 184 | 175 |
| | | 0.875 | 187 | 176 |
| | | 0.900 | 188 | 182 |
| | | 0.925 | 191 | 186 |
| | | 0.950 | 191 | 186 |
| | | 0.975 | 195 | 186 |
| | 10 | 0.825 | 231 | 221 |
| | | 0.850 | 232 | 224 |
| | | 0.875 | 233 | 226 |
| | | 0.900 | 234 | 228 |
| | | 0.925 | 236 | 230 |
| | | 0.950 | 238 | 231 |
| | | 0.975 | 240 | 234 |

**Table 6.2**: Values of time of detachment (minutes) in 0.1M HCl and Phosphate buffer for different formulations at relative density of 0.90

| Formulation Type | Binder Concentration | Time of detachment (min) | |
|---|---|---|---|
| | (%w/w) | 0.1M HCl | Phosphate Buffer |
| CPM/ENTA (WG) | 2.5 | 214 | 166 |
| | 5.0 | 285 | 187 |
| | 7.5 | 300 | 257 |
| | 10.0 | 300 | 282 |
| CPM/ENTA (DC) | 2.5 | 175 | 152 |
| | 5.0 | 187 | 163 |
| | 7.5 | 200 | 177 |
| | 10.0 | 241 | 217 |
| CPM/HPC (WG) | 2.5 | 207 | 172 |
| | 5.0 | 224 | 193 |
| | 7.5 | 313 | 279 |
| | 10.0 | 313 | 291 |
| CPM/HPC (DC) | 2.5 | 200 | 177 |
| | 5.0 | 211 | 186 |
| | 7.5 | 287 | 262 |
| | 10.0 | 313 | 286 |
| CPM/GEL (WG) | 2.5 | 152 | 143 |
| | 5.0 | 160 | 152 |
| | 7.5 | 198 | 189 |
| | 10.0 | 277 | 268 |
| CPM/GEL (DC) | 2.5 | 124 | 109 |
| | 5.0 | 164 | 149 |
| | 7.5 | 177 | 162 |
| | 10.0 | 254 | 241 |

**Table 6.2** continued:

| Formulation Type | Binder Concentration (%w/w) | Time of Detachment (min) | |
|---|---|---|---|
| | | 0.1M HCl | Phosphate Buffer |
| IBUP/ENTA (WG) | 2.5 | 191 | 176 |
| | 5.0 | 202 | 191 |
| | 7.5 | 273 | 266 |
| | 10.0 | 300 | 289 |
| IBUP/ENTA (DC) | 2.5 | 185 | 174 |
| | 5.0 | 197 | 186 |
| | 7.5 | 289 | 277 |
| | 10.0 | 291 | 280 |
| IBUP/HPC (WG) | 2.5 | 196 | 185 |
| | 5.0 | 230 | 217 |
| | 7.5 | 274 | 263 |
| | 10.0 | 313 | 302 |
| IBUP/HPC (DC) | 2.5 | 176 | 165 |
| | 5.0 | 218 | 207 |
| | 7.5 | 255 | 244 |
| | 10.0 | 262 | 251 |
| IBUP/GEL (WG) | 2.5 | 182 | 171 |
| | 5.0 | 194 | 183 |
| | 7.5 | 207 | 196 |
| | 10.0 | 263 | 252 |
| IBUP/GEL (DC) | 2.5 | 174 | 166 |
| | 5.0 | 180 | 176 |
| | 7.5 | 188 | 182 |
| | 10.0 | 234 | 228 |
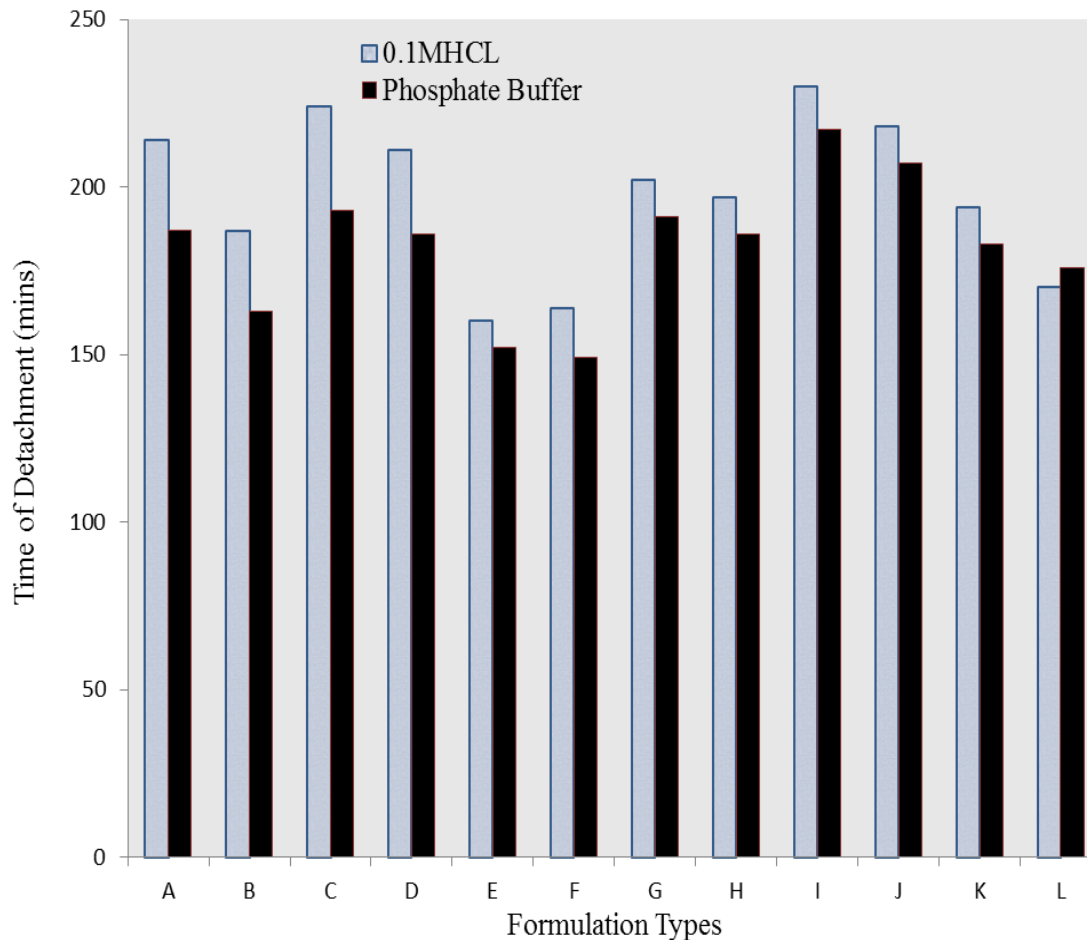
**Fig 6.1**: Plot of Time of Detachment (mins) Vs Formulation Type for Tablets at Relative Density, $(\rho_r) = 0.90$

