EVALUATION OF *IRVINGIA* KERNEL MUCILAGE AS A MATRIX SYSTEM AND COMPRESSION COATING MATERIAL FOR CONTROLLED DRUG DELIVERY

BY

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CERTIFICATION

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DEDICATION

This work is dedicated to the only true God, the grand creator and universal sovereign, Jehovah.

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ABSTRACT

Reliance on imported pharmaceutical excipients has led to increased cost of finished products, necessitating the development of local excipients. Natural polymers have been used extensively as matrix systems for controlled drug release and drug targeting due to their wide-availability, biodegradability, and low toxicity. Previous studies on *Irvingia gabonensis* mucilage (IGM) suggested controlled release potentials. Therefore, IGM obtained from the seeds of *Irvingia gabonensis* (O'Rorke) Bail (*Irvingiaceae)*, was evaluated as matrix system for controlled delivery of ibuprofen and as a compression coating material for colon targeted drug delivery.

Irvingia mucilage was extracted using established methods. Batches of oven-dried, and freeze-dried IGM were characterized for pH, elemental analysis, morphology and crystallinity. *Irvingia* matrices were prepared by direct compression and wet granulation with varying drug concentration(10-50%$^{w}/_{w}$), excipients (lactose, Avicel®, and dicalcium phosphate, DCP), and polymer (xanthan gum, hydroxypropylmethylcellulose) alone and in combination with IGM. The compressional characteristics of IGM and tablets were determined using density measurements, and Heckel and Kawakita equations. The mechanical properties of the tablets were assessed by measuring crushing strength and friability. Drug release from the matrices was evaluated using disintegration and dissolution times. The drug release mechanisms were determined by fitting the dissolution data into classic kinetic equations. *Irvingia* mucilage was used as compression coating material (300 and 400 mg) for ibuprofen (100 mg). Drug release from the matrices and compression-coated tablets was evaluated in simulated gastric conditions. The results were analyzed using ANOVA at $\alpha_{0.05}$.

Irvingia kernel mucilage was slightly acidic, free of heavy metals, with irregularly shaped particles that exhibited some degree of crystallinity. *Irvingia* mucilage was directly compressible and formed intact non-disintegrating tablets. The Heckel and Kawakita equations indicated that IGM deformed plastically with fast onset and high amount of plastic deformation compared to xanthan gum and hydroxypropylmethylcellulose. Wet granulation enhanced the mechanical properties of the matrix tablets while increasing ibuprofen concentration generally decreased the mechanical properties and increased drug release. The ranking of dissolution times was xanthan gum>freeze-dried IGM>hydroxypropylmethylcellulose>oven-dried IGM. *Irvingia* mucilage containing 50%$^{w}/_{w}$ ibuprofen facilitated controlled drug release for over 9 h. Avicel® and DCP improved the mechanical properties of the matrix tablets, facilitated ibuprofen release from IGM, and altered the release kinetics, which was mainly by Korsemeyer-Peppas model while xanthan gum and hydroxypropylmethylcellulose was by Hixson-Crowell. Increasing the proportion of xanthan gum and hyroxypropylmethylcellulose in IGM matrices resulted in decreased rate and percentage of ibuprofen released after 9 h with xanthan gum having the greater effect. The mechanism of drug release at all concentrations for all polymers was super case II except 10%$^{w}/_{w}$ ibuprofen-xanthan gum matrices which was anomalous (non-Fickian diffusion). For the compression-coated tablets, oven-dried and freeze-dried IGM prevented ibuprofen release in conditions mimicking the stomach and small intestine, but fast drug release was obtained in simulated colonic fluid.

Irvingia kernel mucilage compared favourably with xanthan gum and hydroxypropylmethyl-cellulose as matrices for controlled drug delivery and could serve as an alternative to the two standard polymers. *Irvingia* kernel mucilage also showed good potential as a coating material for colon targeted drug delivery.

Keywords: *Irvingia gabonensis* mucilage, Matrix tablets, Controlled drug delivery, Colon targeted drug delivery, Ibuprofen

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LIST OF ABBREVIATIONS

IGM	*Irviginia gabonensis* mucilage
DCP	Dicalcium phosphate
HPMC	Hydroxypropylmethycelulose
CS/FR OR CSFR	Crushing strength friability ratio
HCl	Hydrochloric acid
GIT	Gastrointestinal tract

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CHAPTER ONE
INTRODUCTION

1.1 Background

The ultimate purpose of any medication delivery system is to safely deliver a therapeutic concentration of drug to a desired area in the body in order to attain and sustain the required concentration of medicine within a specific time frame. Due to the fact that drugs can scarcely be administered on their own, usually they are formulated into suitable dosage forms using excipients. Excipients (substances other than the active drug) used in producing the formulation greatly influence the above ultimate goal.

The search for new excipients for probable use in tablet designs continues to be of concern. The reason being different excipients can be engaged to achieve tablets of varying mechanical strengths and drug release properties for diverse pharmaceutical purposes (Odeku and Fell, 2004). Diverse kinds of polymers are used to control the release of drugs from the dosage form for absorption by the body. Matrices of different kinds have been useful for producing controlled release oral drug delivery systems (Odeku and Fell, 2006).

The oral pathway is of key importance in the administration of drugs (Hadgraft, 1977). Its' being the safest, quickest and perhaps most inexpensive way for the delivery of medications accounts for that. Pharmaceutical oral preparations exist as both solid and liquid formulations. The most often utilized of these are tablets and capsules (Wells and Aulton 2007).

Irvingia gabonensis kernel mucilage has been found to be useful as an oral pharmaceutical excipient (Odeku and Patani, 2005). This was the outcome of the research effort towards developing local pharmaceutical additives to curb the rising cost of finished pharmaceutical products in the face of the present economic hardship in Nigeria. The mucilage was used in the production of metronidazole oral tablets. That study suggested

potential usefulness of the mucilage as controlled release excipient (Odeku and Patani, 2005).

Conventional oral dosage forms have the major drawback of frequent dosing and consequent increased side effects. Therefore, several research works were carried out in order to overcome this and other weaknesses. Controlled delivery dosage forms are designed such that release of active drug is at a controlled, predictable rate and may be steady for a long period. The essence is to achieve better therapeutic outcomes, at the same time reducing undesirable side effects (Pallerla and Prabhakar, 2013).

The colon as part of the gastrointestinal tract has and is receiving attention in respect of this improvement in drug delivery research especially the targeted controlled drug delivery approach. This is because the colon, particularly the first-part of the lower intestine can be prone to several disease conditions such as constipation, inflammatory bowel-diseases (e.g Crohn's disease and ulcerative colitis), infections (amoebiasis) and colon cancer (Odeku *et al*., 2006; Amidon *et al*., 2015; Kar and Dinda, 2019). It is reported that overall, 1 in 23 (4.3%) men and 1 in 25 (4.0%) women will have colorectal cancer in their lifetime. The incidence is rising in people age 50 years and younger (Colorectal cancer statistics, 2021). In Nigeria, the crude incidence of colorectal cancer is roughly 3.4%. Anti-inflammatory drugs, chemotherapy drugs or antibiotics are usually recommended for the treatment of such conditions, and these drugs must be transported to the colon. The main constrains in conveying drugs to the colon are the absorption and degradation pathways in the upper gastrointestinal tract. Thus, the need to better treat colon diseases has continued to fuel research interests in colon specific drug delivery (El-kamel *et al*., 2008). Colon specific drug delivery guarantees precise treatment at the ailment site, with smaller drug doses and minimal systemic unwanted effects (Singhal *et al*., 2011).

The targeting of drugs for delivery specifically at the colon also provides a suitable avenue for administering polar drugs (hence inadequately absorbed) or drugs susceptible to chemical and enzymatic degradation in the upper gastrointestinal tract, especially therapeutic proteins and peptides (Singh, 2007; Kar and Dinda, 2019). Vasopressin, insulin

and calcitonin are examples of proteins and peptides that can be administered systematically via colonic absorption. Novel peptides such as cytokine inhibitors and antibiotic nicin are other examples of drugs. Also colonic delivery provides an avenue for oral delivery of vaccines as a result of its rich lymphoid tissue.

Furthermore, colon specific drug delivery can be useful in managing diseases like asthma, arthritis and hypertension, which are affected by circadian biorhythms. This is because these formulations are potentially capable of slowing or preventing systemic absorption of the small intestine (Singh, 2007; Patel, 2015; Kar and Dinda, 2019).

1.2 Statement of research problem

There is a major drawback with conventional oral tablets of dosing at short interval with attendant increase in side effects. Cost of finished pharmaceutical products in the country (Nigeria) is rising as excipients are mainly obtained from foreign sources. There is a gap in indigenous raw materials supply to meet manufacturers' needs for new innovative delivery product. *Irvingia* kernel mucilage as a promising local pharmaceutical excipient suggested potentials for controlled delivery in previous study. There is the need to investigate further to be sure. There is the problem of delivering drugs to the colon for their action there because of possible destruction at upper gastrointestinal tract (GIT). Yet, there is increase in incidence of colon diseases.

1.3 Research questions

i. Can *Irvingia gabonesis* mucilage be compressed directly into tablets of adequate quality without additives and be a wet granulation matrix?

ii. How will *Irvingia gabonesis* mucilage behave under compression force?

iii. Can the concentration of drug incorporated, added excipients and polymers affect the mechanical, drug release and mechanism of release from *Irvingia gabonesis* mucilage matrix tablets?

iv. Can *Irvingia gabonesis* mucilage be a useful tool for targeting drugs to the colon?

1.4 Aim and objectives

The aim of this work is to study *Irvingia gabonesis* mucilage as a matrix for controlled drug delivery and coating device for colon targeted drug delivery.

The specific objectives are to:

i. Characterise the physicochemical and material properties of *Irvingia* kernel mucilage.

ii. Evaluate *Irvingia* kernel mucilage as a direct compressible excipient.

iii. Examine *Irvingia* kernel mucilage as matrix system for wet granulation

iv. Analyse the compressional features and mechanical properties of *Irvingia* kernel mucilage and ibuprofen-*Irvingia* kernel mucilage matrices, compared with xanthan gum and HPMC as standards using Heckel plot, Kawakita plot and density measurement for the former and friability, crushing strength and crushing strength / friability ratio (CSFR) for the latter.

v. Survey the impact of drug concentration, excipient and polymer kind on the mechanical properties and medication release profile, just as determine the medication release mechanism of *Irvingia gabonensis* kernel mucilage matrices containing ibuprofen.

vi. Evaluate *Irvingia gabonensis* kernel mucilage as a coating gadget for colon specific drug delivery.

vii. Determine the quantitative individual and interaction impacts of processing factor, process of preparation and drug concentration on the crushing strength and CSFR of ibuprofen -*Irvingia* kernel mucilage matrices using factorial experiment.

1.5 Rationale for the study

The necessity for the search and development of local pharmaceutical excipients as suitable substitute for imported ones has become more imperative now than ever before with the recent economic depression which the country is said to be recovering from. Sole reliance on imported pharmaceutical excipients not only increased the cost of finished products but also leads to depletion of much needed foreign exchange earnings. With the naira freely depreciating in value, finished pharmaceutical products are increasingly getting out of reach of the average Nigerian due to overdependence on foreign excipients.

Polymers are utilised as excipients in pharmaceutical formulation to regulate the release of drugs from such dosage forms. Several examples of locally available plants polymers have been investigated as useful pharmaceutical excipients. Examples are: *Khaya* gum as emulsifier, binder, matrix system for controlled drug delivery, drug targeting to the colon (Odeku and Fell, 2004 and 2005; Adenuga *et al*., 2008), *Albizia* gum as binder and targeting drug to the colon (Odeku, 2005; Odeku and Fell 2005), inulin as controlled delivery device in matrix form and compression coating of drugs for release specifically at the colon (Odeku *et al*., 2006), *Terminalia* gum as straightforwardly compressible excipient for controlled drug delivery and binder (Bamiro *et al*., 2011; Bamiro, 2011), *Cissus* gum as controlled release agent in theophyiline formulation (Emeje *et al*., 2009), *Albizia*, *Khaya*, *Cissus* and *Irvingia* gums for microbead design for sustained drug delivery (Odeku *et al*., 2013) *Irvinga gabonensis* mucilage as binder in metronidazole tablet formulation (Odeku and Patani, 2005).

These local plant polymers have displayed comparable activity to official ones and in some instances even superior characteristics in their drug release properties. Their natural origin, ready availability, biodegradability and non- toxicity makes them attractive and suitable alternative pharmaceutical excipients. Besides, there is always the need to develop new pharmaceutical excipients in other to satisfy drug formulators' specific requirements and supply more effective and cheaper alternatives to existing ones.

Furthermore, the literature abounds in several works on *Irvinga*. The observation of Odeku and Patani (2005) in their study of *Irvingia* mucilage as binder in metronidazole tablet formulation is of particular interest. *Irvingia gabonensis* mucilage containing metronidazole tablet formulations, although weaker in mechanical properties, were noted to have longer disintegration and dissolution times relative to gelatin standard binder. More still, no report was found in the literature about the use of *Irvingia* mucilage as coating additive for delivering drug to the colon. Thus, in this study, *Irvingia gabonensis* kernel mucilage has been assessed as a matrix for controlled drug delivery and coating device for colon targeted drug delivery.

CHAPTER TWO
LITERATURE REVIEW

2.1 Tablets

Tablets are solid formulations comprising unit portion of one or more medicaments produced when consistent quantities of particle is compressed together (British Pharmacopoeia, 1998; Mahmood, 2012). They are generally round in shape and have flat or convex faces (The Pharmaceutical Codex 1994).

Tablets stand out distinct in being the most outstanding dosage form and this make up 70% of all ethical pharmaceutical preparations produced (Rubinstein, 2000). This ubiquity and adaptability is because of the following advantages:

a. Ease of manufacture. They are economic to produce, that is cost effective, compared to other dosage forms.
b. Convenience of administration. Tablets are suitable, simple and easy means of giving drugs.
c. Accurate dosing. Allow correct dosage of drug to be given.
d. Relative stability. They are more stable and durable than liquid preparations.
e. Due to their compact nature, they are convenient for transport and handling by patient.
f. Tablet is more tamper-proof compared to capsule.
g. They can more easily be produced on large-scale than other oral preparations. It is possible to make large number quickly.
h. Tablets are safer to use compared to parenteral preparations.
i. Release of the tablet's active ingredient may be adequately adjusted to meet pharmaceutical need. This can be achieved by formulation into tablets that uniquely deliver content like enteric coated or delayed-release product.

j. Simple and cheap product identification. Further processing steps are not needed when embossed or monogrammed punch face is used. (Aulton, 2002; Gohel and Jogani, 2005).

However, tablets have the following disadvantages.

a. No immediate onset of pharmacological response. They need to disintegrate, dissolve and get absorbed to act.
b. Constrain in administration in the aged and infants where swallowing is most time a problem.
c. Medicines that are naturally formless or shapeless in nature, with low density also have difficulty compacting densely. Thus, it is difficult to tablet such drugs.
d. Additional manipulation such as encapsulation or coating is needed for drugs having unpleasant odour, bitter taste or sensitive to moisture and oxygen, therefore greater unit cost of production.
e. It is often difficult to formulate and produce as suitable tablets drugs that are needed in medium to large doses or having poor wetting and dissolution properties as well as requiring optimum absorption at the upper gastrointestinal tract.

2.2 Tablet types

One way tablets are classified is according to their preparation process, mechanism and site of action. By this method, we have compressed tablets, multiple compressed tablets, sugar coated tablets, film coated tablets, enteric coated tablets, effervescent tablets and buccal and sublingual tablets (Gohel, 2009). Tablets are also grouped according to their route of administration. Examples are ingestible tablets, tablets meant for oral cavity use, tablets given via other routes and tablets for preparing solution.

2.2.1 Classification based on preparation method, mechanism and site of action.

i. Controlled release tablets

These tablets are prepared such that the release of the medication happens gradually and over an elongated time. They are otherwise called prolonged or sustained release tablets.

They offer the advantage of reduced occurrence of dosing and ensure steady blood concentration or level of drug (Chien, 1992; Sakr and Alanazi, 2013).

ii. Compressed tablets

They are tablets formulated by compression of drug powder or granules either alone or together with other excipients. They are without any form of coating (Sakr and Alanazi, 2013). Both water soluble drugs intended for systemic effect and insoluble drugs such as antacids and adsorbents meant for local action on the gastrointestinal tract are examples of this group.

iii. Multiple compressed tablets

These are manufactured using more than one compression cycle and may be two or three layered tablets. They are of two types, layered and compression coated tablets. The process is useful in the production of prolonged or repeat action products, the separation of active ingredients to ensure stability is necessary and where mixing process is insufficient to allow uniform distribution of ingredients (King and Schwartz, 1985).

iv. Sugar coated tablets

Sugar layer is the coat here. The coating which may be coloured, mask drugs with unpleasant taste and odour and protects materials sensitive to oxidation. Usually the coating result in increase in the tablet weight sometimes as much as twice the original weight (Sakr and Alanazi, 2013).

v. Film coated tablets

They are compacted tablets created by covering water-soluble content with a film or thin layer. Several film forming polymeric substances are used often together with plasticizer and surfactant to enhance spreading of the film. Hydroxyl-propylcellulose and hydroxypropylmethylcellulose are examples of such polymers. In addition to the basic features of sugar coating, film coating confers further benefits of improved mechanical strength of coating because of flexibility and elasticity associated with the polymer coating and much faster coating process (Sakr and Alanazi, 2013).

vi. Enteric coated tablets

These are tablets with a film of covering that guarantees the tablets keep up their wholesomeness in the gastric fluid yet break down in the intestine. The process is useful in situation where drugs substance is prone to inactivation or destruction in the stomach, irritant to the stomach mucosa or delayed release of drug is desired. The coating material must be capable of resisting gastric secretions but permeable to intestinal fluid (Sakr and Alanazi, 2013). Examples of enteric coating materials include cellulose acetate phthalate (very widely used), hydroxypropylmethylcellulose phthalate, and polyvinylacetate phthalate.

vii. Effervescent tablets

These are tablets containing drug, a soluble organic acid and a carbonate salt of alkali metals. Carbon dioxide is discharged when exposed to water, which causes disintegration of the tablet and the escaping gas produces bubbles (King and Schwartz, 1985; Sakr and Alanazi, 2013). Typical examples of alkalis and organic acids used include: sodium bicarbonate, sodium carbonate, citric acid, tartaric acid, fumaric acid, and maleic acid. They are usually produced using direct compression and dry granulation. Traditional wet granulation is rarely used as wet massing it can result partial dissolution. Popular magnesium stearate lubricant which is water insoluble is not used in their manufacture because it forms film on top of the water after the tablet dissolves. Instead water soluble lubricant such as polyethylene glycol and L-leucine are used to overcome film formation.

Effervescent tablets have advantages of providing formulators opportunity for taste improvement, milder effect and greater patient appeal as a result of their fizzy nature. Also there is faster bioavailability because of their raising stomach pH which results in rapid emptying of the stomach, thus quick movement of medicine to the small intestine where more effective absorbtion occur. Their disadvantages are the need for larger tablets, need for specialized packaging materials such as aluminium foils and often requiring a complex production process.

viii. Buccal and sublingual tablets

These are small tablets purposed to be kept in the mouth or under the tongue. They are usually hard tablets but buccal are often harder than sublingual tablets. They dissolve, erode slowly or at other times melt at body temperature depending on the approach used in their production (King and Schwartz, 1985). They can effect local action of active ingredient or systemic action when drug is absorbed under the tongue (sublingual) or in the month (buccal). Nitroglycerin, progesterone etc are formulated as sublingual tablets which dissolve rapidly and get readily absorbed (Sakr and Alanazi, 2013).