**KEY**

| | | |
|---|---|---|
| A | = | Chlorpheniramine maleate tablets containing *Entandophragma angolense* gum formulated by wet granulation |
| B | = | Chlorpheniramine maleate tablets containing *Entandophragma angolense* gum formulated by direct compression |
| C | = | Chlorpheniramine maleate tablets containing hydroxypropylcellulose formulated by wet granulation |
| D | = | Chlorpheniramine maleate tablets containing hydroxypropylcellulose gum formulated by direct compression |
| E | = | Chlorpheniramine maleate tablets containing gelatin formulated by wet granulation |
| F | = | Chlorpheniramine maleate tablets containing gelatin formulated by direct compression |
| G | = | Ibuprofen tablets containing *Entandophragma angolense* gum formulated by wet granulation |
| H | = | Ibuprofen tablets containing *Entandophragma angolense* gum formulated by direct compression |
| I | = | Ibuprofen tablets containing hydroxypropylcellulose formulated by wet granulation |
| J | = | Ibuprofen tablets containing hydroxypropylcellulose gum formulated by direct compression |
| K | = | Ibuprofen tablets containing gelatin formulated by wet granulation |
| L | = | Ibuprofen tablets containing gelatin formulated by direct compression |
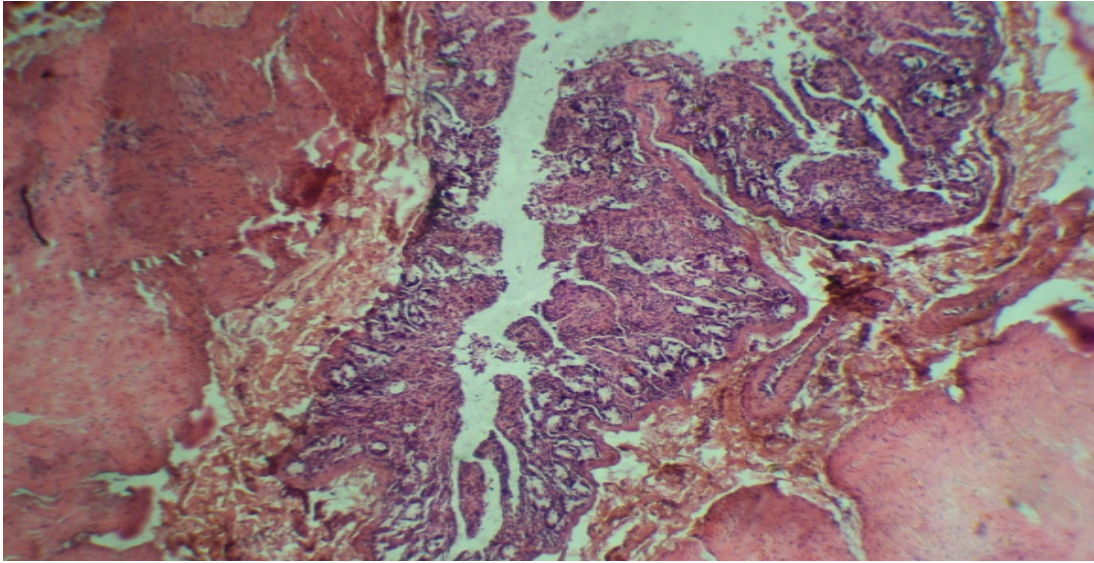
**Fig 6.2A**: Light micrograph of the pig ileum prior to application of the oral tablets.
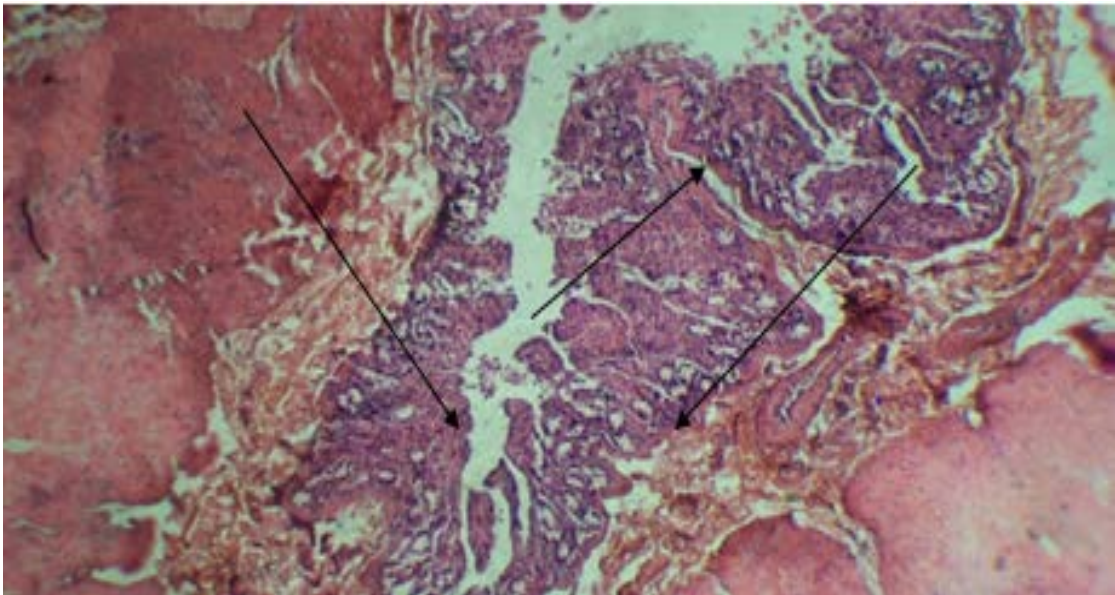


**Fig 6.2B**: Light micrograph of the pig ileum after the detachment of the oral tablets. The arrows show points of attachment of the tablets

**6.2     Matrix Properties of Polymers**

**6.2**.1   **Effects of Polymer Type and Concentration**

The values obtained for the mechanical assessment of the matrix tablets containing different ratios of the drug (chlorpheniramine maleate) and the polymers (*Entandophragma angolense* gum or hydroxypropylcellulose or gelatin) are presented in Table 6.3. It was observed that the crushing strength of the tablets increased as the concentration of the polymers in the tablet matrices increased. There was, however, a decrease in friability values. This could have been due to the fact that polymers are plastoelastic in nature and as the concentration is increased during the process of compression, plastic deformation also increases, leading to the formation of more solid bonds, and consequently, an increase in crushing strength. The resistance of the matrices to fracture and abrasion as the polymer concentration increased could also be attributed to the formation of more solid bonds. (Bamiro *et al*, 2010). The ranking of the crushing strength for the polymers was in the order Hydroxypropylcellulose > *Entandophragma angolense* > gelatin. All the polymers gave friability values less than 1%.

Representative plots of the release profiles of chlorpheniramine maleate from *Entandophragma angolense* gum (Hydroxypropylcellulose or gelatin) matrices are presented in Fig 6.3, while the release parameters derived from the various kinetic models are presented in Appendix II.

The increase in the release rate of the matrices containing 60 %w/w polymers may be due to the weakening of the matrix lattice due to the high concentration of the water soluble chlorpheniramine maleate, which provides a diffusion pathway for erosion/disintegration of the matrix. The reduction in the bond strength of the matrix was as a result of the formation of the gel phase, and increased permeability of solvent in the swollen region (Kalu *et al,* 2007)

The release rate of the drugs decreased as the concentration of the polymers increased as shown in the representative plots in Fig 6.3. This could be due to increase in the extent of viscous gel formation which is more likely to be resistant to drug diffusion and erosion (Sandip *et* al, 2003) The ranking of $t_{25}$, which is the time taken for 25% of the drug to be released, was *Entandophragma angolense* gum > Gelatin > hydroxypropylcellulose, while the ranking for the amount of drug released after 14 hours

was Gelatin > *Entandophragma angolense* > hydroxypropylcellulose. There was no significant difference (p>0.005) between the drug released from *Entandophragma angolense* gum and gelatin.

The release parameters derived from kinetic modeling are given in Appendix II. The parameters (regression equations, correlation coefficient ( $r^2$) diffusional release exponents (n) and kinetic constants ) were obtained by fitting the data obtained into the different release models (Korsemeyer, Higuchi, Zero-order and Hixson-Crowell). The model with the highest correlation coefficient was chosen as the best fit.

The highest correlation coefficient (0.991) was observed in the zero-order model for the matrix containing 90%w/w *Entandophragma angolense* gum, thus indicating non Fickian diffusion. The release kinetics fitted the zero-order model, thus indicating that the release of the drug from the matrix was concentration independent. The real dissolution of a drug substance (intrinsic dissolution rate) undergoes a zero order reaction, if its surface is kept temporarily constant. The release parameters derived from the Korsemeyer's model show an anomalous transport mechanism; with n values decreasing as the polymer concentration was decreased for both *Entandophragma angolense* gum and gelatin, while the reverse was observed for the hydroxypropylcellulose tablet matrices. The values of n, however, indicate that the release of the drug is at least, partially controlled by viscoelastic relaxation of the matrix during solvent penetration.

**Table 6.3:** Values of crushing strength and friability derived from the matrix tablets
containing different concentrations of polymer (Mean± SD, n = 4)

| Polymer | Polymer Concentration (%w/w) | Crushing Strength (N) | Friability (%) |
|---|---|---|---|
| *Entandophragma angolense* gum | 90 | 80.13±0.03 | 0.33±0.04 |
| | 80 | 75.13±0.12 | 0.44±0.07 |
| | 70 | 71.28±0.06 | 0.59±0.11 |
| | 60 | 68.93±0.02 | 0.76±0.02 |
| | | | |
| Hydroxypropylcellulose | 90 | 81.22±0.11 | 0.31±0.04 |
| | 80 | 79.12±0.23 | 0.32±0.05 |
| | 70 | 78.11±0.14 | 0.36±0.02 |
| | 60 | 72.22±0.04 | 0.47±0.13 |
| | | | |
| Gelatin | 90 | 76.24±0.12 | 0.67±0.09 |
| | 80 | 73.15±0.13 | 1.76±0.03 |
| | 70 | 68.43±0.03 | 0.83±0.05 |
| | 60 | 65.39±0.03 | 0.88±0.04 |
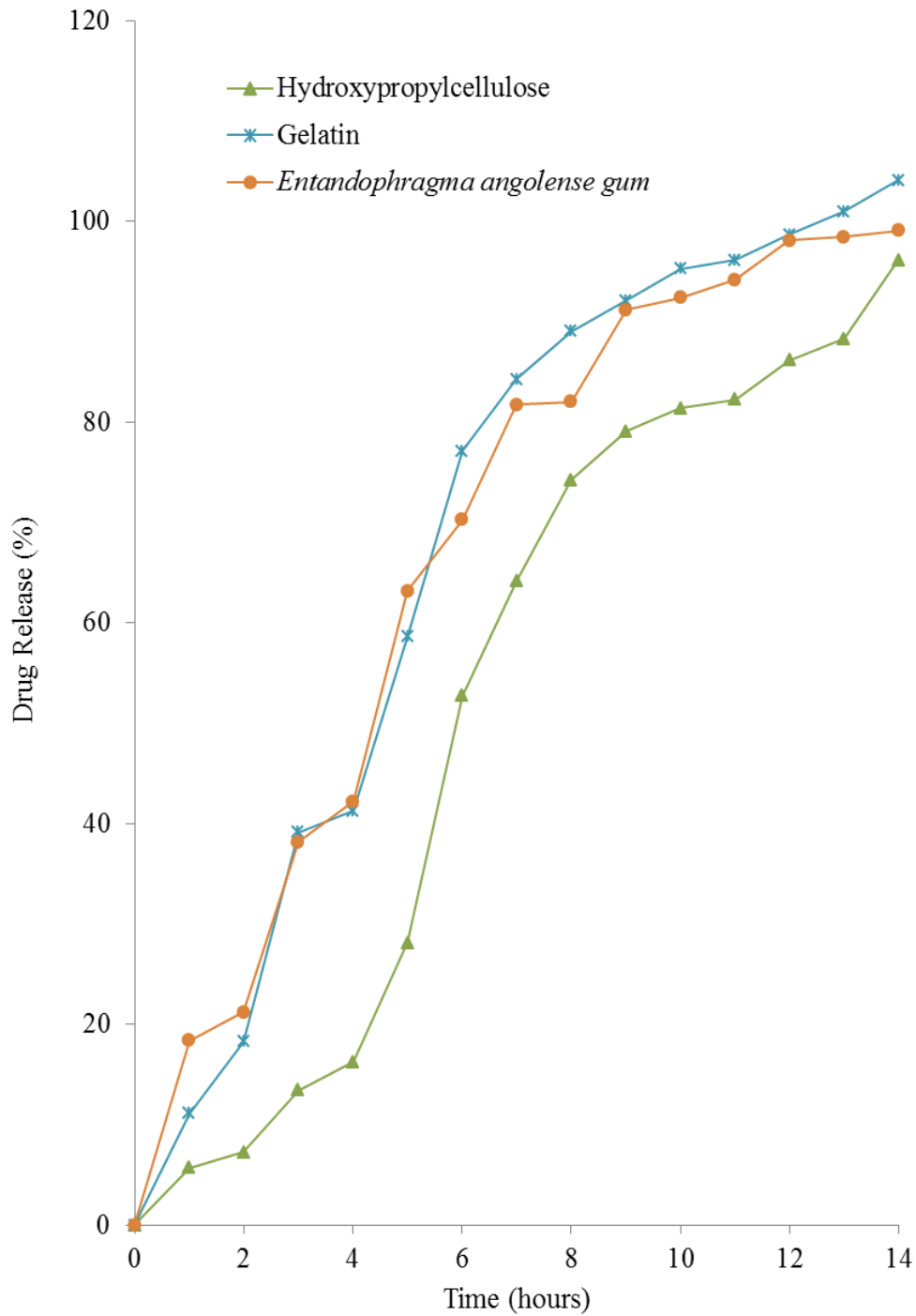
**Fig 6.3:** Release Profile of chlorpheniramine maleate from matrices containing 60% w/w polymers

## 6.3            Factorial Experimental Design

A factorial experiment is a type of statistical experimental design wherein the experiments are carried out at all the possible combinations of the levels of the factors considered in the experiment.