2.2.2 Classification based on route of administration

i. Oral tablets for ingestion

Except chewable tablets, these tablets are intended to be swallowed whole or intact using enough quantity of portable water. They are most popular and constitute over 90% of the total manufactured tablets today. Examples are compressed tablets, multiple compressed tablets, targeted tablets, sustained release tablets, sugar coated tablets dispersible tablets and chewable tablets (Gohel, 2009).

ii. Tablets used in the oral cavity

These tablets are designed and meant to release their active ingredient in the oral cavity for absorption into the blood circulation or to elicit local action at the buccal cavity. They bypass first pass metabolism, inactivation by gastric environment, do not cause nauseating sensations and give the quick beginning of the activity. Models are sublingual tablets, capsules and troches, dental cones and buccal tablets (King and Schwartz, 1985).

iii. Tablets used to prepare solution

They are tablets prepared with the intention to first dissolve them in water or other solvents for ingestion, parenteral use or topical application depending on the active ingredient used. Examples are effervescent tablets, soluble tablets and hypodermic tablets (Sakr and Alanazi, 2013).

iv. Tablets administered by other routes

These are tablets intended for use by inserting into body cavities or directly positioned underneath the skin for absorption through the skin into the systemic circulation. They don't go through the gastrointestinal tract. Examples are implants and vaginal tablets King and Schwartz, 1985).

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2.3 Composition of Pharmaceutical tablets

Tablets usually comprise of the active pharmaceutical ingredient (API) and some inert or inactive components that enhance their quality and facilitate tableting process known as excipients or additives (Sakr and Alanazi, 2013)..

2.3.1 Active Pharmaceutical ingredient (API)

This is any substance or blends of substances planned to be utilized in the production of a medication product. It has pharmacological action or other direct impacts in the finding disease cause, restoring health, alleviation, treatment or warding off of illness or influences the structure and function of the body. It is required that such substance(s) should possess certain desirable properties. These include:

i. High purity: It should be of high purity, devoid of any form of impurities as these can cause unwanted chemical reactions. Active pharmaceutical ingredient must conform with set out standards of purity in the pharmacopoeia.
ii. High stability: It should not be susceptible to any form of degradation such as physical changes in colour, oxidation, hydrolysis or photolysis.
iii. Good organoleptic properties: It must be of pleasant taste and be attractive. However, in their natural form, most are not, but these qualities are improved upon using colourants and taste masking materials.
iv. Good compatibility with excipients: It should not have any interaction with excipients.
v. Optimum bulk properties: It should have optimum bulk property to avert segregation and enhance flowability.

vi. Spherical particle shape: Active pharmaceutical ingredients particles should be predominantly spherically shaped. Spherical shaped particles result in good flow thus better tablet weight and uniformity unlike irregular or needle shape ones.

vii. Best and consistent particle size and particle size distribution: It should be of same particle size and size distribution. This profoundly affects the physicochemical and pharmacokinetic properties of the tablets, for example, consistency of tablet weight, tablet content consistency, friability, disintegration time, flowability and compressibility of powder or granules, drying kinetics of wet granules, stability, dissolution and bioavailability.

viii. Optimum moisture content: It should have optimum moisture content. This is necessary because of its effect on flow and thus content uniformity. Also lack of adequate moisture level will result in brittle tablets while excessive moisture can give rise to stickiness. Optimum moisture content can be ensured by addition of finely powered adsorbent such as magnesium oxide, using non-aqueous solvent, using anhydrous salt or optimum drying time.

ix. Absence of static charge on surface: The surface should be free of static charge. Presence of static charge on the surface of active ingredient can result in segregation during mixing thus non-uniform content. This result weight variation hence non-uniform dose. Also availability of charges can lead to adherence of active ingredient to feed frame which can cause serious damage to tablet equipment. Granulation, addition of diluents or lubricant or surface creation, using colloidal silica are ways static charges can be removed.

x. Good flowability: Active ingredients should have good flow property. This ensures consistency of weight and medication quantity. It can be estimated utilizing angle of repose, Carr's index and Hausner ratio.

Flow problem can be improved upon by addition of glidants or densification using slugging. Addition of fines also helps improve flow by filling the voids and decreasing surface roughness. Furthermore, wet granulation also improves flow by producing spherical shaped granules as well as removing static charge if present.

xi. Good compressibility: Active pharmaceutical ingredient should have good compressibility. This is dependent on its intrinsic property such as brittleness (brittle fracture), elasticity and plasticity.

Brittle materials readily fracture into bits when under compression force and this enhances tableting. Lubricants effect is lesser on them relative to plastic materials. Particles of materials that are elastic in nature revert to their original shape when exerted pressure for compression is withdrawn (ejection). Capping and lamination are likely challenges in tablets made of such materials.

Materials that are elastic are less suited for direct compression. This property can be improved upon or changed by pre-compression, wet massing and using plastic tableting matrix such as microcrystalline cellulose.

Plastic materials may exhibit visco-elastic deformation. The particles get bonded after viscous and elastic deformation. Viscoelastic deformation is affected by time and the tablets hardness depends on the time they spend in the die.

2.3.2 Tablet excipient

Compressed tablets must possess certain attributes to enable them deliver the correct proportion of active drug over the appropriate duration at the desired site. These include stability, elegance and adequate strength, release of active ingredient in an anticipated and reproducible way. The right strength is required to withstand stress of mechanical stun during make, packaging, delivering and administering. Physical and chemical stability ensures preservation of their physical properties and prevent chemical changes of drug. Elegance is needed for maintaining identity while being free of defects such as cracks, capping, discolouration, lamination, chipping and contamination. A combination of these allow for easy and convenient administration, effective drug content control, stability and durability.

Meanwhile, most drug powders cannot be tableted satisfactorily on their own because of problems of lamination, capping, chipping, picking and sticking that may arise during the compression process. This, more often than not, necessitate the inclusion of "different added substances or excipients in the formulation in other to obtain tablets of sufficient quality, disintegration and dissolution time (Koleng *et al*., 2003).

Excipients (additives) are defined by the International Pharmaceutical Excipient Council (IPEC) as substances, different from the active drug or pro-drug of the finished dosage form, proven to be safe and are used during production or component of the final product (Ogaji *et al*., 2012). Tablet excipient refers to all components except the active pharmaceutical ingredient required in the production of tablet of suitable qualities or properties and to facilitate the tableting process. Excipients having best functionality are needed for problem free tablet manufacture (Gohel and Jogani, 2005). They are pharmacologically inert. In selecting them for use, their number and quantity should be kept as low as possible. Preferably, multifunctional excipients should be employed to keep the number low where possible.

They facilitate the manufacturing process of the dosage form, serve as antioxidant to protect or support stability and enhance patient acceptability. Excipients aids innovation at reduced cost in drug product development, a much desired benefit in pharmaceutical industry to produce effective drug delivery products that are affordable. Assisting in product identification, modulation of solubility and bioavailability of the active ingredient are other roles additives perform in pharmaceutical drug delivery system (Robertson, 1999). Excipients in tablets formulation serves as bulking agents (diluents), stability enhancing agents (e.g. antioxidants, preservation), improve patient acceptance (e.g. flavours and colorants), upgrade or adjust medication discharge (for example disintegrants, wetting agents, hydrophilic polymers, biodegradable polymers), assist in product identification (for example colourants) and give vital manufacturing innovation properties (for example lubricants, glidants, binders). Binders, diluent, disintegrants, lubricants, sweeteners, colourants and coating agents are major examples of excipients (Koleng *et al*., 2003).

Excipients are of two categories: those providing adequate compressional charcteristics (diluents, binders, glidants, lubricants) and those imparting additional desirable physical attributes to the tablets which include colourant, disintegrant, sweeteners and flavouring agents (King, 1975).

i. Diluents

These are otherwise known as fillers. They are inert materials included in the tablet formular to increase the mass for practical and feasible compression as well as ensure a finished product convenient for patient to handle (Sakr and Alanazi, 2013). For easier manufacturing and to achieve desired content uniformity, tablet weight and size are required to be not less than 50mg and 2-3 mm respectively (Swarbrick, 1984). However many potent drugs such as diazepam, clonidine hydrochloride etc have low dose, thus necessitating the incorporation of diluents to meet the need for adequate weight and size (Wells and Aulton, 2007). Depending on the situation, diluents may constitute up to 5-80% of the tablet. Other than bulking up, they are added to give increased cohesion, permit direct compression production and to improve flow (Banker and Anderson, 2009). Regardless of the reason for their inclusion, they must satisfy the following basic criteria for optimum performance:

a. They should have no physiological or pharmacological activity - they should be inert.
b. They should also have consistent chemical and physical properties;
c. Separation of the granulation or powder mixture should not be caused or facitlitated by their inclusion.
d. No microbial growth should arise in the tablet formulation because of adding them.

Lactose, starch, sucrose, manitol, microcrystalline cellulose, dibasic calcium phosphate are among most commonly used diluents (Shangraw, 1992; Patel *et al*., 2006).

Diluents are classified into three categories:

Organic: Carbohydrate and modified carbohydrates. Starches, cellulose and sugars are examples in this group. These examples, other than being diluents during direct compression, may play the role of binding agent in wet granulation process.

Inorganic diluents: Calcium phosphate (including dehydrated and anhydrous form of dibasic calcium phosphate and tricalcium phosphate) is an example of this class. Inorganic diluents are granular, insoluble materials. This class does not serve as binders either in wet granulation system or direct compression.

Co-pressed diluents: This class incorporates composite materials. They are a mix of at least two diluents which are co-pressed together by an appropriate process. They give preferable tabletting properties over a solitary substance or the physical blend. Microcellac (made of 75% lactose and 25% microcrystalline cellulose), Di-pac (97% Sucrose and 3% modified dextrins) are examples (Gohel, 2018).

ii. Flavours and sweeteners

These are excipients normally utilized in chewable tablets or other tablets proposed to dissolve in the mouth and also in children formulation (Banker and Anderson, 2009). They mask objectionable taste and odour and impart good flavour to the preparation.

Flavours are of different types and include:

a. Flavoured syrups, examples are raspberry, blackcurrant and cherry (which are produced from juice) and orange and lemon produced from direct peels of citrus fruits.
b. Aromatic oils: Essential oils e.g. peppermint, anise and ginger, with the exception of lemon and orange. Flavours that contain these aromatic oils are more suitable than fruits syrups for neutral preparations.
c. Synthetic flavours: These have a more constant composition, greater stability and are readily available because of these qualities and their more predictable incompatibility. Also, they are relatively less costly and are often preferred to natural materials.

Sweetening agents commonly used in formulation are low molecular weight carbohydrates, particularly sucrose (Billany, 2007). Sucrose desirable attributes include its readily water solubility, colourlessness and stability at pH of about 4 to 8. Also, it has the advantage of increasing the viscosity of liquid preparations, which impart to such products pleasant texture in the mouth. Artificial sweeteners include saccharine and aspartame. Saccharine surpasses sucrose in sweetness close to 500 times but has a significant setback of bitter after taste. Aspartame has the disadvantage of being unstable in the presence of moisture.

Table 2.1. Some diluents used in tablet formulations (Rubinstein, 2000 and Patel *et al*., 2006)

Diluents	Characteristics and comments
Lactose B.P.	Forms good quality granules by moist granulation. It is colourless and tasteless. Not compatible with primary amines. It is not directly compressible, only suitable for use in wet granulation. Relatively cheap.
Lactose (Anhydrous)	Used for direct compression formulation. Dissolves readily in water. It is ductile and deforms easily under pressure thus produces good tablets. It is compatible with primary amines. It is inexpensive.
Lactose (spray dried)	It is used for direct compression formulation and incompatible with primary amines. Tablets get slight spots of brown colouration on storage. It has very good flow properties. It is relatively expensive.
Sucrose	It has suitable binding characteristics. It is somewhat hygroscopic and tastes sweet. It may be diluted with lactose. It is inexpensive.
Mannitol	It has undesirable flow behaviour. It is not hygroscopic unlike sucrose. It has low moisture content hence compatible with vitamins. Has pleasant taste, cooling effect and freely soluble (dissolve readily), thus used in lozenges. It is thought of being the most expensive sugar tablet diluent.

Table 2.1. cont.

Diluents	Characteristics and comments
Microcrystalline cellulose	It exhibits binding properties and fair flowability. Excellent compression properties and used mainly for direct compression formulation. It also has disintegrant and lubricant properties.
Calcium phosphate B.P.	They are directly compressible. Increases granule density. Some grades are rough and can therefore cause tablet tools to wear. It might interact with alkaline sensitive drugs. They are inexpensive.
Sodium chloride	Freely soluble in water. Used in tablets intended for dissolusion in water prior to use.
Starch B.P.	Contains up to 14% moisture, can thus constitute stability problem for moisture sensitive drugs. It has disintegrant property which is one of its main uses.
Dicalcium phosphate	Produces fine, hard, white granules. Insoluble in water.

iii. Colourants

Colourants are components included in tablet formulation to increase patient acceptability of the product. They also serve as a means of product identification and improve elegance. Their inclusion also assists the manufacturer in product quality control during the manufacturing process (Banker and Anderson, 2009; Sakr and Alanazi, 2013). They are more optional ingredients of tablet formulation. A suitable colourant must be non-toxic, stable to heat, light and p^H changes, reducing and oxidizing agents. They are classified into three categories:

a. Natural colourants. Examples includes: cochineal, chlorophyll, anthocyanins, carotenoids.
b. Inorganic pigments e.g. talc, titanium oxide, iron oxide, etc and
c. Synthetic organic dyes and their respective lakes. The dyes are either drug and cosmetic (D & C) or American Food, drugs and cosmetic (FD & C) dyes. The dyes are water soluble while the lakes of the respective dyes are insoluble and are formed by precipitation of dyes in solution on inert base (e.g. aluminium chloride to produce aluminium lake).

The natural colourants are of natural origin and are extracted from animal and vegetable source. Their use in pharmacy does not require meeting the Food and drug administration (FDA) certification. However their use is limited by colour changes across batches and instability in the presence of non-ionic surfactants. Inorganic pigments find main application in external use such as in lotions, ointments and creams. Lakes of synthetic organic dyes are used in tablets and tablet coating because of their stability to light. They are more stable to light than their water soluble dyes.

iv. Disintegrants

These are substances incorporated in the tablet formulation to facilitate tablet fracturing into smaller fragments when placed in water. They enhance quick splitting up of the tablet resulting increased surface area thus speeding up release of the active drug (Desai *et al*., 2016). Disintegrants are of two types, water uptake promoters and tablet rupture facilitators. They can be added before Granulation (granularity) or after granulation (extra-

granulation) or at all processing stages before compression. The disintegrant extra-granulation element, usually 50 percent of the total disintegrant, promotes split up of the tablet to fragments and the intragranular fraction allows the fragments to further break down into fine particulates. Starch, microcrystalline cellulose and aluminum magnesium silicate are examples of disintegrants. etc.

v. Lubricants

Inclusion of lubricants in tablet formulation ensures that granules do not adhere to the punch face and that wall and tablets are ejected from the die without issue. They do this by reducing friction and improving flow. Examples are liquid paraffin, magnesium stearate, talc, polyethylene glycol, stearic acid and boric acid. Mainly, they can either be fluid or solid lubricants. Based on these, we have the hydrodynamic and boundary mechanisms of achieving lubrication respectively (Patel *et al*., 2006). Fluid lubricants e.g. liquid paraffin acts by forming a fluid layer between surfaces in motion hence reducing friction. Solid lubricants e.g. magnesium stearate are more effective and often used. The greater efficiency of these types is borne out of sticking of polar ends of their molecules (usually consisting long carbon chains) to the metal surfaces of the die wall in a process referred to as boundary mechanism. The addition of lubricant reduces cohesiveness and result weaker tablets as they interfere with particle-particle bonding. On the other hand, lack of adequate lubrication can bring about tablet ejection problem and lead to tablet machine strain, damage to lower punch heads, die seats and other associated components. The choice and quantity, method of adding, and mixing time of lubricant are important factors to be considered for satisfactory result.

vi. Glidant

They enhance flow of the granules or powder from the hopper into the die i.e flow promoters (Koleng *et al*., 2003). Glidants also assist in particle rearrangement inside the die at the beginning phase of compression. They act by reducing friction between particles, inserting theirs between the material's particles and decrease the total interparticulate friction via their lower adhesive tendencies. They are needed at the surface of feed

particles, in finely divided form and incorporated in the mixture appropriately. Examples include colloidal silica, asbestos free talc and starch (Sakr and Alanazi, 2013).

vii. Binders

Binders are excipients included in the tablet formulation which impart cohesiveness to powder (Odeku and Patani, 2005; Adenuga *et al*., 2008) and improve structural strength to the formed tablets (Itiola, 1986). They are also known as granulating agents. Binders serve to adhere powder together during granulation process as well as binds granules together when compressed. They give rise to tablets of desired mechanical and physico-chemical qualities (Esezobo & Pilpel, 1974). Depending on the granulation method, they can be added either (a) as a powder in the formulation (in dry granulation or in slugging) or (b) as solution to the mixed powder (in wet granulation).

A suitable binder should have the following qualities:

a. Should be pharmacologically inert and free from any microbial contaminant.
b. It should not be hydroscopic (Carstensen, 1980).
c. It should be of low viscosity
d. It should have high cohesive property
e. It should be highly soluble in cold solvent to reduce the amount of solvent used.
f. Readily mix with other formulation constituents.
g. The bio-availability of the active component in the product should have no adverse impact on it.

Examples of binders comprise gelatin, starch mucilage, acacia, tragacanth, polyvinyl-pyrolidone (PVP), cellulose derivatives, Khaya gum, *Irvingia* mucilage, *Terminalia* gum etc.

2.4 Pharmaceutical powders

Nystrom *et al*., (1993) defined powders as discrete solid particles of varying sizes and shapes having voids among them. They are sub-divided solids and are complex materials. The British Pharmacopoeia (2005) they were categorized using the size of their powder elements, varying in diameter from under 1.25 μm to 1.70 μm. A storage form is referred to as a powder at any time, meaning a formulation consisting of a drug powder combined

with other powder additives to give the final product (Summers, 1998). Excipients added plays different roles depending on the intended use of the product.

Compression powder content must be fast flowing, i.e. fluid and quickly permeable (Staniforth, 1996). Fluidity allows the powder to flow from the tableting machine hopper to the die, preventing air trapping and ensuring proper filling of the die. This ensures tablets of uniform weight, strength and without defect (capping and lamination -common with poor fluid powder in high speed tableting machine) are produced. Compressibility is the powder ability to form a stable compact under compression force. Granulation process is utilized to convert powder mixture of poor cohesiveness aggregates that can be compacted into.

2.4.1 Powder density

This is the material mass (M) divided by its volume (V). Marshal (1986) defined three different densities, true density, granular density and bulk density, as expressed by the following equations.

$$\frac{M}{V_t} = \ell_t \text{ the true density} \quad (2.1)$$

$$\frac{M}{V_g} = \ell g \text{ the granular density} \quad (2.2)$$

$$\frac{M}{V_b} = \ell_b \text{ the bulk density} \quad (2.3)$$

Where V_t, V_g and V_b are true volume, granular volume and bulk volume respectively.
When the bulk density (ℓ_b) of a sample under specific test conditions is compared with the true density (ℓ_t) or particle density, a dimensionless quantity D, referred to as the relative density (packing fraction - P_f) is obtained i.e.

$$D\ (P_f) = \ell_b / \ell_t \quad (2.4)$$

The relative density or packing fraction is inversely related to tablet porosity. During compressional, this will rise to a highest value of one (1), at which point no air space remain.

i. True density (Particle density)

The true density is the density of the solid material devoid of all air spaces. It can be measured using the gas or liquid pycnometer method (Wang and Williams, 2013). The gas pycnometer operates on the principle that within a sealed system containing helium, a non-absorbing gas, the pressure change caused by finite change in volume of the system is a function of its total volume. The liquid pycnometer method use a liquid, which does not readily wet the powder such as mercury, or solvent of low surface tension viz xylene or benzene as a displacement fluid.

Particle density may affect tablet porosity, compressibility, dissolution and different properties. A higher compressional force may be needed for dense, hard granules or particles to produce a cohesive compact.

ii. Bulk density

This is a term used to portray the packing of particles or granules. It is a property of powder and is expressed as the quotient of the powder mass (M) and its known bulk volume V_b as stated in equation 2.3 earlier. It changes with the degree of packing of the granules and is affected greatly by the particles shape and size (Wang and Williams, 2013). The more spherical the particles become the greater the bulk density. It decreases with increase in granular size which is as a result of smaller granules getting packed more closely than the bigger ones. Because air spaces or voids are present in powder, usually the true or particle density of component particles is always greater than the bulk density of the powder bed.