The purpose of using a full factorial design was to carry out a complete study of the effects of the process parameters and their interactions, with the aid of a suitable statistical software (Minitab[c] 16). The factorial experiment design for this study involved the use of four independent process parameters (Nature of Binder, Concentration of binder, Relative density and Tabletting Technique) which were applied at two levels (high and low, denoted by H and L respectively) and are summarized in Table 6.4. A $2^4$ full factorial design was used as the research methodology, which required sixteen combinations to be prepared (Table 6.5). The sequence of the responses (Disintegration Time, Tensile Strength, Brittle Fracture Index and Mucoadhesion) were randomized. Statistical analysis of the effects of the various parameters on the responses was compared by Student's *t*-test. At 95% confidence level, a *p* value lower than or equal to 0.05 was required for significance. The summary of the individual and interaction coefficients of the factors are presented in Tables 6.6 and 6.7 respectively.

Table 6.4: Independent process parameters and their levels

| Independent process parameters | Associated variables | Low Level (coded L) | High Level (coded H) |
|---|---|---|---|
| Nature of Binder | X1 | *Entandophragma angolense* gum | Hydroxymethylcellulose |
| Concentration of Binder | X2 | 2.5%w/w | 10.0%w/w |
| Relative Density | X3 | 0.85 | 0.90 |
| Tabletting Technique | X4 | Direct Compression | Wet Granulation |

Table 6.5: Values of Disintegration Time ($D_T$), Tensile Strength (T), Brittle Fracture Index (BFI) and Mucoadhesion time ($M_T$) for the Factorial Experimental Design obtained from the process parameters at low (L) and high (H) levels

| Combination Codes | | | | $D_T$ | T | BFI | $M_T$ |
|---|---|---|---|---|---|---|---|
| N | C | D | M | (mins) | ($MNm^{-2}$) | | (mins) |
| L | H | H | H | 7.71 | 1.291 | 0.277 | 205 |
| H | H | L | L | 7.42 | 0.992 | 0.223 | 308 |
| L | H | H | L | 7.39 | 1.799 | 0.268 | 241 |
| L | H | L | H | 6.22 | 1.271 | 0.219 | 209 |
| L | L | H | L | 2.09 | 1.779 | 0.158 | 176 |
| H | L | H | H | 2.47 | 1.812 | 0.182 | 207 |
| H | H | H | H | 8.37 | 1.331 | 0.290 | 322 |
| H | L | H | L | 2.76 | 2.113 | 0.173 | 200 |
| H | H | H | L | 9.71 | 1.798 | 0.281 | 313 |
| L | L | H | H | 2.92 | 2.156 | 0.169 | 214 |
| L | H | L | L | 5.96 | 1.123 | 0.217 | 233 |
| H | H | L | H | 6.83 | 1.198 | 0.232 | 321 |
| H | L | L | L | 1.94 | 0.817 | 0.122 | 181 |
| L | L | L | H | 1.63 | 1.173 | 0.118 | 203 |
| H | L | L | H | 2.10 | 0.982 | 0.131 | 204 |
| L | L | L | L | 1.45 | 1.017 | 0.109 | 184 |

N = Nature of Binder

C = Concentration of Binder

D = Relative Density of Tablet

M = Tabletting Technique

**Table 6.6**: Summary of the individual coefficients of the variables on Disintegration time, Tensile strength, Brittle Fracture Index (BFI) and Mucoadhesion time

| Variable Factor | Coefficient | Disintegration Time (min) | Tensile Strength ($MNm^{-2}$) | BFI | Mucoadhesion Time (min) |
|---|---|---|---|---|---|
| Nature of Binder ($X_1$) | Effect | 0.389 | -0.035 | 0.006 | 24.437 |
| | p-value | 0.018 | 0.599 | 0.000 | 0.009 |
| Concentration of Binder ($X_2$) | Effect | 2.641 | -0.065 | -0.053 | 36.437 |
| | p-value | 0.000 | 0.338 | 0.000 | 0.001 |
| Relative Density ($X_3$) | Effect | 0.617 | 0.344 | 0.027 | 2.188 |
| | p-value | 0.001 | 0.000 | 0.000 | 0.780 |
| Tabletting Technique ($X_4$) | Effect | -0.029 | -0.014 | 0.004 | 3.063 |
| | p-value | 0.839 | 0.834 | 0.000 | 0.697 |

**Table 6.7**: Summary of the interaction coefficients of the variables on Disintegration time, Tensile strength, Brittle Fracture Index (BFI) and Mucoadhesion time

| Variable Factor | Coefficient | Disintegration Time (min) | Tensile Strength ($MNm^{-2}$) | BFI | Mucoadhesion Time (min) |
|---|---|---|---|---|---|
| $X_1X_2$ | Effect | 0.242 | 0.015 | 22.563 | 43.13 |
| | p-value | 0.035 | 0.762 | 0.001 | 0.001 |
| $X_1X_3$ | Effect | 0.011 | 0.040 | 1.312 | 0.15 |
| | p-value | 0.905 | 0.437 | 0.718 | 0.718 |
| $X_1X_4$ | Effect | -0.229 | -0.036 | 3.437 | 1.00 |
| | p-value | 0.043 | 0.475 | 0.363 | 0.363 |
| $X_2X_3$ | Effect | 0.227 | -0.140 | -0.938 | 0.07 |
| | p-value | 0.043 | 0.029 | 0.796 | 0.796 |
| $X_2X_4$ | Effect | -0.139 | -0.064 | -7.813 | 5.17 |
| | p-value | 0.160 | 0.227 | 0.072 | 0.072 |
| $X_3X_4$ | Effect | -0.306 | -0.0984 | -0.812 | 0.06 |
| | p-value | 0.732 | 0.086 | 0.822 | 0.822 |

## CHAPTER SEVEN

## GENERAL DISCUSSION

Hydrophilic polymers have attracted a lot of attention in the design of oral drug delivery systems due to their flexibility, cost-effectiveness, and broad regulatory acceptance. Gums from natural sources are biodegradable and non-toxic, they hydrate and swell in contact with aqueous media and have been used for the preparation of single unit dosage forms (Adeleye *et al*, 2011). Naturally occurring gums have also been investigated for their use as binders, suspending, emulsifying or stabilizing agents (Nasipuri, 1997; Odeku and Itiola, 1998; Femi-Oyewo *et al*, 2004; Odeku, 2005; Emeje *et al*, 2009; Bamiro *et al*, 2010). Binders confer the structural strength required by tablets during processing, handling, packaging and transportation, and naturally occurring gums have been used in producing tablets with different mechanical strength and drug release properties for different pharmaceutical purposes (Bamiro *et al*, 2010). Gums are generally non-toxic and widely available, hence the continued interest in their development as excipients for pharmaceutical formulations (Kalu *et al*, 2007).

The overall objective of the present study was to investigate the suitability and relative efficiency of *Entandophragma angolense* gum as a binder and mucoadhesive component in oral tablets. Flat-faced uncoated tablets containing *Entandophragma angolense* gum were formulated using chlorpheniramine maleate and ibuprofen as model drugs. *Entandophragma angolense* gum was compared with similar formulations containing Gelatin BP and Hydroxypropylcellulose. The matrix properties of *Entandophragma angolense* gum were also investigated and the quantitative effects of the process parameters of the tablet formulations were also analyzed using a computer aided full factorial experiment designed by Montgomery (1991).

Gums are considered as non-wood forest products, which are end products of metabolic pathways in plants. Millions of people worldwide, especially in developing countries, depend on the collection of gum as a means of livelihood. However,

overexploitation of the commercial tapping of gum has led to a decline in this profit oriented business (Bhatt and Mohan, 1990). The main reasons for this decline are the unscientific and brutal methods of gum collection, which is done mainly by blazing,

The amount of polymer incorporated into the oral tablets was an important factor in defining the residence time of the tablets on the intestinal mucosa during the ex-vivo mucoadhesive studies. There was an increase in residence time as the concentration of the polymer was increased. The same linear relationship was observed by Ch'ng *et al* (1985), Harris *et al* (1989) and Alur *et al* (1999). A possible reason for an increase in the mucoadhesive bond strength with an increase in the content of the polymer might be due to enhanced water uptake by the polymer, which resulted in tablets swelling and mobilization of flexible chains (Alur *et al*, 1999).

The photomicrographs observed following application and removal of the tablets from the pig ileum during the *ex-vivo* mucoadhesive studies (Fig 6.2) show that there was no erosion of the mucosa after the tablets detachedpeeling or making extremely deep cuts; activities which are injurious to the tree trunk. Nair (2007) proposed a more scientific approach to gum collection to ensure optimum yield and regeneration of tapped trees. The use of ethephon (2-chloroethyl phosphoric acid), which is a safe, inexpensive and non-toxic plant growth regulator, was adopted for the collection of the *Entandophragma angolense* gum (Nair, 2007). Poor soil, drought and hostile environmental conditions have been reported to promote the production of gums in temperate regions (Bhatt and Mohan, 1990). Burkhill (1997) reported that trees grown in tropical regions produce more gums and resins in the early hours of the day. Bellal *et al* (2005) reported that gum exudates from incisions made on tree trunks are produced more in the early hours of the morning, especially during the dry season than during the wet season. Preliminary studies carried out in the present work suggested that there was need to pick the gum at particular times of the season. In the light of this, collection of *Entandophragma angolense* gum was done in the early hours of the day between December and February. The percentage yield of *Entandophragma angolense* gum obtained as exudates from the incised trunks of *Entandophragma angolense* tree was 48.46 %w/w. This yield is considerably high for a natural gum due to the time of collection of the exudates (Bellal *et al*, 2005). The gum has applications in the paper industry where it is used in regular distribution of pulp fabrics, in

the textile industry as a thickening agent for pigment in printing fabrics, and also in the petroleum and gas industry where it is used as a component in drilling fluids (Nair, 2007). *Entandophragma angolense* gum also has applications in traditional medicine where it is administered as a febrifuge (Burkhill, 1997).

The physicochemical composition of the polymers varied considerably. The results showed that *Entandophragma angolense* gum had the highest swelling capacity of the three polymers utilized. The swelling power provides evidence of the magnitude of interaction between the amorphous and crystalline domains that make up the polymers (Avachat and Kotwal, 2007). The extent of the swelling power of a gum could be used in the preliminary determination of some excipient properties of the gum (Emeje *et al*, 2009). The swelling capacity test is used to evaluate the degree to which fluid can be held within the gum as this can also affect the release of a drug from tablet matrices (Adetunji *et al,* 2012). The ranking of the swelling capacity of the polymers at both 27 $^0$C (room temperature) and 80 $^0$C was *Entandophragma angolense* gum > Gelatin > Hydroxypropyl cellulose.

Thus, *Entandophragma angolense* gum showed the highest swelling when compared with gelatin and hydroxypropylcellulose. There was a slight variation in the percentage solubility of the gums in water at both temperatures used. The ranking of the solubility of the gums at room temperature (27 $^0$C) was *Entandophragma angolense* gum > Hydroxypropylcellulose > Gelatin, while the ranking at 80 $^0$C was *Entandophragma angolense* gum > Gelatin > Hydroxypropylcellulose. The difference in the solubility of the polymers at 27 $^0$C and 80 $^0$C could be attributed to the difference in the forces of molecular association present within the granules. Gelatin is a proteineous biodegradable polymer obtained from partial hydrolysis of the collagen derived from skin, connective tissues and bones of animals, and at temperatures above 72 $^0$C, if forms loosely wrapped structures which could enhance its solubility (Jayan *et al,* 2009). Soluble cell-wall materials make up a larger proportion of *Entandophragma angolense* gum (Burkhill, 1997), and thus, could be responsible for enhanced solubility at the higher temperature.

Particle shape has been shown to influence the compaction characteristics and eventually the packing behaviour of polymers (Bamiro *et al*, 2010). This is because there is a tendency for particle rearrangement to occur in the initial compaction process at low

pressures (Wray, 1992). The photomicrographs of the polymers (Fig. 4.6) showed irregular shaped granules for the polymers with the polymers existing as aggregates, while granules of *Entandophragma angolense* gum were observed to be the smallest. The irregular shape and high specific surface area observed for the granules of *Entandophragma angolense* gum could facilitate high bond formation during compaction.

The packing and cohesive properties of polymers influence the various aspects of powder processing such as milling, blending, flow from hoppers, compression and packing into capsule shells or containers. These properties depend to a large extent on the particle size distribution and shape of the granules (Adeleye *et al*, 2011). The angle of repose is inversely related to the particle size of the granules, which is in turn directly related to the cohesiveness of the granules (Shotton and Obiorah, 1973). The angle of repose has been defined as the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane (Keith, 1986). Such measurements give a qualitative assessment of the internal cohesive and frictional effects under low levels of external loading, as might apply in powder mixing or in tablet die filling. Angle of repose is particularly sensitive to changes in particle size distribution and moisture content, and the limitation of this measurement is primarily due to the assumption that a perfect cone will be formed during experimentation to conform with the relevant equation (Eqn. 40), though in practical situations, this is not the case. In addition, the dynamic angle of repose measurement is preferred since it most closely mimics the manufacturing situation in which the powder is in motion (Keith, 1986). The ranking of the angle of repose obtained for the polymers was Hydroxypropylcellulose > *Entandophragma angolense* gum > Gelatin; thus, *Entandophragma angolense* gum, with a lower angle of repose, is expected to be less cohesive and more free flowing than hydroxypropylcellulose.