2.4.2 Powder porosity

Martin *et al*., 1993 defined powder porosity or void "ℓ" as the ratio of the void volume to the bulk volume of the powder

$$\ell = \frac{V_b - V_t}{V_b} = \frac{1 - V_t}{Vb - 4b} \qquad (2.5)$$

Where V_b is bulk volume of the powder

$$\ell = \frac{V_b - V_t}{V_b} = \frac{1 - V_t}{Vb} \qquad (2.6)$$

Where V_b and V_t are bulk volume and the true volume of the particles respectively. It is expressed as percentage (Webb, 2001).

$$\ell = \frac{(1-\ell_b)}{\ell_t} x\ 100 \qquad (2.7)$$

Where ℓ_b is bulk density and ℓ_t is true density (Iwuagwu and Onyekweli, 2002 and Okhamafe *et al*., 1991).

Furthermore,

$$E = 1 - D \qquad (2.8)$$

Where E represents fractional air spaces (the powder bed porosity) which is normally related as percentage and referred to as powder porosity (Staniforth, 2002; Odeku, 2007).

2.4.3 Powder flow

The properties of powder are of great significance in all volume filling of powder such as tablet and capsule production. Under gravity influence, a powder flows more or less or not at all. Friction between particles opposed gravity and its magnitude depends on particle shape as well as the particle surface properties like electric charge and humidity. Carr's or compressibility index, Hausner ratio and angle of repose measurement are three indirect methods of assessing powder flowability (Staniforth, 2002).

i. Carr's or compressibility index

This is determined employing the following equation:

$$Carr's Index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} x\ 100 \qquad (2.9)$$

The percentage compressibility can be related to a qualitative descriptive evaluation of the powder flowability. Values of 5-15%, 16-18, 19-25 and 26-35 shows excellent, good, fair and poor flow respectively, while very poor flow characteristics and cohesive powder are represented by values above 40% (Carr, 1965).

ii. Hausner ratio

Hausner ratio is indicative of interparticle friction and could be useful in predicting powder flow properties. It is evaluated using the equation:

$$\text{Hausner ratio} = \frac{Tapped\ density}{Bulk\ density} \quad (2.10)$$

Values below 1.25 and above 1.25 portray good and poor flow respectively (Staniforth, 2002). Addition of glidant improves flow of situations where Hausner ratio is between 1.25 and 1.5. This ratio (Hausner) gives an insight to the extent of densification that can take place during tableting. The possibility of the powder densifying becomes greater as the ratio increases. Densification can give rise to production of tablets with non-uniform weight and content.

iii. Angle of repose

This is expressed as

$$\theta = Tan^{-1}\ h/r \quad (2.11)$$

Where h equals the height of the heap of powder and r is the radius of the powder heap base. It is the highest angle that can be obtained between the free standing surface of a powder heap and the horizontal plane. It gives understanding on powder cohesiveness extent, thus useful in assessing flowability. It is a qualitative measure of the internal cohesive and frictional effects under low-levels external loading as encountered in powder mixing or tablet die or capsule shell filling (Marshall, 1986). Several methods involving either static or dynamic heap formation have been employed in determining θ. Examples are fixed funnel, tilted box, free-standing cone, revolving cylinder and sliding shutter. θ values below 30^0, above 40^0 and more than 50^0 shows good, irregular and poor flow respectively. Variation in moisture content and particle size distribution readily affect angle of repose and give a quick way of monitoring significant batch to batch differences (Staniforth 2002).

2.5 Tablet production process

There are three popular tablet production procedures: direct compression, dry granulation (compression granulation) and wet granulation (Pharmapproach, 2021). Table 2.2 gives a comparison of these methods stating the major steps involved in each.

Table 2.2. Major steps involved in tablet production approaches (Gohel and Jogani, 2005; Odeku, 2014)

Step	Direct compression	Dry granulation	Wet granulation
1	Mixing/blending of active pharmaceutical ingredient and adjutants or excipients	Mixing/blending of active pharmaceutical ingredient and excipients	Mixing/blending of active pharmaceutical ingredient and Excipients
	↓	↓	↓
2	Compression	Compression into slugs	Preparation of binder solution
		↓	↓
3		Size reduction of slugs and Sieving	Massing of binder solution of step 2 with powder mixtures of step 1
		↓	↓
4		Mixing of granules with pharmaceutical aids	Wet screening of damp mass
		↓	↓
5		Compression	Drying of wet granules
			↓
6			Resifting of dried granules and blending with pharmaceutical aids
			↓
7			Compression

2.5.1 Direct compression

Over the years, tablet manufacture by direct compression has gained more attention. The reason being, newer materials are found, improvement of old materials (e.g. spray-dried lactose and avicel) and invention of new machinery (Sam and Fokkens, 1997). It is the cheapest and simplest tablet production method (Singh *et al*., 2014).

The methods involve the direct compression of powder mixtures of active ingredient(s) and appropriate additives without subjecting powder blends to any form of pre-treatment. That is simply milling drug and excipients, mixing them together and compressing into tablet. It is particularly useful for materials with free flowing, good cohesion and lubricant properties. However, only a few pharmaceutical materials such as sodium chloride, sodium bromide, potassium chloride, ammonium chloride are directly compressible (Banker and Anderson, 2009). This problem is overcome by the use of certain excipients known as directly compressible diluents which inclusion allows for direct compression. Examples of directly compressible diluents include dibasic calcium phosphate (Encompress^{A}), microcrystalline cellulose (avicel) direct compressible starch (Starx^{R}), spray dried lactose, anhydrous α lactose, anhydrous β lactose (Singh *et al*., 2014). In addition to good flow ability and compressibility, such materials for direct compression tablet production should be inert, tasteless, inexpensive and be able to disintegrate. Therefore, their selection is of immense importance. But in practice, no single direct compressible diluent is known to possess all the aforementioned qualities, thus necessitating a blend of two or more. Such mixtures are usually of superior properties than the individual components (Wells and Aulton, 2007).

Direct compression method of tablet manufacture has the following advantages:

a. It is more economic and efficient compared to other processes. It is economic because it saves time, lower labour expense, has few prcoesses, easier validation and requires less number of equipment.
b. The process eliminate heat and moisture, thus enhancing stability and is more suitable for thermolabile and moisture sensitive pharmaceutical materials.

c. Direct compression process requires fewer validation and documentation requirements as only few unit operations are involved. Also less likelihood of microbial growth because it is a dry process.

Nevertheless the process has the following limitations:

i. Static charge build up can take place during screening and mixing because of the dry nature of the process. This may cause the drug to be spread unevenly in the granulation.

ii. The process may have problem in handling large-dose drug that is poorly compressible on its own. To aid the compression, the medication could need a quantity of diluent so big that the final tablet is not only expensive but also uneasy to swallow.

iii. In a few occasions, there can be interaction between the drug and the direct compressible diluent. An example is Millard reaction, a yellow discolouration that occurs as a result of interaction between spray dried lactose and amine compounds.

iv. The compressed tablets may have dissatisfactory medication content consistency because of stratification of drug and diluent particles which arises from variation in particles size and density between the two. This is a serious challenge when low dose drugs are involved.

2.5.2 Dry granulation (compression granulation)

This method is not accompanied with heat and solvent in compression of the powder blend. Therefore the process is appropriate for granulation of materials sensitive to moisture and heat needed in doses beyond what direct compression can cater for (Banker and Anderson, 2009).

Two methods can be used for dry granulation process i.e. slugging method and roller compaction method. Slugging method is more popular and involves the compression of initial powder mixture in special tablet press with large flat-faced punch (2-5 cm) giving rise to compact masses called slugs. The slugs are then reduced in size by milling or screening to obtain granular form of tableting material which exhibit better flow property than the starting powder blend. The roller compaction method uses a compacting mill or machine known as chilsonator. The powder mixture is pressed between two rollers

removing air to produce a sheet of densified or compact material. Like the slugs, the compact mass or aggregates are screened or milled to form granules (Kotamarthy, 2018).

The method does not involve complex mixing equipment and expensive and time consuming drying processes thus is relatively cheaper compared to wet granulation. It however generate more dust and not allow uniform colour distribution. Examples of drugs that are commonly processed by dry granulation process include ascorbic acid, aspirin, antacid powders, thiamine hydrochloride (Banker and Anderson, 2009).

2.5.3 Wet granulation

This is the most popularly employed tablet production technique in the pharmaceutical company. The approach produces large semi-permanent aggregates or granules from powder particles on addition of liquids to the powder, the liquid acting to bring the particles together (Snow *et al*., 1997). Both capillary and viscous forces arising from the liquid serves to bind the particles in the wet stage (Iveson *et al*., 2001). The general steps engaged in a wet granulation process are: the blending of medications and additives, getting the binder solution ready, mixing of binder solution with powder blend to obtain a wet mass, coarse screening of wet mass utilizing an appropriate sieve, drying of moist granules and screening of dry granules through an appropriate sieve to get granules of various sizes.

However, the unique operations in the process are wet massing of powder, wet milling (sizing) and drying (Banker and Anderson, 2009). The binder is added either as a solution, suspension or slurry to powder mixture. How exactly this is done is dictated by binder solubility and the composition or constituents of the mixture. Liquid bridges develop among particles as liquid is added and the bonds tensile strength increasing with the quantity of liquid added. When only little volume of liquid is required, the binder is mixed dry with the powder mixture. But where the volume of liquid is sufficient, the binder is dissolved in the solvent and introduced as such. Then the moist powder is mixed until a uniform dispersion is obtained. The duration of granulation, usually fifteen minutes to an hour in a large blender, depends on the efficiency of the mixer, the granulating fluid and the wetting properties of the powder mixture. The end point may be ascertained by

pressing a small, but enough quantity of the mass, made a ball, in the palms of the hands. The mixture is ready for wet screening once the ball crumbles under moderate pressure.

During granulation, agglomeration growth occurs i.e. coalescence, as particles come in contact and remain together. The particles and agglomerates undergo consolidation under the combined influence of inter-particulate forces and machine part action. Particles nucleation, coalescence between colliding agglomerates, layering of particle from the degradation of established agglomerates and ball growth are the mechanisms of the wet agglomeration process (Werani, 1988). The agglomeration process is known to proceed as a balance between the dynamic processes of size enlargement and size reduction. A very complex interaction between factors associated with the powder blends properties, the process conditions and granulator and its mode of operation determines the final product of a particular process (Jaiyeaba and Spring, 1981).

Various factors affect the granule structures and strength, therefore the physicochemical features of the resultant tablets. These include: the concentration and volume of binder (Chalmer and Elworthy, 1976), the quantity of granulating fluid utilized, the beginning ingredients particle size distribution (Hunter and Ganderton, 1972; Ebube *et al*., 2002), the temperature of granulation (Rankell and Higuchi, 1968) the nature of binder (Healey *et al*., 1972), solute migration during drying, rate of drying (Rubinstein and Ridgewat, 1974) and type of mixer (Ganderton and Hunter, 1971). Among all these, the concentration of binder and quantity of granulating fluid used exert the greatest influence.

2.5.3.1 Stages in the development of moist granule

Moist granules develop in stages during wet granulation process on addition of granulation liquid to the powder blend. Newitt and Conway-Jones (1958) described the pendular, funicular, capillary and droplet states as the different stages (illustrated in Fig. 2.1). Added liquid to the powder mix gets distributed as film around and between the particles. The practice is to add enough liquid to exceed that required for an immobile layer to produce a mobile film.

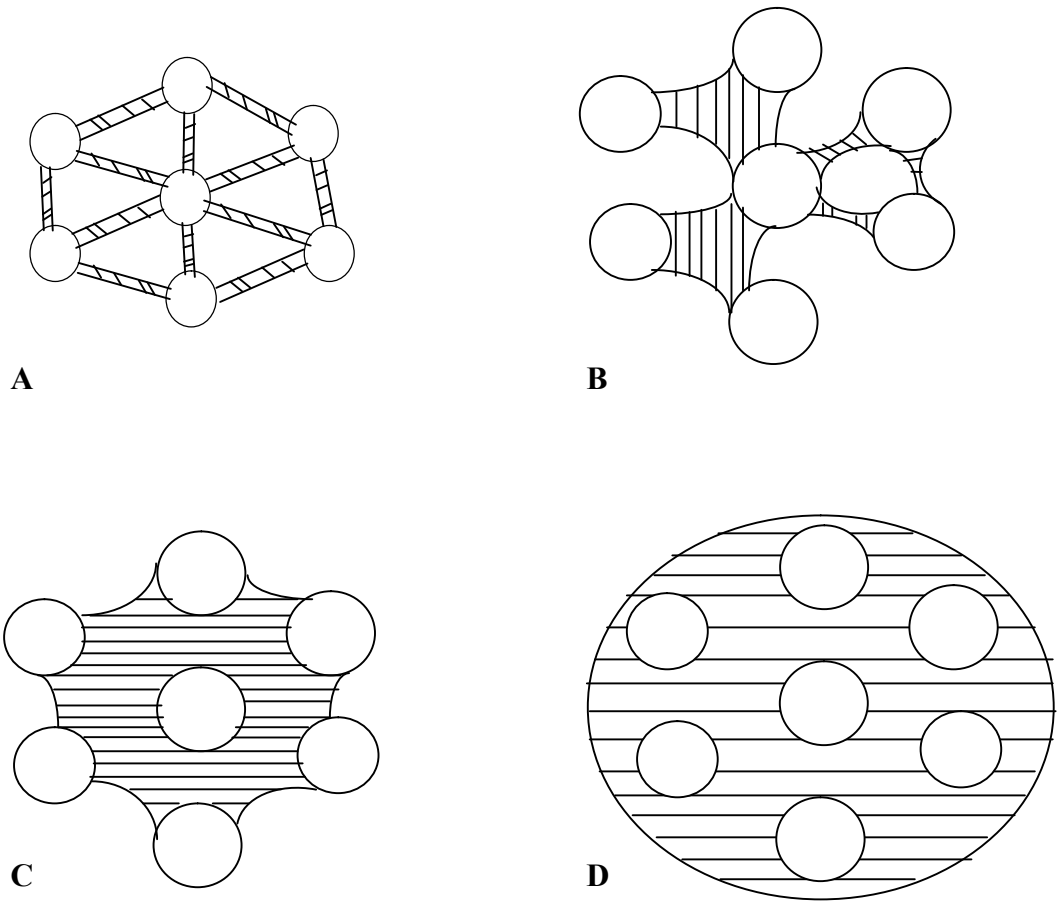


Figure 2.1. Stages in the development of moist granule

The pendular state is the onset of the stages in moist granule development. As the powder particles get wetted at the start of liquid addition, liquid films begin to form on the surface. These films may combine to give rise to liquid bridges at the point of contact. The bridges supplies cohesive forces to hold the moist granules together by virtue of surface tension and negative capillary pressure present within them. Thus, the pendular stage (A, Fig. 2.1) is reached, which is a state of relatively low mechanical strength.

Funicular state (B, Fig. 2.1) is formed with the coalescing of several liquid bridges following increase in the liquid content i.e as more liquid is added. This results in a further modest rise in the strength of the moist granule.

Capillary state (C, Fig. 2.1) is arrived at as more liquid is added and the mass kneaded to bring particles tightly closer thus eliminating completely all void space within the granule. At this point, both interfacial forces at the granule surface and negative capillary pressure throughout the interior liquid filled spaces are responsible for binding. This state coincides with the maximum strength of wet granules and optimization of many granulation processes involves ensuring that this state has been achieved.

Further adding of liquid brings about formation of droplets (D, Fig. 2.1) i.e the droplet state. In this state, particles are held together by surface tension but without intragranular forces. These structures are weaker.

2.6 Tablet compression

Tablets are prepared by the compression of particulate solid in a die using applied forces through two punches. The punches are referred to as upper and lower punch. The lower punch travel upward and downward inside the die without leaving it while the upper punch moves down to enter into the die delivering the compression force and withdraws to allow the tablet to be ejected from the die. In some machines, only the upper punch moves and they are called stamping presses (Banker and Anderson, 2009).

Tableting machines or presses comprises of the following main components: the hopper(s), dies, punches, cam tracks and a feeding mechanism. The hoppers function as transitory storage and feeding of granules intended for compression. Dies determine the tablet shape and size. Punches serve in compressing the granule inside the die while the cam tracks guide the movement of the punches. Feeding mechanism ensures the movement of granulation from the hopper into the dies.

Depending on the degree of sophistication and associated efficiency, tablet presses are of three main types :

i. The one station or eccentric presses
ii. The multi-station or rotary presses
iii. The advanced high speed presses (King and Schwartz, 1985). Difference in the speed of rotation and magnitude of compaction load explains the variation in the extent of compaction obtained from the different types of tablet presses (Armstrong, 1989).

2.6.1 The eccentric or single station presses

They comprise of a single compression station i.e just a die and a pair of punches and are stamping presses. They are the simplest and most economical tablet machines. They can be operated manually or power driven and are of limited use in commercial production (Sakr and Alanazi, 2013). The power driven press has a production output of 2,400 to 5,400 tablets per hour (King and Schwartz, 1985).

2.6.2 The multi-station or rotary press

These presses have several compression station i.e several sets of dies and punches. The passes on are set in a focal roundabout turning circle or table known as the turret and the punches are set in tracks mounted above and underneath the turret. The rotating disc or turret passes each set of punches and dies in sequence such that a die is always associated with a pair of punches throughout the filling, compression and ejections stages (King and Schwartz, 1985). As the turret (head) turns, the punches are guided above and below by stationary cam tracks, which regulates the cycle of filling, compression and ejection. These

presses are suitable for commercial tablet production. The rate of die filling with granules is the main factor determining the production capacity of the multi-station press (King and Schwartz, 1985).

2.6.3 Advanced high speed presses

The ultra-high speed tablet presses or machines, the double and triple-rotary machines were developed following advances in technology that brought about the development of devices for granule flow promotion, die-filling and removal of air during compression (King and Schwart, 1985). Some examples of these press include the Perfecta series (Wilheim Fette GmbH, Germany), Ratapress, Excelapress and Novapress.

2.7 Compaction of pharmaceutical powders

Compaction as it relates to pharmaceutical powders includes the concurrent procedures of compression and consolidation of particulate solid-gas system consequent on pressure application (Odeku, 2007; Mohan, 2012; Ayorinde *et al*., 2013; Kamranian, 2018). It refers to the instance of exposing powdered solids to mechanical force of varying degree. In the pharmaceutical company, the effect of such forces are especially vital in tablet and granule production, capsules shell filling and powder handling for the most part (Marshall, 1986; Jones, 2001; Silver-line services, 2015).

Compression refers to when the bulk volume of material is reduced by expelling air, while consolidation is the enhancement of mechanical strength of material resulting from particle- particle interaction (Marshall, 1986; Odeku, 2007; Ayorinde *et al*., 2013; Kamranian, 2018).

Fig. 2.2 shows the powdered solids bulk reduction stages and these are discussed under the succeeding sub-sections.

2.7.1 Mechanism of particulate compression

When a die cavity is filled with the powdered solid, prior to the upper punch entering it, at the outset of compression, the phase of densification under zero applied pressure is attained. Under this circumstance, the only forces existing between the particles at this

stage are those as a result of the packing attributes of the particles, particles density and the total mass of the materials filling the die (Wray, 1992). The packing behaviour of a material is dictated by its material features, like shape of particle, size, surface characteristics and size distribution. Irregular shaped particles hampers dense packing while high surface irregularities together with wide size distribution with resultant higher contact area give rise to increased resistance to particle slippage and rearrangement (Paronen and Justin, 1983).

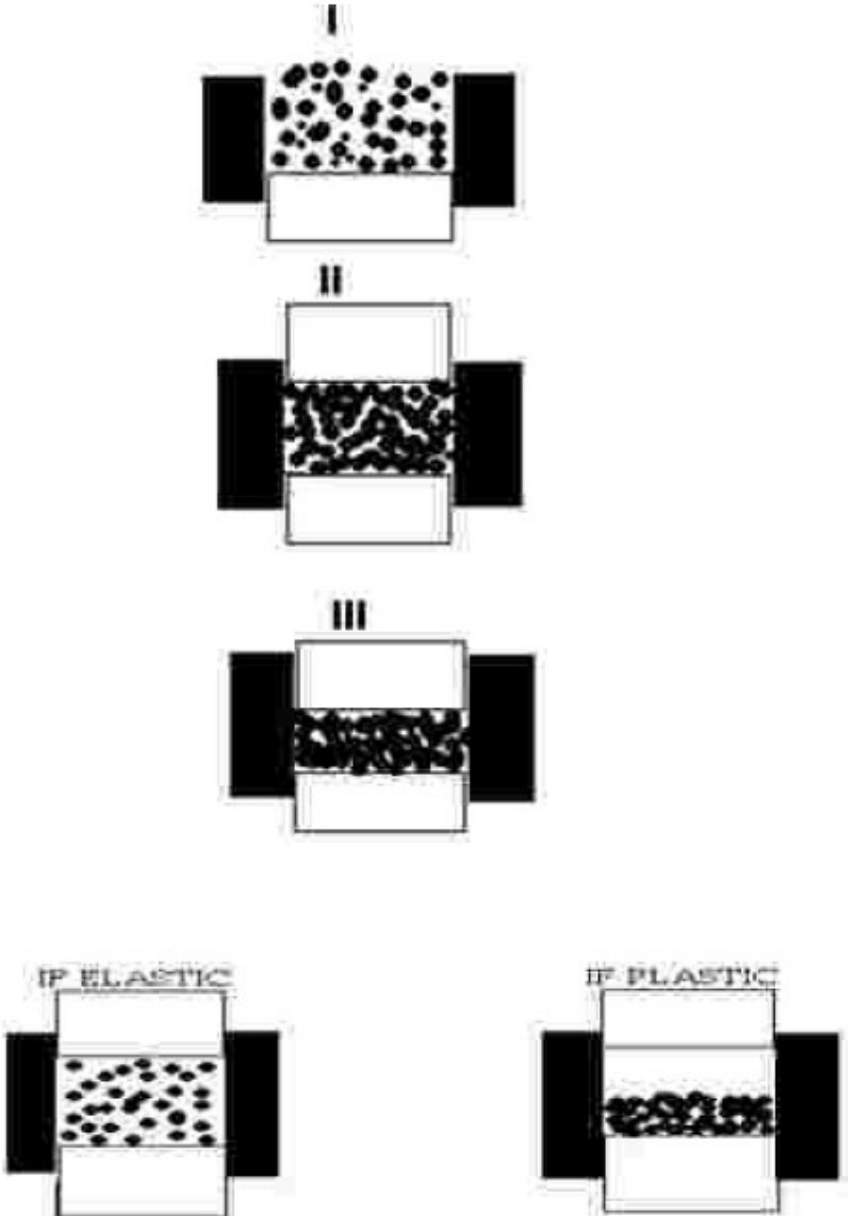


Figure 2.2. Compression stages (I-III) and Decompression (Odeku, 2007)

2.7.1.1 Elastic deformation

The very beginning of volume reduction is mainly by this process at commencement of compression on application of external mechanical force to a powder bed. This type of deformation is reversible (II in Fig. 2.2). It occurs when the magnitude of the applied force is below the materials yield point. With increasing applied forces, particles rearrangement occurs with difficulty and additional compression causes some form of deformation of particle (III, Fig. 2.2). The deformation is said to be reversible, if the material returns to the previous state significantly, on removal of applied pressure, in which case the substance is rubber-like in behavior. Under sub-yield point or elastic limit forces, all solids exhibit elastic behavior i.e deform elastically. At the scope of greatest forces experienced during pharmaceutical processes, the prevalent mechanism of compression for most pharmaceutical materials including acetylsalicylic acid and micro-crystalline cellulose is elastic deformation (Marshall, 1986).

2.7.1.2 Plastic deformation

It is irreversible type of deformation that arises when the applied load on the particle is beyond the elastic limit or yield point of the material. Decrease in bulk volume in such situations is caused by plastic deformation as well as viscous flow of particles, that are pushed inside the rest of the voids, looking like how modeling clay behaves (Odeku, 2007; Mohan, 2012). The deformation in this instance is not instantly reversible after compression force is removed. The plastic tendency of a material is influenced by its constituent particle size and shape, moisture content and the presence or not of lattice structure defect (Marshall, 1986; Bamiro 2011). Materials with lower shear strength than tensile or breaking strength predominantly deform plastically.

2.7.1.3 Brittle Fracture

This is the prevalent mechanism of compression by hard and brittle materials. The shear strength of such materials is higher than their tensile or breaking strength. They usually have high yield point or elastic limit and are preferentially fractured i.e undergoes fragmentation and the smaller pieces then assist to fill up any bordering airspace. Lactose, sucrose and dicalcium phosphate are examples of such materials (Marshall, 1986 and

Kochhar, *et al*., 1995). The preferred deformation manner of a material relies upon its lattice structure and the presence or not of weakly bonded lattice planes.

2.7.1.4 Microsquashing

Regardless of how large particle of material behaves, little particles may deform plastically via a procedure referred to as microsquashing. Thus fine powder content of material appears important as it can influence its plasticity. Equally significant are rough edges (asperities) broken off large, very irregular particles, which likewise act in a similar manner as fine particles.

Concisely, pharmaceutical compression may be said to occur in the following four stages: initial packing of particles, elastic deformation of the particles until elastic limit (yield point) is arrived at, plastic deformation and/or brittle fracture then dominate until all voids are essentially filled and lastly, compression of solid crystal lattice occurs (Marshall, 1986).

2.7.2 Consolidation

This is the rise in mechanical strength of material because of interaction between particles during compaction. Closer packing of particles gives room for bonds to form which in turn result in a compact of certain strength. Solid bridges, mechanical interlocking, intermolecular forces are some of the bond types reported in the literature (Fuhrer, 1977).
Mechanisms of consolidation that have been explained include cold welding, fusion bonding and asperities melting. These are discussed as follows:

2.7.2.1 Cold welding

This is the process where free surface energies on the surface of two closely approaching particles within less than 50nm separation give rise to strong attractive forces. Intermolecular forces are the main attractive forces between particles of pharmaceutical compacts (Nystrom *et al*., 1993). In addition, solid bridges and mechanical interlocking because of irregular surfaces contribute to various extend, particle consolidation (Fuhrer,

1977). Powder bed mechanical strength increase with application of greater compressive pressure is thought to be because of cold welding.

2.7.2.2 Fusion bonding

Fusion bonding is where melted contact points of particles under frictional heat solidify leading to increment in the mechanical strength of the mass. During compression, any applied force to the powder bed spread through out it via particle contact points. When the force is considerable, remarkable frictional heat can occur from the spread or transmission. Where the heat is unable to escape, there is increase in temperature within the powder bed, and this is enough to result melting at the particles points of contact (Marshall, 1986). The melting absolves the stress in the area. When the melt solidify, fusion bonding takes place and this give rise to elevation of the compact mass mechanical strength.

Consolidation occurs mainly by the processes of fusion bonding and cold welding. Both processes are influenced by such factors as, the extend of available surface, the inter-surface distance, presence of contaminants such as moisture and lubricants, the porosity of the material and chemical nature of the material (Marshall, 1986). Traces of absorbed moisture facilitate consolidation by serving as internal lubricant. Also, presence of moisture at contact points of soluble drug particles may lead to surface dissolution that may be enhanced by high compression load. Solid bridges are formed on subsequent crystallization as the stress is relieved (Marshall, 1986).

On the contrary, surface contaminants such as lubricants often interfere with bonding thus giving rise to weak compacts (Oladimeji and Jaiyeoba, 1989). The extent of available surface area is largely dependent on the compression force. Brittle fracture and plastic deformation usually result clean surfaces which when brought into close contact by the applied compression force give rise to strong bond.

2.7.2.3 Asperitic melting

It involves the melting of rough surfaces of the powder particles (Rankell and Higuchi, 1986; York and Pilpel, 1973). This mechanism is particularly significant when materials of

comparatively low melting points are encountered. For such materials even especially hard rough surfaces or asperities are pushed into a more plastic substrate.

2.8 Tablet decompression

Decompression stage succeeds compression during tablet manufacture on withdrawal of exerted force. Complete tablet production sequence entails compression, decompression and ejection stages (Mohan, 2012), although compression theories and applicable equations often talks about only compression. Thus they are unable to account for certain unforeseen situations that occur in normal tableting process (Odeku, 2007). Typical scenarios are where certain pharmaceutical powder blends result tablets that crumble and others form tablets which fracture giving several strong fragments, also, why little variation in powder mixture and processing, profoundly alter property of material and final tablet quality.

Therefore decompression is now acknowledged to be relevant as (and dependent on) the compression stage in knowing the possibility or otherwise a powder blend eventually produce suitable tablets (Patel *et al*., 2006; Odeku, 2007). This is exemplified by the time dependence and occurrence at different rate of certain deformation activities as compaction process unfolds. In such instances, the rate of application and removal of load is likely a serious factor (Patel *et al*., 2006; Odeku, 2007). Precisely, solids that deform plastically may show brittle fracture when loaded or unloaded too fastly in the compaction process. As a result, lately, studies now consider linking tablets capping and lamination likelihood to their plastic and elastic behaviours within the compression/decompression/ejection cycle (Rees and Rue, 1978; Patel *et al*., 2006; Odeku, 2007; Dudhat *et al*., 2017).

Fresh set of stresses are caused inside the tablet by decompression because of elastic recovery. Forces necessary for tablet ejection enhances these stresses (Patel *et al*., 2006; Odeku, 2007; Mohan, 2012; Hemander, 2017). Regardless of the mechanism of consolidation, the tablet is expected to be of adequate mechanical strength in other to overcome these stresses, without which structural failure will result.

Notably, the extent and stress relief rate inside tablets, just beyond highest compression has been demonstrated to be an identifying mark for a given system. This phase of the cycle can give useful clue as to why tablets of inadequate quality form and may offer insight for resolving it (Odeku, 2007).

Stress relaxation process arising from plastic flow may go on after removal of all compression force and the residual radial pressure wear off with time. Plastic flow has been explained using viscous and elastic parameters in series by David and Augsburger (1977) and Odeku (2007). This translation gives rise to the following relationship:

$$\text{Log } F_t = \text{Log } F_m - K_t \qquad (2.12)$$

Where

F_t = the force remaining in the visco-elastic region at time, t,

F_m = total amount of the force at time t = 0 (i.e. onset of decompression)

K = the visco-elastic slope and a measure of the degree of plastic flow.

Higher k values are typical of materials that experiences greater plastic flow and usually produce hard tablets under comparatively low forces of compaction (Odeku, 2007).

2.9 Tablet ejection

The formed tablet after compression and decompression remain in the die until it is ejected. Within this period, the die wall is acted upon by a left over die wall force from the tablet. The forces needed to eject the tablet tend to follow three clear patterns (Mohan, 2012):

(i) An initial force strong enough to surmount the tablet-die wall adhesion. This is usually the highest of the ejection forces and last for a short while.

(ii) A second comparably smaller force needed to force the tablet up the die wall.

(iii) Thirdly, a declining force needed to push the tablet off the lower punch to release the tablet from the die.

2.10 Physical properties of materials that affect compaction characteristics

Factors affecting materials compaction characteristics include: the surface properties of the material, the particle shape and crystallinity (Wray, 1992). Also, moisture (Sebhatu *et al*.,

1997 and Jones, 1981) and the particle size (Ganderton and Shotton, 1961) affect the compaction behaviour of materials.

Crystalline materials more often than not exhibit elastic deformation while amorphous materials preferentially deform plastically. Surface purity, total surface area, ionic property of the surface as well as crystalline perfection are some material surface properties that influences compaction characteristics of material. Pure and crystalline surfaces devoid of contamination have greater cohesive tendencies with strength equaling that of the bulk strength of the substrate. On the other hand, the presence of contaminants such as moisture, lubricants or gases reduces cohesion (Wray, 1992).

Particle shape effect of compaction characteristics is manifested in the manner particles are packed during compaction. Spherical shape enhances favourable packing of particles at the outset of compaction when particles rearrangements occur more readily. Moisture presence profoundly affects the deformation/relaxation of particulate bulk solid (Sebhatu *et al*., 1997). Usually, wet powders are more deformable than dry ones (Jone, 1981).

2.11 Compaction data analysis

The mechanical strength and integrity of tablets is dependent on the pharmaceutical formulation or powder behaviour during compaction (York, 1979; Hoag and Rippie, 1994; Paronen and Ilka, 1996). Therefore so much interest has been elicited in the study of the process and mechanism of powder and formulation compaction. Facilitating these studies is the availability and utilization of high-tech equipments (Patel *et al*., 2006; Odeku, 2007 and Celik, 2016). Such studies include monitoring different compaction parameters like measurement of changes in temperature axial and radial load transmission, ejection forces and die wall friction (Patel *et al*., 2006; Odeku, 2007; Abdel-Hamid and Betz, 2011). As a result many hypothesis and mathematical models are now in place to represent the compaction process, although none independently can adequately explain the mechanism of compaction of solid particulate matter (Heckel, 1961; Kawakita and Ludde, 1970/71; Odeku, 2007; Mohan, 2012; Kamranian, 2018). Among these equations, the Heckel (1961 a and b) and the Kawakita equations have been widely used, and are found to be more

applicable across a limited set of applied pressures, at high and low pressures respectively (Odeku, 2007).

2.11.1 Heckel equation

This is the most often applied and useful of all the mathematical equations used in analyzing the compaction behaviour of pharmaceutical materials (Heckel, 1961a; Mohan, 2012). It relates the degree of compact densification to the porosity. As compression pressure increases, the degree of compact densification varies directly with porosity. That is,

$$\frac{dD}{dP} = KE \tag{2.13}$$

where D = relative density

P = Pressure

E = Porosity

K = Constant

The relative density is the compact density divided by the material or powder true density that is compact density when no voids exist (Patel et al, 2006; Odeku, 2007; Vivek and Moolchandani, 2008). The porosity can also be defined as:

$$E = \frac{(V_p - V)}{V_p} = 1 - D \tag{2.14}$$

Where V_p and V represent the volume at any applied load and volume at theoritical zero porosity respectively (Odeku, 2007).

Thus equation 2.13 can be expressed as:

$$\frac{dD}{dP} = K(1 - D) \tag{2.15}$$

And from this, Heckel equation below is derived

$$In\left[\frac{1}{(1-D)}\right] = KP + A \tag{2.16}$$

Where P = applied pressure

K and A = constants.

In the relationship, a plot of $In\left[\frac{1}{(1-D)}\right]$ i.e the relative density term against the pressure (P) used gives K as slope of straight line portion and A, intercept (Patel *et al*., 2006; Odeku, 2007; Ohwoavworhua *et al*., 2007). The slope, K, is a material dependent constant which is

inversely proportional to its yield strength known as the mean yield pressure (P_y) (Okunlola and Odeku, 2011). A, the intercept of the extrapolated straight portion influences the initial compact volume. It describes two stages of consolidation, one because of the start relative density of the powder and the other as a result of densification by particle rearrangement (Patel *et al*., 2006; Odeku, 2007). From the value of A, the relative density, D_A, representing the total degree of densification, (Paronen and Juslin, 1983; Itiola, 1991; Mitrevel *et al*., (1996) In Odeku, 2007; Ayorinde *et al*., 2013) can be computed using the following equation:

$$A = In\frac{1}{(1-D_A)} \quad (2.17)$$

Hence

$$DA = 1 - e^{-A} \quad (2.18)$$

(Humber-Droz *et al*., 1983; Robert and Rowe, 1986; Okunlola and Odeku, 2011)

The relative density of the powder bed at zero or no applied pressure, D_O, is used to represent the beginning of rearrangement phase of densification due to die filling. Its value is ascertained experimentally and is the ratio of the loose density (i.e bulk density at zero pressure) to the particle density or true density of the powder (Chowhan and Chow, 1981; Vivek and Moolchandani, 2008).

The phase of rearrangement of particles at the outset of compression is described by the relative density D_B. D_B is the difference between D_A and D_O i.e.

$$D_B = D_A - D_O \quad (2.19)$$

The theoretical point of densification where particles deformation commences determines the extent of the rearrangement phase (Odeku, 2007; Ohwoavworhua *et al*., 2007).

Heckel plot is especially relevant in establishing the prevalent material deformation type that is occurring. They are useful in:

i. Differentiating between materials that consolidate by fragmentation or deformation.
ii. Assessment of plasticity.

Relatively soft materials preferentially deform plastically. On the other hand, harder ones, characterized by higher mean yield pressure values get compressed firstly by fragmenting and result ultimately in denser packing. Soft materials are easier to compress than hard, brittle ones (Odeku, 2007).

Three groups or types of powder, A, B and C exists using Heckel plot and their material compaction behaviour (York and Pilpel, 1973 and Odeku, 2007; Mohan, 2012), as illustrated in Figure 2.3.

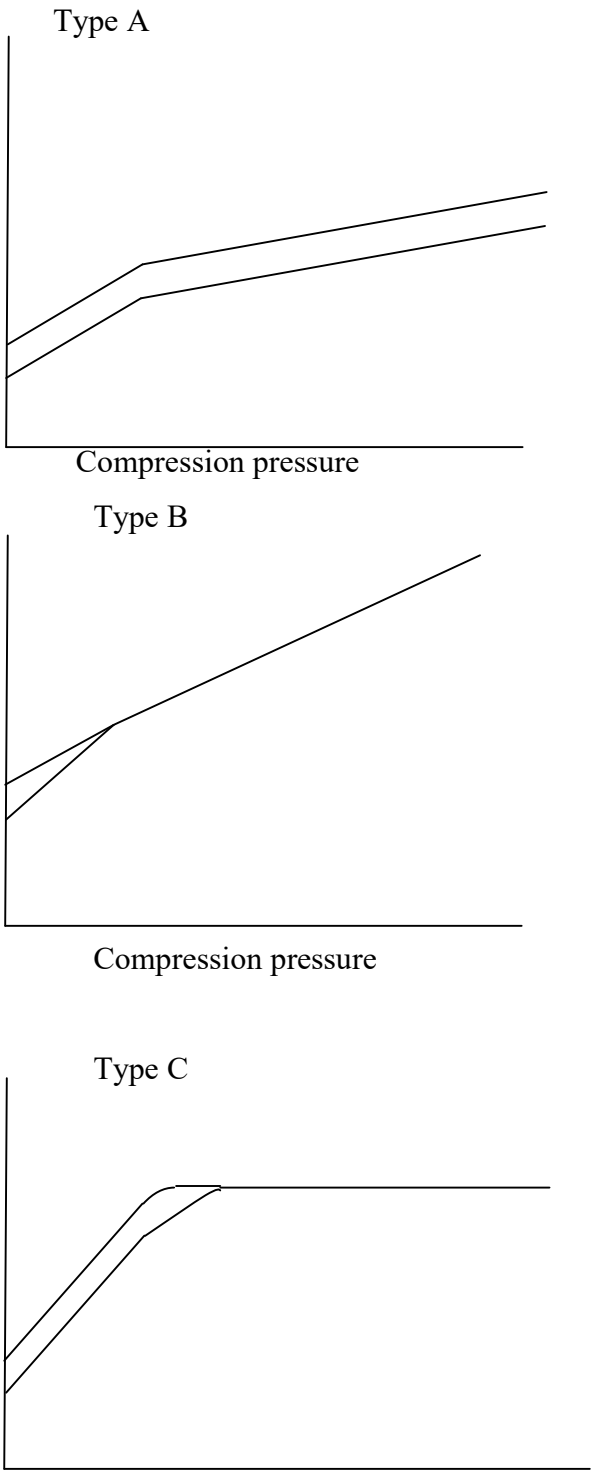


Figure 2.3. Different types of Heckel plots (Odeku, 2007; Mohan, 2012)

Type A materials, e.g sodium chloride, exhibit straight line equidistant graphs with rising compression pressure showing clearly that deformation is via plastic mechanism alone (Type A in Fig. 2.3) (Odeku, 2007; Mohan, 2012). Such materials are relatively weak and easily deform plastically maintaining varying level of porosity based on the way the powder was packed in the die at the beginning (Odeku, 2007; Mohan, 2012).