The need for a proper understanding of the rheological properties of pharmaceutical materials is an essential fundamental aspect to the evaluation of pharmaceutical dosage forms (Marriott, 1988). The variation in rheological properties of a material under varying environmental conditions, is, however, well recognized (Sinko, 2011). The rheological properties of *Entandophragma angolense* gum were determined using the Rapid Visco Analyser (RVA 3-D model). The pasting temperature (which is the

temperature at which a perceptible increase in viscosity occurred) was slightly higher for *Entandophragma angolense* gum than gelatin. Generally, the final viscosity of all the polymers had a direct relationship with their concentration. The viscosity of a polymer is a measure of the molecular chain structure of the polymer, which determines the manufacturing characteristics of the polymer (Stanley, 1986). Rippie and Danielson (1981) had earlier reported that a highly viscous substance has the tendency of demonstrating good binding characteristics during tabletting; thus, *Entandophragma angolense* gum with the highest viscosity among all the three polymers is expected to exhibit good binding properties as was generally the case from the experimental results. Thus, viscosity properties of materials may offer some predictable value of binding properties.

The bulk density of a powder describes its packing behaviour during the various unit operations of tabletting such as die filling, mixing, granulation and compression. Higher bulk density is advantageous because of reduction in the fill volume of the die. The ranking of the bulk density was Gelatin > Hydroxypropylcellulose > *Entandophragma angolense* gum. The differences observed in the bulk density values could be due to the granule size which is known to affect the packing arrangement of powder particles. Such properties should therefore be monitored and taken into account when developing tablet formulations, and determining the relevance of fundamental properties in such studies.

Heckel and Kawakita plots were used in assessing the compressional characteristics of the polymers and formulations. Each of the plots is known to have its limitations. Heckel plots generally exhibit linearity at high pressures while Kawakita plots generally exhibit linearity at low pressures (Celik, 1992). However, both plots were used to obtain a more comprehensive understanding of the compressibility of the various materials (Alebiowu and Itiola, 2002).

The results obtained showed that the Heckel plots exhibited some degree of linearity at both low and high pressures, with the regions at high pressures generally having higher correlation coefficient values ($r > 0.997$). The plots generally showed an initial curvilinear region at low pressures (Figs 5.5-5.7). This suggests that fragmentation and probably some degree of plastic deformation were taking place. This is probably due to the fact that the system would start deforming plastically from the moment the yield

value for one particle is exceeded during compression. Thus, it should be expected that, to some extent, the process of fragmentation would occur simultaneously with plastic and elastic deformation of the constituent particles.

The mean yield pressure, $P_y$, obtained from the second more linear portion of the Heckel plots for the formulations were of the order Hydroxypropylcellulose >*Entandophragma angolense* gum > Gelatin, indicating that there was a faster onset of plastic deformation exhibited by *Entandophragma angolense* gum when compared with hydroxypropylcellulose. Roberts and Rowe (1986) studied the effect of the relationship of punch velocity and particle size on the compaction behavior of materials with varying deformation mechanisms. The sensitivity to changes in the compression rate of formulations containing *Entandophragma angolense* gum as additive should be higher than those containing hydroxypropylcellulose. Strain Rate Sensitivity (SRS) (Roberts and Rowe, 1986) is a slope of the yield stress Vs velocity plot, or, where the plots are non-linear, percent increase in yield stress. Low SRS values indicate relative time independence (for brittle fracture or fragmentation), while high SRS values suggest time dependent deformation, which is usually for plastic flow which is generally dependent on the period of time of compression. Stress rate is a function of change in compression pressure, while strain rate is a function of change in the thickness of the tablet due to the speed of compression.

The values of $\rho_{rO}$ represent the densities of the materials at zero pressure. Generally, Formulations containing *Entandophragma angolense* gum had higher values of $\rho_{rO}$ than those containing gelatin, but lower values when compared with formulations containing hydroxypropylcellulose. This indicates that formulations containing *Entandophragma angolense* gum exhibited a higher degree of initial packing in the die as a result of die filling than formulations containing gelatin. This could be as a result of the granule shape and size of the *Entandophragma angolense* gum which would facilitate closer packing of the particles when compared with gelatin. Although the particles of hydroxypropylcellulose were observed to be larger than those of *Entandophragma angolense* gum, the higher value of $\rho_{rO}$ exhibited by hydroxypropylcellulose than *Entandophragma angolense* gum in the formulations could be as a result of the more tightly packed constituent particles of hydroxypropylcellulose (Fig 4.6). The relative

density $\rho_{rB}$, which describes the phase of densification after the application of low pressures due to rearrangement and/or fragmentation of the particles before appreciable deformation begins, is affected by the packing geometry of the materials (Alebiowu and Itiola, 2002). The values (Tables 5.8 and 5.9) indicate that formulations containing hydroxypropylcellulose had the highest extent of fragmentation followed by formulations containing *Entandophragma angolense* gum, with a higher degree of fragmentation than formulations containing gelatin.

The Kawakita plots showed good linearity throughout the range of compression pressures employed with correlation coefficient $r>0.999$. The high correlation is an indication that the Kawakita equation can be employed in describing the densification mechanisms of the polymer tablets. The value of $P_K$, which represents an inverse measure of the amount of plastic deformation occurring during the compression process (Odeku and Itiola, 1998), was found to decrease with increase in concentration of the gums. The ranking of $P_K$ for the formulations was Gelatin $>$ *Entandophragma angolense* gum $>$ Hydroxypropylcellulose. Thus, hydroxypropylcellulose appears to have exhibited the highest plastic deformation followed by *Entandophragma angolense* gum.

The values of $\rho_I$, i.e. (1-a), which are significantly influenced by the packing geometry of the powders resulting from vibration and packing of the powder bed was found to be of the ranking order of Hydroxypropylcellulose $>$ *Entandophragma angolense* gum $>$ Gelatin. Generally, the values of $\rho_I$ were higher than the corresponding values of $\rho_O$, as observed also by Odeku and Itiola (1998), Odeku (2005) and Adetunji *et al* (2006). This supports the assertion that $\rho_I$ provides a measure of the packed initial relative density of the formulations with the application of small pressure to provide the densest packing possible (Podozeck and Sharma, 1996).