Usually, type A Heckel plots display a higher final slope than type B, suggesting the former materials have a lower yield pressure. Hard, brittle materials are most times more cumbersome to compress than soft yielding ones. This is due to the fact that void filling by plastic deformation is more effective than fragment percolation resulting from fragmentation (Odeku, 2007). For all materials, as the porosity nears zero, plastic deformation is likely the prevalent means of compression.

For type B materials, e.g lactose, a curved portion precedes a linear part (Type B in Fig. 2.3). This point out that particles are fragmenting at the beginning stage of compression process i.e brittle fracture taking place first and is followed by plastic flow. The two regions of the type B Heckel plots are considered to describe the start of repacking stage and the subsequent deformation process, the point of intersection coinciding with the lowest force at which an intact tablet is formed. Type B Heckel plots are commonly encountered in hard materials which have higher yield pressures, and normally get compressed by fragmenting first to give denser packing (Odeku, 2007; Mohan, 2012).

Type C materials Heckel plot start with a steep straight portion that get superimposed, then become flat with increase in compression load (Type C in Fig. 2.3) (Odeku, 2007; Mohan, 2012). This is because there is no rearrangement stage during compression and densification as a result of plastic deformation and asperity melting (York and Pilpel, 1973 and Odeku, 2007; Vivek and Moolchandani, 2008). Examples of type C materials include stearic acid, palmitic acid, lauric acid (Esezobo and Pilpel, 1977).

The quantity of lubricant, die size and total compression duration can affect Heckel plots (Odeku, 2007; Mohan, 2012). These factors are important and should be taken into

consideration. Thus, classification of compaction behaviour based on changes in Heckel plots need to be done with caution as experimental conditions of compaction may vary. The K values of the Heckel plot have a correlation with the crushing strength of tablets. Larger values indicate harder tablets and this information is useful in binder choice during tablet formation. P_y value computation is influenced by several factors (Rues and Rees, 1978). Among these are: punch diameter (York, 1979), amount of powder tested and filling method i.e manual or automated, type of compression equipment - rotary press, uniaxial press, a compaction simulator, compression speed (Robert and Rowe, 1986), contact time, type and quantity of lubricant (DeBoer *et al*., 1978; Ragnerson and Sjogren, 1984). Also, the initial particle size, the particle type being compressed (i.e whether powder, granules, mixed powder or granules) as well as the accuracy of displacement measurement and compact volume after ejection for the in-die and out-die methods respectively, affect the calculation of P_y i.e. mean yield pressure (Paronen and Ilka, 1996).

The Heckel equations applicability to a wide range of powders was reported by Roberts and Row (Roberts and Rowe, 1986). Their studies showed that, yield stress values obtained using the Heckel relationship were reasonably in harmony with those measured independently using indentation hardness. Choi *et al*., (2010) used the Heckel equation to study compressional behavior of some commonly used pharmaceutical excipients. Adeyemo and Itiola (1993), Odeku and Itiola (1998) and Odeku (2007) reported the application of the equation in studying the compressional properties of some indigenous Nigerian pharmaceutical excipients. Its usefulness in studying the compressional behaviour of tablet formulations made with local gums and mucilage has also been documented (Adeyemo and Itiola, 1993; Odeku and Itiola, 2002; Odeku, 2005 & 2007 and Odeku and Patani, 2005).

2.11.2 The Kawakita equation

Kawakita and Ludde (1970/71) advanced this equation to evaluate powder compression utilizing the level of volume reduction, C under pressure. This parameter, i.e extent of volume decrease, C, is equal to the engineering strain of the particle bed and represented by the following equation (Patel *et al*., 2006; Odeku, 2007; Mohan, 2012):

$$C = \frac{(V_0 - V_p)}{V_0} = \frac{abP}{(1+bP)} \quad (2.20)$$

In practice, this equation can be simplified as follows:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \quad (2.21)$$

Where:

C = degree of volume reduction

V_0 = Initial volume of the powder bed

V_p = volume of powder bed following compression

a and **b** = constants, which are gotten from the slope and intercept respectively of the P/C versus P plot (Odeku, 2007; Mohan, 2012; Kamranian, 2018).

The constant **a** is equal to the lowest porosity of the powder bed before compression while **b**, known as coefficient of compression, relates to the plasticity of the material (Patel *et al*., 2006; Odeku, 2007; Vivek and Moolchandani, 2008). The material's relative density at the beginning D_i, is obtained by subtracting **'a'** from 1 i.e"1- **a**". This term 'D_i' has been shown to provide a measure of the initial relative density of tablets with the application of small pressure or what may be referred to as tapping (Odeku *et al*., 2005; Mohan, 2012). The inverse of **b** gives a pressure term P_k, which is the pressure needed to reduce the powder bed by 50% (Alderborn, 2002 and Odeku, 2007). P_k is inversely related to plastic deformation, thus lower values indicate a higher degree of plastic deformation taking place during compression (Adams and Mckeown, 1996; Odeku *et al*., 2005). Soft materials usually have low P_k values and readily undergo plastic deformation when pressure is applied.

The Kawakita constant, **a**, is influenced by the particle size and shape. The values of **a** decrease as particle size increase (Kawakita and Ludde, 1970/71). For single powders, it is smallest and largest for spherical and irregular particles respectively. Angular particles improved the packing properties of microcrystalline cellulose and the addition of spherical and needle shaped particles generally give rise to lower **a** value at equivalent concentration.

The Kawakita equation has two limitations (Odeku, 2007; Mohan, 2012). Firstly, it can apply to powdered materials alone. Nonetheless, the equation can be altered for application to granular materials by replacing the beginning compaction volume with an initial bulk volume, which then gives a better fit. Secondly, the equation can only describe the compression process up to a given pressure beyond that point it seizes to be straight line. It is more suitable for low pressures and high porosities (Denney, 2002; Patel *et al*., 2006; Odeku, 2007).

The two popular equations (Heckel and Kawakita) have their best applicable pressures range where linear relationship is guaranteed - Kawakita at low and Heckel at higher compression pressures. The literature has reported the simultaneous use of these two equations to best describe the compression process (Alebiowu and Itiola, 2001 and 2002; Odeku and Fell, 2006).

2.12 Evaluations of tablets

The evaluation of manufactured tablets quality is necessary for the design and production of tablets of satisfactory quality. To accomplish this, physical, chemical and bioavailability properties of tablets are assessed. Routinely, the following in-process tests are required to determine and thus ensure tablet production quality: different methods of assessing elegance, various methods of evaluating mechanical strength (friability, hardness test or crushing strength, tensile strength and brittle fracture index) and estimation of drug content and release (tablet weight, disintegration time and dissolution time), (Rudnic and Schwartz, 1990).

2.12.1 Assessment of elegance

The overall elegance of tablet is a very important factor for consumer acceptance of the product. It is relevant in controlling the between batch and general tablet to tablet uniformity, as well as production process monitoring. The entire appearance, visual identity and organoleptic attributes of tablet are means of evaluating overall elegance (Odeku and Itiola, 2008). Tablet size, shape, colour, physical flaws and consistency,

surface texture, absence or presence of odour are all factors to consider in assessing general appearance.

The tablets thickness, diameter and shape are dictated by the kind of tooling used in producing them. At a particular die fill, tablet thickness changes with variation in compression pressure. While maintaining a constant compression pressure, the tablet thickness, changes with variation in tablet weight, packing of the powder mix and particle size distribution. When tablets press is working optimally and the punch tooling is of consistent length, the batch or within batch tablet thickness is consistent as long as the powder blend or granulation is consistent enough in particle or granule size and size distribution. Accurate measurement of thickness is achieved with micrometer screw gauge which enable ascertaining differences in thickness between tablets. When viewed with the ordinary eye, such thickness inconsistency in a batch or from batch to batch should be imperceptible (Pharmawiki, 2019). A limit of within ± 5% variation from a standard value is allowed. Conformance with this permits easy packaging (The United State Pharmacopoeia, 2007).

Tablet weight is determined by its physical dimensions, the component material density and their proportions in the tablet formulation. The British Pharmacopoiea set limits for the mean weight of uncoated compressed tablets. It applies in instances where the tablets drug content is 50mg or excess of that or the drug substance is 50% or higher the dosage form weight. The average weight of twenty tablets weighed individually is calculated. Each tablet weight is then compared to the mean weight. Acceptable limits are shown on Table 2.3. Up to two tablets may differ from the stated values, but not beyond two times.

Table 2.3. Tablet weight variation requirements (B.P, 1998)

Average weight	Percent difference
130mg or smaller	10.0
Greater than 130mg through 324mg	7.5
Above 324mg	5.0

Colour serve as an important means of identification of pharmaceutical tablets. Aesthetic appeal and overall elegance is enhanced when colour is uniform. It improve consumer acceptance of product. Colour variation in tablet is undesirable and is referred to as mottling (Bista, 2021). It results in low consumer acceptance, drug content inconsistency and general poor product quality.

Stability problem can be indicated by the presence of odour in a batch of tablets. An example is the characteristic odour of acetic acid in aspirin tablets beginning to go bad. In other instances, as in vitamins and flavouring agent excipients, odour could be a unique feature of the product.

Taste is another vital factor in consumer acceptance of certain tablets. This is particularly so in chewable tablets. A lot of companies use taste panels to decide the preferred flavours and flavour levels in developing new products (Odeku and Itiola, 2008).

2.12.2 Mechanical properties

It is important that tablets possesses adequate measure of strength (hardness) and resistance to surface abrasion (friability) to cope with the stresses encounterd in production and supply chain and patient handling (Odeku and Patani, 2005; Odeku and Fell, 2006). Different methods are used in quantifying the mechanical properties of pharmaceutical tablets. These include: friability (Fell and Newton, 1970; Odeku and Patani, 2005) hardness, crushing strength-friability value (Odeku and Itiola, 2003; Odeku, 2005) tensile strength (Down and McMullen, 1985; Odeku and Patani, 2005) and brittle fracture index (BFI) (Odeku and Patani, 2005).

2.12.2.1 Friability

This evaluates tablet resistance to fracture and wearing or rubbing off. It indicates how weak a tablet is (Odeku and Itiola, 2003; Odeku and Patani, 2005; Odeku and Fell, 2006). Friability is associated with the loss of powder from tablets when subjected to mechanical shaking. Friabilator is used in testing friability of tablet. The commonly used laboratory

friabilator is the Roche friabilator. Other examples include: Veego friabilator and DBK friabilator.

The test is carried out by subjecting tablets of known weight (pre-weighed) and dimensions to the combine effect of shock and abrasion in a plastic chamber in the friabilator. The apparatus is revolved at specific rotations in one minute (usually 25 revolutions a minute) for four minutes dropping six inches distance per cycle. The tablets are dusted after four minutes, weighed again and friability (% weight loss) ascertained. The acceptable value for conventional compressed tablets is less than 1% (B.P, 1998).

2.12.2.2 Hardness or crushing strength

The crushing strength of a tablet is the force just sufficient to fracture it when applied along the radial axis of the tablet. It is the load required for tablet split up diametrically (Odeku and Itiola, 2003). Tablets of satisfactory quality must have some measure of strength to withstand mechanical shock during manufacture, handling, packaging and shipping. It also affects the disintegration time and dissolution rate of drugs. Excessively hard tablets are unlikely to meet disintegration and dissolution requirements. On the other hand, if they are too soft, they will be unable to withstand handling and other operations.

Hardness or crushing strength tester is the device used in determining tablet hardness or crushing strength. Several types made by different companies are available. Some examples include: Erweka, Pfizer, Ketan, Shreeji, Strong-Cobb, Monsato tablet hardness testers and PTB 301 crushing strength tester.

The test is done by placing the tablet between the spindle and the anvil, then pressure is applied by turning the knob just enough to hold the tablet in position. The reading of the pointer on the scale adjusted to read zero. Subsequently, the pressure is increased uniformly until the tablet breaks. The pressure when this occurs is read from the pointer.

Tablets generally become harder several hours after compression. Hardness also increases with applied compression force until after a certain maximum force beyond which lamination or capping begins to occur in the tablet.

2.12.2.3 Tensile strength

This gives an assessment on the bond strength of tablet (Odeku and Itiola, 2003) and the most widely accepted measurement technique is the diametrical compression test. Bending or flexural test and indentation test are two other methods used in determining tensile strength. When assessing radial tensile strength, the fracture takes place via a preplanned diametral cross part of the tablet. Thus, the radial tensile strength is thought to be the mean strength of tablet, as against the strength of the weakest plane in the tablet (Fell and Newton, 1970).

The radial tensile strength, T, is expressed as:

$$T = \frac{2L}{\pi dt} \qquad (2.22)$$

Where T is the tensile strength, L is the load needed to cause fracture; d and t are tablet diameter and thickness respectively (Odeku and Itiola, 1998; Odeku and Patani, 2005). Several factors such as the tablet shape, adhesion conditions between compacts and its support, test conditions and deformation properties of the material may influence the measurement of tensile strength (Odeku and Itiola, 2003).

Three different types of tablet failure may occur during diametrical compression test: normal tensile failure, compression and/or shear failure and triple-cleft failure. The tablet splits into two halves along the loaded diameter in normal tensile failure. Irregular fracture of the specimen resulting in several irregular fragments takes place in compression and /or shear failure. Lastly, in triple-cleft failure, the tablet specimen splits symmetrically about the loaded diameter into four pieces.

Axial tensile strength (Tx) measurement is preferred by some authors due to influence of crack propagation changes on radial tensile strength (Jarosz and Parott, 1982). It is represented by the equation:

$$Tx = \frac{4L}{\pi d^2} \quad (2.23)$$

2.12.2.4 Brittle fracture index (BFI)

BFI test is explained using Griffith fracture theory. The theory state that a defect or flaw present in a tablet will propagate if stress equals bonding energy (Heistand *et al*., 1977). It was proposed to study the tendency of materials to fracture. Brittle fracture index is used in assessing the comparative elasticity to plasticity compression property of powder i.e plastoelasticity (Ejiofor *et al*., 1986; Onyekweli *et al*., 2004 in Okoye *et al*., 2010). It is also employed in measuring tablet capping or lamination tendency when under diametral stress (Alebiowu and Itiola, 2002; Iwuagwu and Onyekweli, 2002; Okoye *et al*., 2010).

BFI is calculated from the tensile strength of a tablet without a central hole, T, and that from a similar tablet with a hole at the center T_o using the equation below (Okoye *et al*., 2010).

$$BFI = 0.5\left[\left(\frac{T}{T_0}\right) - 1\right] \quad (2.24)$$

The hole plays the role of a built in stress concentrator "defect". BFI values are between 0 and 1. Lower figures approaching 0 means low tendency to fracture, while high values nearing 1 indicate high fracture likelihood or material easily laminating or capping (Okoye *et al*., 2010).

2.12.2.5 Factors affecting mechanical properties of tablets

i. Effect of compression pressure

Juppo *et al*., (1995) reported a linear relationship between tensile strength and compression pressure for lactose tablets. Itiola (1986) also observed an increase in tensile strength and brittle fracture index with increasing compression pressure in metronidazole tablets. Again, tensile strength and porosity increased and decreased respectively with higher compression pressure in a study involving convex faced aspirin tablets (Pitt *et al*., 1991). As compression pressure is raised, the porosity decreases and particles become more strongly bonded together thus harder tablets are produced (Adeleye *et al*., 2015). This relationship

holds up to a maximum hardness value, beyond which further pressure increase give rise to tablet capping or lamination.

ii. Effect of granule size and shape

Esezobo and Pilpel (1976) observed that different granule size fractions of the same formulation produced tablets of varying tensile strength values. Tablet hardness increases when granule size decreases (Li and Peck, 1990; Riepma *et al*., 1993). Sun and Grant (2001) noticed that at constant compression pressure, smaller particles formed tablets of greater tensile strength. However, fragmentation of larger particles tended to equalize the particle size and reduce its influence.

Large granules entrap less air than small ones (Itiola, 1983) and interlock more readily (Esezobo and Pilpel, 1976). Under high compression force, they fragment and fill void spaces easily than small granules. This enhances solid bonds formation within the compressed tablets in such condition. Thus tensile strength of tablets prepared from large granules is usually higher than might be expected for such granule size.

The effect of granule shape on the mechanical strength of tablet has been observed by Johansson and Alderborn (2001). Granules of irregular shape formed stronger tablets than spherical ones of similar intragranular porosity. Akin-Ajani *et al*., (2005) attributed this to increased sites for interlocking and formation of more solid bonds.

iii. Effect of temperature

Increase in tablet strength at higher compression temperature has been reported in the literature. Britten and Pilpel (1978) observed that, the tensile strength of tablets was very small at low temperature, but increased as the temperature was raised between -20ºC and 90ºC in their study of some tablets. Similarly, Esezobo and Pilpel (1986) noted tensile strength increase with compression temperature rise during a study of paracetamol and chloroquine phosphate tablet formulations at constant pressure and temperature range of -10ºC to 60ºC.

Raising the temperature increased the number of welded bonds formed. Frictional heat release at particles contacts during compression of powders and/or granules causes rise in ambient temperature (Hanus and King, 1968). Under high pressure, localized melting of the material may occur (Rankell and Higuchi, 1968; York and Pilpel, 1972). On dissipation of the pressure, solidification takes place giving rise to welded bonds which enhances strength.

iv. Effect of binding agents

This improve cohesiveness (Odeku and Patani, 2005; Adenuga *et al*., 2008) and enhance structural strength (Itiola, 1986). Tensile strength and brittle fracture values increases and decreases respectively (Odeku and Patani, 2005; Adenuga *et al*., 2008). The extent of increase or decrease depends on the concentration and nature of binder.

v. Effect of moisture content

The presence of moisture in powder mass for tableting influences the mechanical strength of the final tablets produced (Ahlneck and Alderborn, 1989; Nokhodchi *et al*., 1995; Abdel-Hamid and Betz, 2011). During a study on ibuprofen tablets, Nokhodchi *et al*., (1995) observed consistent tablet hardness rise with additional moisture till 2.5% w/w. The tablet strength decreased with increase in moisture content at beyond 3.5% w/w moisture content. Both formation of moisture film around the drug and hydrodynamic lubrication effects of moisture (encouraging best transmission and compaction force use) were given as probable reason for the tablet strength increase at lower humidity. The decrease in tensile strength with increasing moisture content beyond 3.5% w/w moisture, was attributed to hydrostatic resistance of the excess moisture in the void spaces producing force transmission that in-turn reduces particle-particle contact areas, surface energy and adhesive forces.

Ahlneck and Alderborn (1989) gave two likely mechanisms for the observed increase in tablet tensile strength with increasing relative humidity during storage at atmosphere of low to intermediate moisture content. On one hand, absorbed moisture may serve as a surface restructuring medium giving rise to more solid bridges. This likely is the

mechanism at fairly low humidity. On the other hand, immobile water layer absorbed at particle surfaces can facilitate particle-particle interactions leading to strength increase.

Sebhatu *et al*., (1997) work on bond deformation properties of amorphous lactose particles gave further explanation for the increase in tensile strength with moisture content increase. Tensile strength increases with moisture content increase because of increase particle deformation. Increase particle deformation lead to increase area of contact between the particles during compression, thus increased tensile strength.

vi. Effect of coating

York and Pilpel (1973) and Ejiofor *et al*., (1986) found that the tensile strength of loosely packed pharmaceutical powder beds was affected by coating. The homologous temperature and surface energies of the coated powders (Igwilo and Pilpel, 1988), the quantity, nature and hardness of coating materials, dictate the strength of the tablets produced from them (Malamaturis and Pilpel, 1982; Irono and Pilpel, 1982a, b).

Viscosity increase in paraffin as lactose tablets coating substance caused tensile strength increase in the coated tablets (Irono and Pilpel, 1982a). Formation of liquid/molton bonds between neighbouring particles which increases with viscosity of coat was suggested as reason for the increase in strength. The scope and intensity of forces between particles acting upon coated and uncoated particles surfaces is changed by the paraffin coating (Igwilo and Pilpel, 1988).

2.12.3 Drug content and release

This assessment is done to monitor and control tablet quality, employing several tests. These include weight variation test (discussed in section 2.12.1) drug content uniformity, disintegration and dissolution tests. The first two tests assess the drug content in the tablet formulation while the later two are for drug release determination.

To be sure every tablet in a batch contains stipulated drug quantity except minimal differences, drug content consistency evaluation is carried out. It is done by randomly

selecting thirty tablets from the lot and assaying ten of them individually with appropriate assay method for the active ingredients. Valid results are when nine of the ten tablets have not less and more than 85% and 115% respectively and the 10^{th} tablet content not less than 75% and more than 125% of stipulated drug amount. If the above fails, then the other twenty tablets are tested separately and for the batch to pass, all must be within the 85 to 115% range.

Disintegration and dissolution tests are discussed in the following sub-sections.

2.12.3.1 Tablet disintegration time

Disintegration is the process where tablets break up into granules of smaller particles when in contact with water (Guyot-Herman, 1992). The time it takes for a tablet to get to the state where no residue of the tablet except fragments of undissolved coating or soft mass with no palpable firm core remains on the screen of the test apparatus is known as disintegration time. Disintegration is the initial vital step towards solution for most tablets, which is needed for drug availability in the body (Banker and Anderson, 2009).

The USP equipment to test disintegration is a framework of heating system to maintain temperature at 37 ± 2ºC, cylindrical beaker, basket rack station of tubes of specific size, arranged according to specifications and a mechanism to move the basket rack vertically (Al- Gousous and Langguth, 2015). The test is carried out by placing a tablet in each tube and the basket rack brought into a one liter beaker containing the simulated gastric or intestinal fluid. It is positioned in a manner that the tablets at all times keep a 2.5 cm distance below the liquid surface and above bottom of beaker during the upward and downward movements accordingly. Plastic discs with perforations can be placed on each tablet to avoid them floating. The discs also impart abrasive action on the tablet. A limit of 5-30 minutes as the endpoint for uncoated tablets and 1-2 hours for coated tablet is set in the USP. When the tablet split completely and resultant particles pass through the basket rack mesh screen within set limits or leave behind a soft impalpable soft mass or undissolved coating, USP standard is met.

2.12.3.1.1 Disintegration theories

Various disintegration mechanisms have been suggested. These include: effect of water absorption, swelling mechanism, heat of wetting, evolution of gas and porosity of tablets.

i. Effect of water absorption

Tablets disintegrate on absorption of water. Solubility of both the active ingredient and formulation additives influences this (Ringard and Guyot-Herman, 1981; Lowenthal, 1973; Fouad *et al*., 2020).

ii. Swelling mechanism

This is one of the main mechanisms of action of tablet disintegrants (Quodbach and Kleinebudde, 2016; Maclean *et al*., 2021). Swelling occurs as disintegrants (especially starches) get in contact with water. This give rise to pressure that causes splitting of the tablet (Ringart and Guyot-Herman, 1981; Kanig and Rudnic, 1984). The process of break up of tablet is slower in formulations containing aqueous soluble drug than ones with insoluble medicament using starch as disintegrant (Shangraw *et al*., 1986). This was attributed to reduction in starch water absorption capacity in the former case.

iii. Heat of wetting

Tablets disintegrate due to pressure from expansion of entrapped gases arising from heat produced when the tablet is placed in water (Matsumaru, 1959; Lowenntal, 1973).

iv. Evolution of gas

Disintegration by this mechanism involves the release of gas as a result of chemical reaction when the tablet is placed in water. This is what happens in effervescent tablets containing for example sodium bicarbonate, citric acid and tartaric acid which release CO_2. Also tablet formulations having peroxides component disintegrate by this mechanism. They decompose in the presence of moisture to release oxygen which causes disintegration.

v. Porosity of tablet

The porosity (mean pore diameter) determines the penetration of water into the tablet. The more porous a tablet is the faster the rate of water penetration (Ganderton, 1969) and the shorter the disintegration time. Porosity and water permeability decreases with increase in tableting pressure (Kurup and Pilpel, 1977). Decreased porosity lead to increase disintegration time (Kaing and Rudnic, 1984).

Based on assumption that water penetration into pores is affected by interfacial tension, contact angle, viscosity and geometry of solid surface, Nogami *et al*., (1967) developed an equation to calculate the time for water penetration into a tablet. The equation is:

$$P_t = \left(\frac{25\eta}{\gamma}\right) \cdot \frac{(d_A \cdot H)}{d_p Cos\theta} \qquad (1.25)$$

Where P_t is the penetration time, d_A is the diameter of drug particles in the tablet, H is thickness of the tablet, d_p is the average pore diameter, Θ is the contact angle between liquid and drug particles η and γ are the viscosity and surface tension of the liquid. The use of this equation enable water penetration time to be calculated and a quantitative correlation between water penetration time and disintegration time established.

2.12.3.2 Dissolution of tablet

The process of a solid drug or chemical (solute) passing into solution is known as dissolution. In biological systems, drug dissolution in aqueous medium is vital pre-requisite for systemic absorption. Bioavailability of drug depends largely upon it being in the dissolved state. Therefore, dissolution test is one of the most essential quality assurance tests in pharmaceutical analysis. It measures the amount of time it takes for certain percentage of the assessed solid to go into solution under specified conditions. A direct connection has been established between *in vitro* dissolution rate of many drugs and their bioavailability and this is generally known as *in vitro-in vivo* correlation, IVIVC (Odeku and Itiola, 2005).

2.12.3.2.1 Dissolution theories

Three physical models or processes, either alone or in combination, can be used to describe the dissolution mechanisms (Higuchi, 1967). They are: diffusion layer model, interfacial model and Danckwert's model.

i. Diffusion layer model

This model is based on the assumption that a liquid layer H cm thick, next to the solid surface stays stationary as the liquid pool moves over the surface at a particular pace. The reaction at the solid/liquid border is thought to be immediate resulting to a saturated solution, Cs, of the solid in the immobile liquid layer. The dissolution rate is determined solely by the diffusion of the solid molecules from the motionless liquid film to the liquid mass in accordance with Fick's first law:

$$J = \frac{-D_f d_c}{d_x} \qquad (2.26)$$

Where J is the quantity of solute passing at right angle through a unit surface area per time, D_f is the diffusion rate constant and dc/dx is the concentration gradient. After a time t, the concentration between the limit of the immobile liquid film and the liquid pool becomes C_t. Once the solid molecules pass into the liquid mass, it is assumed that there is quick mixing and the concentration gradient no longer exist. The theory predicts that if the concentration gradient is constant at all times i.e C_s-C_t is constant because $C_s >> C_t$ ("sink" conditions which usually means $C_s > 10C_t$) then a consistent dissolution rate is obtained.

ii. Interfacial barrier model

The interfacial barrier model is hinged on the assumption that the reaction at the solid/liquid boundary is not instantaneous because of a high actuation free energy obstacle which must be overcome to enable solid dissolution. Beyond this, the dissolution mechanism is basically the same as the diffusion layer model, with the concentration at the limit of the static layer of liquid becoming C_t after time t. The diffusion rate in the static layer is relatively fast when compared with the overcoming of the energy barrier. Thus the phase of surmounting the energy barrier is the most critical point in the dissolution process.

iii. The Danckwerts model

This is based on the assumption that solute get transported away from the solid surface by microscopic pockets of solvent at the solid/liquid interface facilitated by disorderly eddy diffusion causing dissolution. The pockets of solvent are able to absorb solute in accordance with diffusion laws at the interface and are replaced by fresh pockets of

solvent. Assuming the solid surface reaction is instantaneous, this surface renewal is said to be linked to the solute transport rate, thus dissolution rate.

Noyes and Whitney (1897) were the earliest to propose a quantitative expression of the dissolution rate as follows:

$$\frac{d_c}{d_t} = K(C_s - C_t) \qquad (2.27)$$

Where dc/dt is the concentration change rate at any given time and K being the rate constant.

Higuchi (1967) also later discussed the rate laws predicted by the different mechanisms both alone and in combination.

The integrated form of the Noyes-Whitney equation is:

$$In\left[\frac{C_s}{C_s - C_t}\right] = kt \qquad (2.28)$$

The equation fashioned like the rest rate law equations, Higuchi (1967), predicts a first-order reliance on the concentration gradient (i.e C_s-C_t) between the still liquid layer adjacent to the solid surface and the liquid pool. Noyes and Whitney (1897) elucidated their dissolution data using a concept comparable to that used for the diffusion model (Higuchi, 1967).

The foregoing considerations were at instances where the solid shape remains intact within the dissolution exercise (i.e unchanging surface area). But pharmaceutical tablets surface area varies with time as disintegration occurs during the dissolution process.

Wagner (1969) modified Aguiar *et al*., (1967) suggestion of drug dissolution occurring only in small particles. Wagner demonstrated dissolution occurrence from whole tablet and disintegrated aggregates and/or granules employing plots of percentage dissolved against time on logarithmic-probability graph sheet. Kitazawa *et al*., (1975) proposed a modification of this approach of using integrated version of Noyes and Whitney equation (equation 2.28) to ascertain the dissolution rate constant of uncoated caffeine tablets. The following equation for time at 100% (t_{100}) of solute dissolved was derived:

$$t_{100} = \frac{6.909 + 2.303 \log C_s + t_1 (K_2 - K_1)}{K_2} \qquad (2.29)$$

2.12.3.2.2 Mechanism of drug release from matrix tablets

Diffusion, erosion and swelling followed by diffusion are the three main mechanisms via which active ingredient get released from matrix system. A single mechanism or combination of two or all three mechanisms may take place for drug release in a particular matrix delivery system. When the matrix tablet get in contact with water, diffusion of the active drug occur by dissolving in the water that filled the matrix surface pores (Quintanar-Guerrero *et al*., 1999). This diffusion can take place on a macroscopic scale i.e through polymer matrix pores or on a molecular (between polymer chains). The nature and polymer concentration determines the release rate of drug from the matrix system (Varshosaz *et al*., 2006). As the release progresses, the rate of drug release usually decreases from matrix system because of progressively longer distance the active drug must travel thus longer diffusion time. The rate is fairly constant for reservoir system where a solid drug, dilute solution or a highly concentrated drug solution with a polymer matrix is enveloped by cover of a rate-controlling material.

2.12.3.2.3 Mathematical models for describing the dissolution process

Several mathematical models are available to describe the dissolution process. These include zero-order, first-order, Higuchi, Korsemeyer-Pappas and Hixson-Crowell models or equations (Bamiro *et al*., 2011; Ramteke *et al*., 2014).

i. Zero-order model or release kinetics

This model describes a process of drug release at a constant rate from the delivery device. i.e drug release rate is independent of the drug concentration (Singhvi and Singh, 2011). Trans-dermal systems, oral osmotic tablets and matrix tablets with low soluble drugs are examples of drug delivery system following this release model. Drug release by this model is the preferred or ideal mode as blood concentration of drug will remain constant throughout the delivery period. The zero-order release equation is:

$$Q = Q_o + K_o t \qquad (2.30)$$

Q being the drug quantity let out at time, t, Q_o is the start drug concentration in the solution arising from a burst effect and K_o is the zero-order release constant or apparent dissolution rate constant (Bamiro *et al*., 2011; Ramteke *et al*., 2014).

ii. First-order kinetics

This describes drug release from dosage form which rate rely on concentration (Bourne, 2002). It is mathematically expressed as:

$$InQ = In\ Q_o + K_1 t \qquad (2.31)$$

K_1 is the first-order model coefficient. Drug release at each time relies on the drug concentration remaining in the delivery device.

iii. Higuchi model

Higuchi (1968) was the first to derive an equation to describe the release of drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion. His equation is:

$$Q = K_H t^{1/2} \qquad (2.32)$$

Where Q is the total drug let out at time t and K_H is the Higuchi release rate constant (Bamiro *et al*., 2011; Singhvi and Singh, 2011). This model has the limitation of not being applicable to matrix systems that undergo swelling upon hydration and those that gradually erode (Reza *et al*., 2003).

iv. Korsemeyer-Peppas model

The drug release from mucilageic systems is described by the following relationship put forward by Korsemeyer *et al*., (1983):

$$\frac{Q_t}{Q_a} = K_k t^n \qquad (2.33)$$

Where Q_t is the quantity of drug let out in time t and Q_a is the total quantity of drug let go after infinite time. K_k is the drug release rate constant, which takes into cognizance the structural and geometric features of the tablet and n is the release exponent. The value of n is used to identify the drug release mechanism:

n = 0.5 indicates Fickian Diffusion (Higuchi matrix), n = 1.0 indicate case II transport (zero-order release, n>1.0 indicates super case II transport and 0.5<n<1.0 represent anomalous (non-Fickian) diffusion (Odeku and Fell, 2004 & 2006; Bamiro *et al*., 2011; Ramteke *et al*., 2014).

v. Hixson-Crowell / Cube root law

This law portrays drug release from delivery systems where particles or tablets surface area and diameter changes and particularly apply to systems that erode overtime (Hixson *et al*., 1931). Hixson-Crowell equation is as follows:

$$Q_0^{1/3} - Q_t^{1/3} = K_s t \quad (2.34)$$

Where Q_o is the initial amount of drug in the tablet, Q_t is the amount of drug remaining in the dosage form at time t and K_s is a constant incorporating the surface/volume ratio.

The model holds for products such as powders and tablets where the dissolution takes place in the planes that are parallel to the surface of the dosage form (Kumar and Hiremath, 2013).

2.12.3.2.4 Factors affecting dissolution of tablets

Drug release from tablet formulation is influenced by various factors among which are: the physicochemical futures of the drug (such as solubility, particle size, surface area), dosage form formulation factors (including compression pressure, binding agent, disintegrants, lubricants) and factors relating to the dissolution test apparatus.

i. Drug solubility

From the modified Noyes and Whitney equation, drug water solubility is the main determinant of its dissolution rate (Kumar and Hiremath, 2013). The aqueous solubility is inturn affected by polymorphism, amorphous state, free base or salt form among others. pH (potency of hydrogen ion) influences the aqueous solubility of electrolytes. Solubility of weakly acidic drugs increases with pH.

ii. Particle size and surface area of the drug

Drug dissolution rate increases with increase in effective exposed area to the dissolution medium. The dissolution rate becomes faster with increase in effective surface area. This is in accordance with Nernst-Brunner's theory. The surface area of the drug can be increased by reducing the drug particle size. The increased dissolution rate of certain sparsely soluble drugs following particle size reduction beyond regularly milled forms highlights this.

Examples of such drugs include griseofulvin, phenacetin, chloramphenicol, tetracycline salts and sulfadiazine. All these were found to show increased absorption rate consequent on particle size reduction (Kumar and Hiremath, 2013). Study by Finholt (1974) on five size ranges of phenacetin found the amount of drug dissolved increased as the particle size decreased and surface area increased. However, if the drug is hydrophobic, particle size reduction may result less effective surface area, thus decreased dissolution rate.

iii. Effect of polymorphism and drug crystal form

Different polymorphic forms of drugs exhibit varying solubilization pattern, hence dissolution rates. Polymorphism, crystallinity, solvation, complexation and state of hydration have been reported to affect the dissolution characteristics of drugs. Examples of drugs manifesting polymorphism influence include chloramphenicol and tolbutamide. Studies show that the crystalline forms of drugs are generally less soluble than the amorphous ones (Muedande *et al*., 2011). Novobiocin, griseofulvin, phenobarbital, cortisone acetate are other examples of drugs displaying this behaviour (Kumar and Hiremath, 2013).

iv. Effect of compression pressure

Depending on the interplay of two competing scenarios that occurs, compression pressure effect on dissolution rate can present in diverse forms. On one hand compression pressure can lead to increase surface area because of the crushing effect, thus facilitating dissolution. On the other hand, increasing the compression pressure can lead to increase in tablet density and hardness with resultant decrease in permeability due to enhanced particle bonding, therefore lower dissolution rate (Kumar and Hiremath, 2013).

v. Effect of binding agents

The concentration and nature of binder affect the dissolution rate of drugs. Binding agent concentration increase results longer disintegration time and thus the dissolution time (Esezobo and Ambujam, 1982; Odeku and Patani, 2005). Different binders incorporated in the same drug tablet formulation have giving rise to different disintegration and dissolution times (Odeku and Patani, 2005).

Kumar and Hiremath (2013) reported that phenobabital tablets containing gelatin binder dissolve faster than similar ones made of sodium carboxymethylcellulose or polyethylene glycol 6000 binders. Gelatin imparts hydrophilic properties to the hypophobic drug surface hence facilitating dissolution. On the contrary, sodium carboxymethylcellulose gets converted to the less soluble acid form at low pH while polyethylene glycol 6000 forms a poorly soluble complex.

The relevance of wetability of drug formulation in disintegration and dissolution process was highlighted by Itiola and Pilpel (1986b) in a study of metronidazole tablet formulation using polyvinylpyrolidine (PVP), gelatin and methylcellulose as binders. It was found that incorporation of these binders altered the disintegration and dissolution times of the tablets by reducing their wetability as measured by adhesion tension of water.

vi. Effect of disintegrants and diluents

Disintegrants promote quick splitting up of tablet when in contact with water enhancing rapid release of active drug. The overall dissolution rate of tablet formulations has been found to be influenced to a large extent by the type and quantity of disintegrant incorporated in it. Formulation of aspirin tablets containing Ac-Di-Sol disntegrant showed better dissolution properties than ones prepared with primojel and polyplasdone (Zhao and Augsburger, 2005).

Diluent has also been reported to significantly affect the dissolution rate of tablets. An increase of 5% to 20% of starch content as diluents in aspirin tablets manufactured by the dry, double-compression process brought about a nearly three times increase in disslolution rate (Kumar and Hiremath, 2013). Also nimodipine and cinnarizine tablets containing spray dried lactose diluents were found to dissolve faster than similar tablets produced with dicalcum phosphate (Singh *et al*., 2006).

vii. Effect of lubricant

Lubricants can either retard or facilitate the dissolution rate of drug dosage form depending on their nature, drug granules attributes and quantity of lubricant used. Hydrophobic lubricants exemplified by magnesium stearate, aluminium stearate, talc, and stearic acid

have been reported to slow down drug dissolution rate. On the contrary, hydrophilic lubricants such as sodium lauryl sulfate improve dissolution especially when the granules are hydrophobic and slow disintegrating (Kumar and Hiremath, 2013). Wang *et al*., (2010) reviewed the role of lubricants in tablet formulation. Rizk *et al*., (1995) in a comparative study between magnesium stearate and sodium stearyl fumarate lubricants on the release rate of theophylline matrix found that the former and the latter prolonged and enhanced the release rate respectively.

viii. Effect of polymer type

The type of polymer (plastic, hydrophobic or hydrophilic) has been found to influence the drug release profile of matrix drug delivery system. Reza *et al*., (2003) observed a statistically significant difference in the drug release profile of plastic, hydrophobic and hydrophilic polymeric matrices. In the study, carnauba wax (hydrophobic) was found to have the strongest retardation of the release of theophyline, diclofenac sodium and diltiazem HCl, followed by Kollidon SR (plastic mucilage) and lastly hydroxy propylmethylcellulose (hydrophilic mucilage). Polymer concentration was also noted to be of relevance in the drug release profile of the matrices. The higher the concentration the greater the retardation in all three class of polymers.

Radesh *et al*., (2009) noticed that a combination of xanthan and locust bean gum together as matrix system gave a more precise control release of propranolol hydrochloride than the individual polymers alone. It was attributed to burst effect and fast release by the solitary polymers employed separately.

ix. Others

Several factors relating to both the test apparatus and medium also affect the dissolution rate. Eccentricity of the stirrer (which can be controlled by properly guiding the shaft), alignment of the stirring element (affected by the tilt and agitation intensity) and vibration (that can be caused by many reasons) are all apparatus related features that affect dissolution rate. 50 rpm or 100 rpm are the selected official compendium speed of rotational device. The viscosity, temperature of the medium (usually 37ºC and maintained

within ± 0.5ºC), pH, and surface tension are important dissolution medium conditions that influences the dissolution rate (Kumar and Hiremath, 2013).