The mechanical strength of a tablet may be characterized by two properties: bond strength and brittleness (Itiola and Pilpel, 1991). Bond strength can be evaluated by the tensile strength (T) of the tablet, while the tendency of a tablet to cap or laminate can be measured by the brittle fracture index (BFI) of the material. Roberts and Rowe (1986) and Armstrong and Palfrey (1987) established the effect of compression speed on the mechanical properties of tablets. As the punch speed increases, the tensile strength of tablets, especially for plastic and viscoelastic materials, decreases, while the tendency for

tablets to undergo capping or lamination increases as a result of an increase in elastic energy due to axial recovery, and perhaps also to the expansion of entrapped air during decompression and ejection (Bateman, 1987; Garr and Rubinstein, 1991). The tablets formulated by the wet granulation techniques exhibited higher T values and lower BFI values than the tablets that were compressed directly (Table 5.14). The ranking of T for the formulations containing the polymers was Hydroxypropylcellulose > *Entandophragma angolense* gum > Gelatin, while the BFI ranking was the reverse. A low value of BFI is desirable for the minimization of lamination and capping during tablet production, while the desirable effects of tensile strength depends on the intended use of the tablets (Alebiowu and Itiola, 2002). Thus, *Entandophragma angolense* gum could be more useful as a binder for tablets in which high mechanical strength is desirable when compared with gelatin.

In the evaluation of *Entandophragma angolense* gum for its mucoadhesive properties, it was observed that tablets formulated by wet granulation techniques adhered more to the intestinal mucosa when compared with tablets formulated by direct compression technique. This is probably as a result of adhesion by hydration as explained by Smart (2007). The tablets formulated by wet granulation had an intrinsic ability to swell more in both hydrochloric acid and phosphate media than directly compressed tablets. This is probably as a result of the presence of more hydrogen bonds in the matrix of the tablets formulated by wet granulation, thus amplifying the mucoadhesive ability of the gum in those tablets (Smart, 2001; Vitaliy, 2011). In addition, the tablets attached more in the 0.1M HCl medium than Phosphate buffer. The observed mucoadhesive rank order of the polymers was Hydroxypropylcellulose > *Entandophragma angolense* gum > Gelatin.

The phenomenon of mucoadhesion can be used as a model for controlled drug delivery approaches for a number of drug candidates. The various advantages of the oral mucoadhesive drug delivery systems like prolongation of the residence time of the drug which in turn increases the absorption of the drug are important factors in the oral bioavailability of many drugs. The factors which are determinant of the overall success of the mucoadhesive drug delivery are the polymer physicochemical properties and the *in-vivo* factors such as the mucin turnover rate and mucin flow (Pranshu and Madhav, 2011).

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As earlier mentioned, several theories have been described to explain the processes of mucoadhesion (Section 2.17.2). The amount of polymer incorporated into the tablets was a critical factor in defining the resultant mucoadhesive attachments. The experiments showed that there was a direct relationship between increasing the concentration of polymer and the time of adherence on the porcine intestinal mucosa. A possible reason for this could be an increase in water uptake due to the increased polymer content, which resulted in tablet swelling and consequent increase in the surface area of flexible chains responsible for increased mucoadhesion time (Alur *et al*., 1999; Hirofumi *et al,* 2010). The release of chlorpheniramine maleate (or Ibuprofen) and the duration of mucoadhesion can thus be optimized by varying the amount of polymer contained in the tablet.

The pH of a medium can influence the formal charge on the surface of the intestinal mucosa as well as certain ionizable mucoadhesive polymers. Mucous will have a different charge density depending on pH due to the difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. Some studies have shown that the pH of the medium is important for the degree of hydration of the polymer (Kamath and Park, 1994; Chickering *et al*, 1997; Ahuja *et al*, 1999; Asane *et al*, 2008). The difference in retention time as a result of pH differences in polymer-substrate interface was also docqsumented by Ch'ng *et al* (1985) when they worked on polycarboxyl-based polymers. The observed retention time, which was higher in the more acidic 0.1M HCl (with a lower pH) could thus be as a result of chemical modification between the porcine surface and the polymer. The presence of an acidic mucoadhesive polymer, such as *Entandophragma angolense*, in an acidic medium will result in a relatively long residence time in the acid environment of the stomach. Moreover, ibuprofen, which is a relatively weak acid with a pKa of $4.43 \pm 0.03$, is expected to exhibit a low solubility at acidic pH, thus reducing its absorption in the gastric medium and enhancing its retention time (Asane *et al*, 2008).

Release of drug from polymeric matrices occurs when a matrix is placed in contact with a compatible solvent. Progressive swelling of the polymer particles is observed, leading to considerable structural changes. These include changes in the mobility of the macromolecular chains, macromolecular relaxations, and changes of the porous structure including alteration of the shape and size distribution of the pores (Lingmin *et al,* 2010).

These will change the porosity and tortuosity of the polymer during swelling and diffusional release (Korsmeyer *et al*., 1983). The results of the release profiles of chlorpheniramine maleate from the polymer matrices showed an increase in the release rate of the drug as the concentration of the polymer decreased. Generally, when *Entandophragma angolense* gum comes in contact with the dissolution medium, the polymer absorbs water, swells and becomes a hydrated gel (Adetunji *et al,* 2011a). The decrease in the release rate of the drug as a result of increase in polymer concentration may therefore be accounted for by the reduction in the number of low microviscosity pores. Generally, the ranking for the release rate of the drug from the matrix was Gelatin > *Entandophragma angolense* > hydroxypropylcellulose.

The results of the factorial experimental design (Tables 6.6 and 6.7) provide a clear indication of the effects of the four independent process parameters: Nature of Binder ($X_1$), Concentration of binder ($X_2$), Relative density of tablet ($X_3$), and Tabletting Technique ($X_4$), on the four responses studied.The ranking of the individual effects on disintegration time was $X_2 > X_3 > X_1 > X_4$ ;  on tensile strength, was $X_3 >  X_2 > X_1 > X_4$ ; on BFI,  $X_2 >  X_3 > X_1 > X_4$ and on mucoadhesion time,  $X_2 >  X_1 > X_4 > X_3$ . The rankings show the relative magnitudes of the effects of the factors on these variables. A positive effect signifies that the response variable has increased in value or magnitude, while a negative effect shows a decrease.  Concentration of binder ($X_2$) had the largest positive effect on disintegration time of the tablets. This effect shows that changing the concentration from lower (2.5 %w/w) to higher value (10 %w/w) caused an increase in the disintegration time of the tablet formulations. This effect was significant ($p < 0.05$) and it can be inferred that more compact tablets were formed as the binder concentration was increased, thus causing a reduction in the rate of disintegration. Two other factors (relative density of tablet, $X_3$ and nature of binder, $X_1$) also had significant positive effects on disintegration time, while tabletting technique had a negative insignificant effect. Concentration of binder ($X_2$) had the highest positive effect on mucoadhesion. The implication of this is that increasing the concentration of the polymers had a direct relationship with the mucoadhesion of the tablets. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains

(Vitaliy, 2011), thus it is important to choose the optimum polymer concentration that will release the drug from the tablet matrix during adhesion.

Brittle Fracture Index (BFI) is a measure of the tendency of a tablet to cap or laminate during decompression. It is measured by comparing the tensile strength ($T_0$) of a tablet with a central hole with the tensile strength (T) of a normal tablet. The hole is a built-in model defect that simulates the actual voids formed in the tablets (due to air entrapment, or packing irregularities) during manufacture. The voids or low density regions in a tablet are usually the weak points from which cracks emanate when stress (at the die wall) is applied to the tablet. The influence of $X_2$ (concentration of binder) on BFI was negative and the strongest. This implies that changing the concentration of the gum from lower (2.5 %w/w) to higher value (10 %w/w) will cause a reduction in the BFI. This result shows that under the compressive forces employed in compaction, more of the polymer will facilitate more plastic deformation, to give tablets with reduced capping or lamination tendency.

Tensile strength was mostly affected by relative density of formulation ($X_3$) and the coefficient was positive, thus indicating that increasing the relative density led to an increase in the tensile strength of the formulations. This can be attributed to the fact that as the relative density of the tablet increases, more solid bonds are formed between the particles. This leads to increase in bond strength and hence a subsequent increase in the tensile strength of the tablets (Alebiowu and Itiola, 2002).

The interaction coefficient values shown in Table 6.7 indicate the effects of the variable factors in combination. The ranking for the interaction effects on disintegration time was $X_3X_4 > X_1X_2 > X_1X_4 > X_2X_3 > X_1X_4 > X_2X_4$, on tensile strength, $X_2X_3 > X_3X_4 > X_2X_4 > X_1X_3 > X_1X_4 > X_1X_2$, on BFI, $X_1X_2 > X_2X_4 > X_1X_4 > X_1X_3 > X_2X_3 > X_3X_4$ and on mucoadhesion, $X_1X_2 > X_2X_4 > X_1X_4 > X_1X_3 > X_2X_3 > X_3X_4$. The results show that the interaction between the nature and concentration of the binder had the highest influence on mucoadhesion and BFI, while the interaction between relative density and tabletting technique and between concentration of binder and relative density had the highest influence on disintegration time and tensile strength respectively. Disintegration of tablets determines, to a large extent, the area of contact between the solid and liquid in the dissolution process. Many correlations have been made between disintegration time and

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parameters such as water penetration rate (Shangraw *et al,* 1980) and dissolution rate of tablets (Najib and Jalal, 1988; Singh *et al*, 2007). The disintegration time was mostly influenced by the interaction between tabletting technique and relative density of tablets. It was observed from the study that tablets formulated by the wet granulation technique had higher relative density and disintegration time values when compared with tablets formulated by direct compression (Table 5.20). The ability of polymers to swell in the presence of water could be responsible for the difference in the disintegration time as a result of the different tabletting techniques applied during the study. The increased concentration of polymer binder which had the highest influence, in combination with relative density, on tensile strength can be attributed to the presence of more polymer particles available for bond formation and subsequently enhanced mechanical strength as characterized by the tensile strength values.

From the present work, it has been observed that the variables employed in the formulations can greatly affect the mechanical and mucoadhesive properties of the tablets formed. Generally, the rankings show that the greatest factor-factor interactions generally occurred between nature and concentration of the binder. This is probably because the nature of the binder determines its plastoelastic properties and the amount of plastic deformation it will undergo under compression forces (Alebiowu and Itiola, 2002). The higher the binder content, the more the plastic deformation that will be manifested (Adeleye *et al,* 2010).

# CHAPTER EIGHT

## CONCLUSION

The study of *Entandophragma angolense* gum for its tablet binding and mucoadhesive properties in comparison with official gelatin and hydroxypropylcellulose has shown that:

i.  *Entandophragma angolense* gum is amorphous in nature and acidic with a pH of 4.27. The absence of heavy metals in the gum is an indication that it would not be hazardous to health. This supports the use of the gum as a febrifuge in traditional medicine in Nigeria. Moreover, the yield of the dried gum obtained from the exudates (48.46 %w/w) suggests potential availability of the gum as an excipient in pharmaceutical formulations. The ranking of the final viscosity of the polymers is *Entandophragma angolense* gum > Gelatin > Hydroxypropylcellulose. Hence, the data obtained from the rheological studies of the polymers appears to be of significance in predicting the binding properties of the polymers.

ii.  The tendency of materials to undergo plastic deformation and fragmentation could be expressed as numerical values of parameters derived from Heckel and Kawakita plots and from density measurements. The results of the present study reveal *Entandophragma angolense* gum to be more plastic than gelatin, but of lower plasticity than hydroxypropylcellulose. *Entandophragma angolense* gum appears to impart a higher degree of plasticity than gelatin to both chlorpheniramine maleate and ibuprofen, as measured by yield value, $P_y$, from the Heckel plots, and a higher degree of total plastic deformation, as measured by the parameter, $P_K$.

iii.  The binding efficiency of the polymers depends on the nature and concentration of polymer used in the formulation. There is a direct relationship between the polymer concentration and the binding properties. Evaluation of the binding properties of *Entandophragma angolense* gum, using tensile strength, shows that the binding ability of *Entandophragma angolense* gum is generally comparable

with that of hydroxypropylcellulose and gelatin. Moreover, wet granulation method produces tablets of higher tensile strength than direct compression. This information is a useful indication that tablets of high bond strength can be prepared

iv. by incorporating *Entandophragma angolense* gum using wet granulation technique, which will probably be more economical when compared with gelatin or hydroxypropylcellulose. The dissolution profiles show an inverse relationship was observed between concentration of polymers and $t_{80\%}$ values for the tablets. Direct compression technique gave better release profiles when compared with wet granulation technique with the more water soluble chlorpheniramine maleate showing faster release rate than ibuprofen.

v. When used as a directly compressible matrix system for controlled release of chlorpheniramine maleate, drug release is dependent on the polymer concentration, and the release kinetics fit the zero-order model, which is independent of the drug concentration in the matrix. By varying the amount of *Entandophragma angolense* gum, sustained release of chlorpheniramine maleate is achieved, thus indicating the suitability of the polymer as a controlled release component in directly compressed matrices.

vi. The mucoadhesive studies show that the adhesion time of the tablets increases directly with binder concentration, with tablets formulated by wet granulation having a higher adhesion time. Generally, the tablets adhere longer in 0.1M hydrochloric acid medium (pH 1.2) than in phosphate buffer (pH 7.4). This implies that *Entandophragma angolense* gum is better suited for formulations that are intended to be targeted towards the gastric environment where the pH is low.

vii. The results of the factorial experimental design provide a clear indication of the qualitative effects of the independent and combined process parameters on the responses studied. The highest interactions are observed between the nature and concentration of the polymers, thus establishing the need to modulate these two process parameters during the formulation of tablets.

viii. The results suggest that *Entandophragma angolense* gum compares well with hydroxypropylcellulose and gelatin. *Entandophragma angolense* gum can be used effectively as a binder when high mechanical strength is desired using wet

granulation technique, and can also be exploited for its mucoadhesive properties in the controlled release of chlorpheniramine maleate from directly compressed tablets.

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