2.12.3.2.5 Dissolution rate testing methods

Dissolution rate is determined using the dissolution test apparatus. There are four types of this apparatus described in the British, European Pharmacopoieas and the United States Pharmacopoiea (USP). These are dissolution apparatus I, II, III and IV, also known as the basket, the paddle, the reciprocating and the flow-through cell apparatus respectively.

i. Apparatus 1 (The basket apparatus)

Four components make up this apparatus (USP, 2007; BP, 1998):

a) a glass vessel or container of other inert material that one can see through
b) a motor
c) a drive shaft and
d) a cylindrical basket (for stirring).

The dissolution medium is kept at a steady temperature of 37 ± 0.5°C and at continuous smooth motion during the test. This is achieved by partly immersing the vessel in a sizable appropriate water bath or using any standard heat source like heating jacket. Neither the environment where the framework is placed nor any part of it contributes noticeable motion, agitation or vibration exceeding that due to the smoothly rotating stirring element. The most preferred apparatus is one that allows observation of the preparation and stirring element during the test. The vessel is cylindrical with a hemispherical bottom. It may be one, two or four litres in capacity. The sides are flanged at the top. A fitting covering could be used to avoid water loss by vaporization, but it must have enough holes to allow the thermometer to be easily inserted and samples to be removed. The shaft rotates smoothly when correctly positioned, without significant wobbling that could impact the outcome. This is ensured if it is positioned in such a way that, at any point, its axis does not exceed 2 mm from the vertical axis of the vessel. Its rotation speed is selected and sustained with the assistance of a speed-regulating system at a defined rate (within ± 4 percent). The components of the stirring element's shaft and basket are made of stainless steel. The

dosage form is placed in a dry basket maintained at 25 ± 2 mm distance from the inside bottom of the vessel throughout the test (BP, 1998; USP, 2007).

ii. Apparatus 2 (Paddle apparatus)

Apparatus 2 uses the framework of apparatus 1, with the exception of a redesign of the stirring part, which consists of a paddle shaped as a single entity from a blade and a shaft. But, as long as the framework remains firmly involved during the evaluation, an appropriate two-part retractable design may be used. To render them inert, the paddle blade and shaft may be coated with an appropriate coating. Like apparatus 1, the shaft is oriented so that, at any point, its axis is not more than 2 mm from the vertical axis of the vessel, and rotates smoothly without excessive wobbling that could impair the outcome of the test. The blade's vertical center line passes across the shaft axis such that the blade's bottom is flush with the shaft's bottom. Similar to apparatus 1, a gap of 25 ± 2 mm exist between the bottom of the blade and the inner bottom of the vessel. Before rotation of the blade is initiated, the dosage form is allowed to sink to the bottom of the vessel. By adding a small, loose piece of non-reactive material, such as not more than a few turns of wire helix, dosage units that would otherwise float during the test are made to sink,. Other validated sinker devices may be used (BP, 1998; USP 2007). The most frequently used dissolution test apparatus are the BP apparatus 1 and 2. The USP (2007) recently presented apparatus 3 and 4. The 1993 BP listed dissolution apparatus 4 as apparatus 3.

iii. Apparatus 3 (Reciprocating cylinder)

The construction of this apparatus comprises of a collection of cylindrical, flat-bottomed glass vessels, a set of reciprocating glass cylinders, stainless steel inert fittings, and screens built of suitable nonabsorbent and non-reactive material designed to match the reciprocating cylinders' tops and bottoms. Also it consists of an engine and drive framework for vertically reciprocating the cylinders within the vessels and horizontally indexing the reciprocating cylinders to a different row of vessels if necessary. To ensure that the test temperature is kept constant at 37 ± 0.5°C, the vessels are incompletely submerged in an appropriate water bath of adequate size. The nature of the framework and the atmosphere in which it is mounted is such that, it does not introduce substantial

movement or shaking more than one from the orderly vertically reciprocating cylinder. A system that allows the reciprocating rate to be selected and retained within ±5 percent at the specified dip rate is used. The chosen system is one that enables preparations and reciprocating cylinders to be observed (USP, 2007).

iv. Apparatus 4 (Flow-through cell)

The system consisting of a reservoir, dissolution medium pump, flow-through cell and a waterbath for maintaining the dissolution medium at 37 ± 0.5°C. With normal flow rates of 4ml /min, 8ml /min and 16 ml/min, the pump delivers between 240 ml/h and 960 ml/h. It pushes the medium of dissolution through the flow-through cell upwards. Consistent flow (±5 percent of the usual flow rate) must be delivered. With a pulsation of 120 ± 10 pulses /min, the flow profile is sinusoidal. Non-pulsated flow can also be used, however.

The flow-through component is formed of transparent material and is inert. It is installed vertically, with a filtration system which inhibits the escape from the top of the cell of undissolved particles. 12 mm and 22.6 mm are the usual cell diameters. Usually, the lower cone is filled with small glass beads approximately 1 mm in diameter, with 1 bead approximately 5 mm at the top to cover the fluid inlet channel. To keep special dosage forms in place, a tablet holder is also available. The cell is submerged in a heating system that ensures the temperature is set at 37 ± 0.5°C. The framework, in order to stop vibrations from the pump impacting the dissolution unit, the pump is placed separately from the dissolution unit. The pump must not be at a degree greater than the flasks of the reservoir (BP, 1998; USP, 2007).

Not any of the apparatus described so far is able to mimic exactly the conditions of the gastro intestinal tract to reflect the true *in vivo* behaviour of dosage forms. They are also unable to satisfactorily study dissolution rate of drugs from the new modified drug delivery systems. Thus there is still the quest for a universally accepted dissolution test apparatus (Bamiro, 2011). The USP (2000) specified dissolution Apparatus 5 (Paddle over disk) Apparatus 6 (cylinder) and disslolution Apparatus 7 (Reciprocating holder) for transdermal delivery system.

2.13 Controlled release system

Conventional dosage forms often require frequent drug administration to maintain required blood concentration in treating illness. This is with associated side effects. Efforts to overcome these and other related disadvantages, has led to a number of advancements resulting in new methods with capability to control drug delivery rate, therapeutic action sustenance overtime and site specific drug delivery (Chien, 1985, 1989 and 1992).

Controlled release system involves the use of formulation components and devices to release the drug at a predictable rate *in vivo*. These delivery systems are most applicable to drugs that causes gastric irritation, have narrow therapeutic indices and short half life. Such system ensures that the release of the active agent follows a predesigned manner. The release of the drug may be steady over a long time it may be initiated by the environment or other external events. Whatever the scenario, the goal of controlled release system is to get more efficient cures at the same time minimizing the possibility of under and over dosing (Pallerla and Prabhakar, 2013). Therapeutic drug concentration is quickly attained as part of the dose contained is released initially. Subsequently, drug release kinetics follows a well defined pattern to supply the maintenance dose ensuring steady curative drug concentration. This step is greatly influenced by drug elimination kinetics as a result of different factors such as metabolism (Langer and Wise, 1984).

In addition to infrequent dosing and reduction of adverse side effects, controlled release drug delivery systems have the following other advantages:

(i) Enhanced patient compliance.
(ii) Maximization of efficacy- dose relationship
(iii) Maintenance of drug concentration within optimal therapeutic range for prolonged duration of treatment.
(iv) Controlled administration of a therapeutic dose at a desirable rate of delivery.

However, while these advantages are exciting, it is also important not to be silent about likely disadvantages. These include:

i. There may be the need for surgery to implant or remove the device
ii. The possibility of toxicity or incompatibility of the material used
iii. Possible discomfort to patient for using delivery device
iv. Higher cost relative to conventional delivery systems and
v. Undesirable by- products (Wise 2000).

2.13.1 Classification of controlled release drug delivery systems

Controlled release delivery systems are classified into four major groups based on the technical sophistication and drug release behaviour (Theecuwes, 1983). These are:

i. Rate - programmed drug delivery systems
ii. Feedback - regulated drug delivery systems
iii. Site - targeting drug delivery systems
iv. Activation - modulated drug delivery systems

2.13.1.1 Rate programmed drug delivery systems

Here drug release is at a prior specific scheduled rate not susceptible to external biological stimuli. The device is designed in a manner that ensures drug diffusion inside or around it via the filter medium is regulated to achieve the pre-programmed release. This is sub-classified as follows (Theecuwes, 1983) :

i. Polymer membrane permeation - drug delivery system regulated
ii. Polymer matrix diffusion- regulated drug delivery systems
iii. Polymer (membrane /matrix) hybrid- style drug delivery systems
iv. Micro reservoir partition - regulated drug delivery systems

Polymer membrane permeation - controlled drug delivery systems involve encapsulation of a medicament (dilute solution, concentrated drug solution or solid drug) in a drug store chamber and covering the surface from which drug is let out of the reservoir compartment with a rate regulating polymeric membrane. The polymer membrane is usually of consistent thickness and the diffusion rate of the drug can be maintained reasonably constant over the dosage form shelf life. Thacharodi and Rao (1996) reported the

membrane permeation - controlled transdermal delivery of nifedipine with collagen as reservoir and chitosan membrane as rate controlling membrane.

Polymer matrix diffusion - controlled drug delivery systems has drug uniformly distributed in a hydrophilic or hydrophobic matrix. Natural gums, alginate, methycellulose, sodium carboxymethycellulose, hydroxypropylmethycellulose and hydroxypropylcellulose are examples of hydrophilic matrix. While examples of hydrophobic matrix include: ethycellulose, polyethylene, wax and polypropylene (Wise, 2000). Matrices are prepared by simply compressing a thorough blend of adequate ratios of the mucilage, drug and required excipient to obtain the matrix tablet. Alternatively a viscid liquid or semi–solid polymer is mixed with finely powdered drug, then a cross linking of polymer chain to form the matrices. Or solvent swelling technique is employed where the matrix is prepared in advance and placed in contact with a highly concentrated drug solution which is able to swell the matrix. The solvent is later removed, for example, by physical treatment. Drug release rate in this delivery system can be regulated by controlling the loading concentration and mucilage solubility of the drug and its diffusion rate in the mucilage matrix. The drug delivery rate depends on time and therefore not constant. An example of this delivery system available in the market is Nitro - Dur ^{R}, a transdermal patch.

Polymer (membrane /medium) hybrid type drug delivery systems as the name implies is a combined technique of the earlier described two subclasses. Drug release profile is constant. A marketed example is clomidine transdermal therapeutic system known as Catapress-TTS^{R}. Catapress-TTS^{R} is produced by using a rate controlling non-medicated mucilageic membrane to coat the drug containing mucilage matrix. Thus, clomidine release is controlled by membrane permeation as against matrix diffusion (Bamiro, 2011).

Micro reservoir partition - controlled drug delivery systems involves homogenous dispersion of drug particles suspended in aqueous solution of water miscible mucilage (like polyethylene glycol) give rise to discrete microscopic drug reservoirs that cannot be leached High energy dispersion technique is used to accomplish the microdispersion. Extrusion or moulding techniques can be employed to obtain various shapes and sizes of this delivery device. The drugs physicochemical properties and desired release rate, may

necessitate coating the device with a biocompatible mucilage layer for adjusting the mechanism and rate of drug release.

2.13.1.2 Feedback - regulated drug delivery systems

This dosage form let out drug molecule following trigger by certain feedback mechanisms from an initiating substance which may be a biochemical in the body. The drug release rate is regulated by the concentration of a triggering agent defined by a sensor incorporated into the delivery system (Chien and Lin, 2007). Hydrolysis-activated, enzyme-activated, bioerosion-regulated, bio-responsive, and self-regulating drug delivery systems are all some examples (Chien and Lin, 2007).

You and Auguste (2008) reported the feedback-regulated delivery of the antitumor agent, praclitaxel, based on poly (N,N-dimethylaminoethylmethacrylate-co-2-hydroxyethyl-methacrylate) nanoparticles. They showed that, physiological pH variation of a few units (0.2 to 0.6) can actively trigger the release of praclitaxel from poly(N-N-dimethyaminoethylmethacrylate-co-2-hydroxyethylmethacrylate)DMAEMA/HEMA, particles.

2.13.1.3 Site-targeting drug delivery systems.

This is a method of drug delivery that not only controls the drug release rate from dosage form, but also regulates the route of transportation of drug from the delivery system to the particular cell, tissue or organ where drug action is required. This guarantees optimum therapy with maximum safety (Chien and Lin, 2007). The three components of the best site-specific drug dosage form are:

a) A moiety for specific site targeting. This is able to lead the drug dosage form to the target tissue or cell of interest.
b) A solubiliser. It helps the drug delivery mechanism to be conveyed to the target tissue or cell and preferentially taken up by it.
c) A drug moiety that is covalently attached via a spacer to the backbone and includes specific enzyme(s) severable link at the tissue or cell of interest. (Chien and Lin, 2007).

There are two types of site targeting drug delivery systems: passive and active targeting (Rani and Paliwal, 2014). Passive targeting refers to the medication or drug carrier device accumulation at a particular site, such as an anticancer drug. The physicochemical or pharmacological factors of the disease are reason for the mechanism of such drug assembling. The targeting of anti-malaria drugs for the treatment of leishmaniasis and brucellosis are other examples of this form of targeting. On the other hand, active targeting requires a particular interaction of the ligand-receptor type for intracellular localization that only occurs after blood circulation and extravasation. Active targeting is further sub-classified as first-order, second order and third order targeting (Rani and Paliwal, 2014).
First order type entails the selective distribution to the capillary bed of a designated site of the drug carrier systems, such as compartmental targeting in lymphatics, peritoneal cavity, plural cavity, eyes and joints. The targeted distribution of the drug to particular cell types such as tumor cells, for example, Kupffer cells in the liver, requires second order targeting. Finally, third order targeting refers to the direct delivery of drugs to the intracellular site of targeted cells, such as the entry of a drug complex into a cell through endocytosis by receptor-based ligand mediated entry (Rani and Paliwal, 2014).

a. Colon specific or targeted drug delivery system

This approach ensures the site-specific delivery or targeted delivery of drugs into the lower part of the gastrointestinal tract (GI) which takes places primarily in the large intestine i.e the colon (Lavelle, 2001; Singh, 2007; Singhal *et al*., 2011).

Different methods have been used in the targeting of drugs to the colon. These include pro-drugs, timed release dosage forms, pH dependent delivery systems, osmotically controlled delivery devices, pressure-controlled delivery systems and delivery systems that uses carriers or mucilages that are degraded exclusively by colonic bacteria i.e colonic microflora-activated delivery system (Krishnaiah *et al*., 2002; Yang *et al*., 2002; Sinha and Kumria, 2003; Jain *et al*., 2007; Singh, 2007; Shukla and Tiwari, 2012; Amidon *et al*., 2015; Patel, 2015; Kar and Dinda, 2019). So far, the best of these strategies is the colonic microflora-activated delivery system (Krishnaiah *et al*., 2002; Jain *et al*., 2007).

2.13.1.4 Activation-modulated drug delivery systems

Drug delivery in this technique is stirred up by certain chemical, biochemical or physical processes or assisted by externally supplied energy. By controlling the process applied or energy input, the rate of drug release is then regulated. These delivery systems may be categorized as follows, depending on the kind of process or energy type used (Chien and Lin, 2007):

A Chemical means
   a. Drug delivery forms enabled with pH
   b. Drug delivery systems triggered by Ion
   c. Systems of hydrolysis-actuated drug delivery

B Biochemical process
   a. Enzyme-activated drug delivery systems
   b. Biochemical-activated drug delivery systems

C Physical processes
   a. Sonophoresis-actuated drug dosage forms
   b. Iontophoresis-initiated dosage systems
   c. Mechanical force-triggered drug delivery device
   d. Magnetics-turn on drug delivery form
   e. Vapour pressure-driven drug delivery product
   f. Hydrodynamic pressure-activated drug delivery systems
   g. Osmotic pressure-actuated drug doage form

   i. pH activated drug delivery systems

Gastric mucosa irritant medicines or ones labile or unstable in gastric fluid are delivered to the intestinal tract by these delivery systems. The delivery system is intended to coat the medication using a mixture of intestinal fluid-soluble polymer (such as hydroxymethylcellulose phthalate) and intestinal fluid-insoluble mucilage in a core tablet (like ethylcellulose).

The drug molecules are covered by the coating membrane that protect from acidic degradation in the stomach. The delivery mechanism transfers to the small intestine

following gastric emptying where the intestinal fluid-soluble portion of the coat is dissolved. Thus, a microporous membrane of intestinal fluid-insoluble mucilage is produced. Drug release from the core tablet is then governed by drug passing into solution in the core and spreading via the pore channels. Drug delivery rate from the system can be manipulated to a desired one by varying the quantity of intestinal fluid-soluble and fluid-insoluble polymer content of the membrane (Chien and Lin, 2007; Bamiro, 2011).

ii. Ion-activated drug delivery systems

To monitor the conveying of drugs capable of ionizing, these dosage forms were developed. Due to the relatively constant amount of ions in the gastrointestinal fluid, the release of drugs by the delivery system can be controlled at a more or less constant pace.

The devices are formulated by initially complexing the ionizable drug with an ion-exchange resin, such as compounding an anionic drug with a resin containing $N(CH3^{)3+}$ group or a cationic drug with a SO^{3-} containing resin (Guo *et al*., 2009). The drug-resin-complex granules are additionally mixed with polyethylene glycol 4000 saturating agent to decrease swelling rate when it gets to aqueous medium (Guo *et al*., 2009). Air-suspension coating technique is then used to coat them with a polymeric membrane that is water-insoluble but water-permeable, like ethylcellulose. This covering helps to modulate the release of drugs from the device as a rate-control barrier. Chloride and hydronium ions in the gastrointestinal tract enter the delivery system acting on the drug-resin complex, initiating its break up and thereby releasing the ionic drug (Chien and Lin, 2007; Guo *et al*., 2009).

iii. Hydrolysis-activated dosage device

Drug release here is dependent on hydrolysis process. The system is either generated as microcapsules by encapsulating the drug reservoir or homogeneously dispersing it in microspheres or nanoparticles. It may alternatively be produced as an implantable delivery system. Biodegradable or bioerodable mucilages viz. polylactide, poly (orthoester), poly (anhydride) or poly (lactide-glycolide) comucilages, are used in the fabrication of the device. Hydrolytic degradation of the mucilage chain is the trigger for drug release from

the mucilage matrix and the drug delivery rate regulated by mucilage degradation rate (Chien and Lin, 2007).

iv. Enzyme-activated drug delivery systems

Specific enzymes in target tissue hydrolyse biopolymers to cause drug release in this dosage form. The delivery method is formulated by physically trapping or chemically binding the drug reservoir in microspheres to mucilage chains made of biomucilages. The formulations of albumin microspheres that release 5-fluorouracil by protease-activated degradation in a regulated way is an example (Friend, 2004; Chien and Lin, 2007).

v. Sonophoresis-activated drug delivery systems

The driving force for drug release from the polymeric delivery moiety here is ultrasonic energy. Ethylene-vinyl acetate (non-degradable) or poly [bis (p-carboxyphenoxy) alkane anhydride], a bioerodable polymer, can be used to manufacture the delivery form (Kost, 1993; Chien and Lin, 2007; Bamiro, 2011).

vi. Iontophoresis-activated drug delivery systems

This delivery method makes it possible to disperse charged drug molecules through a biological membrane (the skin, for example) fuel by concentration gradient, just like passive diffusion, but faster pace. Electrical current serves as a means of trigger and modulator of the diffusion process (Dhote *et al*., 2012). A common example of this delivery mechanism is the formulation of phoresor through motion control to improve the percutaneous penetration of anti-inflammatory drugs such as dexamethasone sodium phosphate to surface tissue. The new design known as the transdermal periodic iontophoretic method is as a result of improvements in this delivery technique (TPIS). This has enhanced the transdermal delivery of peptide and protein medications greatly (Dhote *et al*., 2012). The transdermal iontophoretic delivery of insulin, a protein medication, to regulate hyperglycemia in diabetic animals is an example (Harris, 1982; Bertolucci, 1982; Chien and Lin, 2007; Bamiro, 2011; Dhote *et al*., 2012).

vii. Mechanical force-activated drug delivery systems

These delivery systems comprise of reservoir of drug formulation as solution inside container provided with mechanical pump that triggers drug release (Mali, 2018). Upon manual activation of the pump, a calculated drug product dose may be consistently administered into a body orifice, like the nose, via the spray head. Regardless of the force and length of activation, a fixed amount of solution is supplied. A classical example of this device is the metered-dose nebulizer for intranasal administration of a precise dose of luteinizing hormone-release hormone (LHRH) and its synthetic analog, buserelin. This means that the first-pass hepatic removal of the peptide drug is prevented as it is absorbed by nasal mucosa (Chien and Lin, 2007).

viii. Vapour pressure-activated drug delivery system

Drug release is enabled by vapour pressure in this type of delivery system.

Two compartments, an infusion and a pumping compartment, make up the unit. The drug reservoir found in the infusion compartment is a solution formulation. The pumping compartment contains a vaporizable fluid that vaporizes at room temperature to produce a vapor pressure, such as fluorocarbons (Mali, 2018). These two compartments are physically separated by a freely movable partition. The partition moves upward under the influence of the vapour pressure created and propels the drug solution infusion compartment to be released, through a system of flow controller and delivery cannula, into the blood circulation at a fixed rate. The delivery cannula size, formulation viscosity and the differential vapor pressure regulates the drug delivery rate (Chien, 1992). A common example of this delivery scheme is the implantable infusion pump, infusaid®, developed by Metal Bellows. It is used in the continuous infusion of heparin for anticoagulation treatment, morphine for patients with extreme terminal cancer pain, and insulin for blood sugar control in diabetics (Chien and Lin, 2007; Mali, 2018).

ix. Osmotic pressure-activated drug delivery systems

The driving force for the release of drugs from these instruments is osmotic pressure in a controlled manner. The delivery mechanism has a core containing drug, an osmotic agent, an excipient and semi-pervious barrier coating (Auton, 2007; Mali, 2018). There are many

types of osmotic delivery systems, including: elementary, push-pull, regulated porosity osmotic pumps sandwiched osmotic tablets and osmat.

Elementary osmotic pump: This osmotic pump is made of an osmotic core containing a sub membrane with a delivery orifice coating the drug. Water passes through the semi-permeable membrane into the core, allowing it to dissolve, as the device gets in touch with aqueous medium. Hydrostatic pressure builds up after the osmotic center is dissolved and pushes or pumps out the drug containing liquid through the delivery orifice (Keraliya *et al*., 2012). The water ingress rate across the semi-permeable film coating and egress of the liquid having the drug through the delivery orifice dictates the rate of drug delivery. This in-turn is dependent on the coating thickness, quantity of leachable components in the coating, solubility of the drug in the tablet core and osmotic pressure difference across the membrane. The pH and physiological factors also gretly affect drug release (Theeuwes *et al*., 1983; Santus and Baker, 1995; Auton, 2007; Hiren and Vaishnavi, 2017).

Sandwiched osmotic tablets: A polymeric push layer sandwiched or positioned between two drug layers as the core, encased in a partially-pervious cover having two delivery orifices, has this type of osmotic delivery system. The middle push layer containing the swelling agent swells when in contact with the aqueous atmosphere and the substance is extracted from both orifices present on either sides of the tablet (Hiren and Vaishnavi, 2017).

Push pull osmotic pump: This pump is a modification of the elementary osmotic pump. It has the major advantage of being able to deliver both poorly and highly water soluble drugs steadily (Malaterre *et al*., 2009). A bilayer core coated with a partially pervious membrane is the device. The active drug and osmogent form the first layer and the polymeric osmotic agent consists of the second layer. A small delivery orifice is drilled through the membrane by a suitable technique such as a laser or mechanical drill on the drug layer side of the tablet after the semi-permeable membrane coating is applied (Malaterre *et al*., 2009). The polymeric osmotic layer bulges and moves the drug layer to cause drug release through the delivery outlet upon contact with aqueous atmosphere.

Controlled porosity osmotic pump: It consists of a core of active ingredient (drug) together with an osmogent. This is housed in a coating of incompletely pervious film having aqueous soluble excipients. Delivery orifice is created by adding of leachable components. The soluble components dissolve causing the production of a sponge like structure or a microporous membrane when the dosage form is placed in water. Water diffuses into the core through this membrane, creating an osmotic gradient which leads to controlling the release of drug (Edavalath *et al*., 2011; Hiren and Vaishnavi, 2017).

Osmat: It is a novel in-situ osmotically operated matrix system. It is base on the principle that hydrophilic polymers swell in aqueous environment to form a semi-permeable membrane in situ followed by drug release from the matrix system in the presence of osmogen (Keraliya *et al*., 2012). The system combines both features of matrix and osmotic attributes giving rise to tremendous enhancement of drug delivery from swellable matrix systems. It is a simple, easy to fabricate, cheap and versatile controlled delivery system (Hiren and Vaishnavi, 2017).

2.14. Polymers in drug delivery

Polymers have been widely used in controlling drug release rate from formulations. Their extensive application is due to their unique properties (Pallerla and Prabhakar, 2013). Several novel drug delivery systems have been developed due to advances in polymer science.

Polymers used in drug delivery are classified based on the following characteristics:
(a) Origin - natural, synthetic or a combination of both
(b) Backbone stability - biodegradable or non-biodegradable
(c) Chemical nature - polyester, cellulose derivative, protein-based, polyanhydride etc
(d) Solubility - hydrophilic or hydrophobic (Raizada *et al*, 2010; Agrawal, 2014 and Priya *et al*., 2016). However, there is no rigid boundary between these classes as a polymer may belong to several class e.g all natural polymers, cellulose derivatives (chemical nature) and polymers of acrylic acid (synthetic) are also hydrophilic polymers (Bamiro, 2011).

Reza *et al*., (2003) reported a comparative evaluation of three classes of polymers (plastic, hydrophobic & waxy materials and hydrophilic) as matrices for controlled release drug delivery.

1. Plastic polymers form insoluble or skeleton matrices. They are chemically inert and have a great ability for embedding drugs, thus their wide application for sustaining the release of drug. Liquid penetration into the matrix is the rate- limiting step in this class of polymers except channeling agent is incorporated.
2. Hydrophobic, water insoluble and waxy materials are very much erodable. They control the release of drug through pore diffusion and erosion.
3. Hydrophilic polymers, when subjected to aqueous solutions does not dissolve, but a highly viscous gelatinous surface barrier forms immediately after hydration, which regulates the release of the drug and the penetration of liquid into the center of the matrix (Reza *et al*., 2003; Bamiro, 2011).

Further discussion of some examples of polymers based on the various classification characteristics aforementioned is as follows:

2.14.1 Natural polymers

These are of diverse origin, including plant, vegetable, animal, bacteria algae and fungi (Jain *et al*., 2007). They are hydrophilic. Among natural polymers are starches, protein, latex and cellulose (Priya *et al*., 2016). They are extensively utilized to formulate controlled release dosage products because of their ready availability and non-toxicity. This is exemplified by Khaya gum (Odeku and Fell, 2004), Albizia gum (Bhardwaj *et al*., 2000; Odeku and Fell, 2005; Tiwari and Shukla, 2009), xanthan gum (Talukdar and Plaizier-Vercammen, 1993; Tiwari and Shukla, 2009), locust bean gum (Jain *et al*., 2007; Park and Munday, 2004), guar gum (Choursia and Jain, 2004; Jain *et al*., 2007; Tiwari and Shukla, 2009), karaya gum (Tiwari and Shukla, 2009), chistosan (Tiwari and Skukla, 2009; Jain *et al*., 2007), alginates (Nicholson *et al*., 1990; Jain *et al*., 2007; Tiwari and Shukla 2009; Mandal *et al*., 2009), Scleroglucan (Jain *et al*., 2007).

i. Khaya gum

This is a polysaccharide derived from an incised trunk of the tree *Khaya gradifoliola* family, Meliaceae. The constituent polysaccharides are D-galactose, L-rhamnose, D-galacturonic acid and 4-0-methyl-D-glucuronic acids which are very branched (Aspinal and Bhattacharjee, 1970; Odeku and Fell, 2004; Jain *et al*., 2007). It has been shown that Khaya gum has valuable emulsifying properties (Odeku *et al*., 1997; Odeku *et al*., 1999b; Jain *et al*., 2007). It was also demonstrated to be a helpful binding agent in tablet products (Odeku and Itiola, 1996, 1998, 2003), controlled release formulation (Odeku and Fell, 2004) and as a covering tool during compression to deliver curative agent to the colon (Odeku and Fell, 2005).

ii. Albizia gum

The gum of Albizia is derived from the incised tree trunk of *Albizia zygia* (DC) J.F. Macbr, of the Leguminosae family. It consists of D-galactose units of β-1-3-linked with some D-galactose units that are β-1-6-linked (Drummond and Percival, 1993; Odeku and Fell, 2004; Jain *et al*., 2007). Albizia gum has been assessed as a potential replacement for Arabic gum as a natural pharmaceutical and food emulsifier (Ashton *et al*.,1975; Odeku, 2005; Odeku and Fell, 2004; Jain *et al*., 2007). A study of the binding properties of Albizia gum with gelatin BP as a standard, showed albizia gum resulted tablets with greater mechanical strength and longer disintegration and dissolution times (Odeku, 2005). The gum has also been assessed as a compression envelope material for drug targeting to the colon (Odeku, and Fell, 2005; Jain *et al*., 2007).

iii. Xanthan gum

Xanthan gum is a high molecular weight extracellular polysaccharide produced during fermentation by gram negative bacterium *Xanthamonas campestris*. It is an anionic, white to cream coloured free flowing powder, soluble in both cold and hot water, but insoluble in most organic solvent. The anionic character is due to the presence of both glucuronic acid and pyruvic groups in the side chain (Trease and Evans, 2009; Tiwari and Shukla, 2009). It contains D-glucose and D-mannose as the dominant hexose units along with D-glucuronic acid and pyruvic acid. The pyruvic acid group occurs at the terminal D-mannose residue

and its distribution depends on the bacterial specie and microbial degradation conditions. The non-terminal D-mannose residue in the side chain contains an acetyl functional group (Talukdar *et al*., 1996).

Xanthan gum solution shows a high degree of viscosity even at low concentration compared to other polysaccharides solution. The solutions are highly pseudoplastic but not thixotropic i.e even after high shear rates the initial viscosity is rebuilt instantaneously. Because of its high viscosity, it is used as an effective stabilizer and thickening agent for thickening, suspension, emulsification and stabilisation of water-based systems in the food and pharmaceutical industries as a hydrocolloid (Talukdar *et al*., 1996). It has also been shown to be an effective excipient for controlled release drug delivery (Talukdar *et al*., 1996; Venkataraju *et al*., 2007).

iv. Locust bean gum

It is sometimes referred to as carob gum as it is gotten from carob tree seeds (*Ceratonia siliqua* family Fabaceae). The gum contain unevenly shaped molecule with branched β-1, 4-galactomannan units (Jain et al, 2007). 1- 4-linked β-D mannan moety is the backbone with 1-6-linked α-D-galactose units forming the side chains. It is a nonionic molecule having up to 2000 residues. In cold water, this neutral polymer is only slightly soluble and requires heat for complete hydration and optimum viscosity (Jain *et al*., 2007; Tiwari and Shukla, 2009). Cross-linked galactomannan however result in water-insoluble film forming product-showing degradation in colonic microflora. Locust bean gum has been reported for its usefulness in colon specific drug delivery (Jain *et al*., 2007; Tiwari and Shukla, 2009) and as controlled release excipient in matrix formulations (Park and Munday, 2004; Venkataraju, 2007). It is also observed to reduce elevated plasma cholesterol in healthy subject (Haskell *et al*., 1992).

v. Guar gum

This is extracted from the ground endosperms of *Cyamposis tetragonolobus* (Leguminosae). It consists primarily of hydrocoloidal polysaccharides of large molecular weight, made of galactan and mannan units joined by glycosidic bonds. As a result of the presence of microbial enzymes, it shows degredation in the large intestine (Jain *et al*.,

2007; Tiwari and Shukla, 2009). A straight chain of β-D-mannopyranosyl units connected (1-4) to single α-D-galactopyranosyl units occurring as side chains or branches is the gum structure. It is approximately 80% galactomannan, 12% water, 5% protein, 2% soluble acid ash, and 0.7% fat (Jain *et al.*, 2007). It's molecular weight is around 1 million, resulting in a solution of great consistency. Guar gum is soluble in cold water and readily hydrates and swells to form viscous colloidal dispersions or sols. This gelling property retards the drugs release from the dosage form.

Guar gum and its derivatives have been used as thickening agents, ion exchange resin and dispersing agent. Krishnaiah *et al*. (2002) reported its use as a binding agent and disintegrant in solid dosage forms and control release excipient. The gum was found to be useful in colon specific drug delivery (Jain *et al*., 2007; Tiwari and Shukla, 2009 and 2012). Al-Saidan *et al*. (2005) prepared guar gum-based matrix tablets of rofecoxib for intended use in the chemoprevention of colorectal cancer.

vi. Karaya gum

The vegetable tree *Sterculia urens* (family Sterculiaceae) produces Karaya gum or gum sterculia, also referred to as Indian tragacanth. It is a mucilage of galactose, rhamnose and glucuronic acid, partly acetylated, (Tiwari and Shukla, 2009). Karaya gum has been shown to have better adhesive qualities than guar gum when used to prepare mucoadhensive tablet for buccal delivery. The study observed that karaya gum formulated mucoadhensive tablets were able to give zero-order drug release but concentration more than 50% w/w is likely needed to provide efficient sustain release (Park and Munday, 2004; Tiwari and Shukla, 2009). It is also used as a thickener, emulsifier in food and as a laxative and denture adhesive. Because of its similar physical characteristics with tragacanth gum, it is use to adulterate it.

vii. Chitosan

Chitosan is a polycationic polysaccharide with a high molecular weight produced by alkaline N-deacetylation of chitin (the most abundant natural polysaccharide next to cellulose). Chitosan is processed easily and economically from naturally abundant chitin

(the principal component in crustaceans). It is non-toxic, biodegrable, multifunctional and biocompatible. Chemically, chitosan is a co-polymer made up of 2-amino-2-deoxy-D-glucose units linked with β - (1→4) bond (Jain *et al*., 2007; Panos *et al*, 2008; Tiwari and Shukla, 2009 & 2012). It is structurally analogous to cellulose.

Significant progress has been made in evaluating chitosan for its application in drug delivery. A wide range of chitosan based pharmaceutical formulations are undergoing clinical trials with much prospect that chitosan may be the carrier material in drug delivery devices in the near future (Tiwari and Shukla, 2012).

Tozaki *et al*. (2002) developed chitosan capsules for colon-specific insulin delivery. For chitosan-based hydrogels, a pH responsive drug conveyor has also been identified. Microspheres of chitosan are used for the controlled release of many drugs and to enhance the bioavailability of sensitive protein drugs (Tiwari and Shukla, 2009). Chitosan has been tested as a direct compression excipient, but other components need to be added to produce satisfactory compacts (Rege *et al*., 1999; Mir *et al*., 2008). Also, Gupta and Ravi (2001) reported the use of chitosan and polyethylene glycol for the controlled delivery of isoniazid.

viii. Alginate

Alginates are natural polysaccharides from algae origin (Jain *et al*., 2007). They are extracted from brown seaweed (Family Phaeophyceae). Dilute alkaline solution is used to extract the seaweed and stabilizes the alginic acid present. The free acid is released by the treatment of the resulting dense and viscid mass with mineral acids and can then be changed into a salt. Alginates are linear polymers that consist of 1→4 linked β-D mannuronic acid and α-L-glucuronic acid residues arranged as blocks of either type of unit or a random distribution of each type (Tiwari and Shukla, 2009). Alginates differ in their blocks constituent according the sources. Alginates form gel easily in the presence of a divalent cation such as calcium ion. This gelation or crosslinking is as a result of the stacking of the glucuronic acid blocks of the alginate chains. Alginic acid when hydrated gives rise to a viscid acid gel because of intermolecular bonding. After gelation, the water

molecules are physically entrapped inside the alginate matrix, yet free to migrate. This is greatly significant in many applications e.g alginate gels for cell immobilization encapsulation (Bamiro, 2011).

Eudragit L-30D-coated calcium alginate bead has been reported to successfully deliver 5-aminosalicylic acid to the colon (Tiwari and Shukla, 2009). Also, calcium alginate microparticles have been used to effectively deliver 5-aminosalicylic acid to the colon following oral administration (Mladenovska *et al*., 2008).

The release of furosemide (a poor water soluble drug) from commercial sodium alginate of different viscosity grade placed in both single unit and multiple units (mini-tablets) hard gelatin capsules has been assessed (Efentakis and Koutlis, 2001). Formulations containing lower viscosity grade sodium alginate were found to exhibit greater erosion and faster drug release relative to high viscosity sodium alginate products which showed lower erosion and higher sustained drug release.

ix. Scleroglucan

This is a natural polysaccharide from fungal source. Scleroglucan is a generic term that refers to a class of glucans with structures that look alike produced by fungi, especially those of the genus Sclerotium. It is a branched homopolysaccharide composed of a main chain of (1-3)-linked β-D glucopyranosyl units with a single β-D-glycopyranosyl unit (1-6) linked to each third unit (Jain *et al*., 2007). Scleroglucan is highly hydrolysis-resistant. The viscosity stays almost entirely consistent even at high ionic strength up to pH 12 and at temperatures up to 90^0C. It exhibits unusual and fascinating behavior..

Pharmaceutical uses of scleroguca include, as a tablet coating material, stabilizing agent in suspension and as a laxative. Its unique rheologic properties and resistence to hydrolysis, electrolyte and temperature enable it to have several industrial applications particularly in the crude oil industry for thickening drilling muds and for enhanced crude oil recovery (Jain *et al*., 2007).

x. Tragacanth

Tragacanth, with a molecular weight of 840,000 $gmol^{-1}$is a naturally occurring dried gum. It is obtained from *Astragalus gummifer*, Labillardiere and other Astragalus species.

Bassorin gum (60-70 percent), which is a water-insoluble polysaccharide and water-soluble tragacanthine, are the main constituents. It also contains cellulose, sugar, protein and ash traces. On hydrolysis, L-arabinose, D-xylose, D-galactode and D-galacturonic acid are made from tragacanth. It is stable in its natural forms in the absence of water, but become vulnerable to microbial spoilage in aqueous conditions. Tragacanth gum is employed as a suspending and emulsifying agent in the drug industry (Jones, 2004; Trease and Evans, 2009).

2.14.2 Synthetic and semi-synthetic mucilage

These include the following,

A. Vinyl polymers e.g polymethacrylates, polyvinyl alcohol, polyvinylpyrolidine (povidone), polyacrylic acid (carbomer).
B. Polyesters e.g polycaprolactone (E-Caprolactone), polylactide and related comucilages
C. Silicones
D. Cellulose ethers. These are semi synthetic and are formed by alkylation of cellulose. They have wide pharmaceutical application and arguably are most important class of ethers used in pharmaceutical formulations. The quality of their gelling is independent of the medium's pH. Examples are: methylcelulose, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, ydroxyethylmethylcellulose, hydroxyethylcellulose, sodium carboxymethylcellulose (Jones, 2004)

i. Polymethacrylates;

Polymethacrylates are synthetic anionic and cationic polymers of dimethylaminoethyl-methacrylates, methacrylic acid esters and methacrylic acid in varying ratios. They are non-toxic and non-irritant and are mainly used as film coating for soild dosage forms. They also serve as viscosity modifiers in some topical formulations, matrix layers in transdermal delivery systems and binders for both aqueous and organic wet granulation process.

Polymethacrylates are popularly known by the trade name Eudragits (Chang and Shukla, 2003; Jones, 2004).

ii. Polyacrilic acid (Carbomer or carbopol resin)

Polyacrilic acid is high molecular weight polymer that is crosslinked with either allylsucrose or allylethers of pentaerythritol. It contains between 56-68% w/w carboxylic groups (Jones 2004). It is a white fluffy powder. Carbomer or carbopol resin is highly compressible and ideal for direct compression processes. Carbopol 974P is the oral pharmaceutical grade of the carbomers. Polyacrilic acid is hydrophilic and together with its highly crosslinked structure makes it suitable for controlled release drug delivery. It is also used as a binder in granule and tablets formulation. Polyacrilic acid is widely used as a viscosity modifier in the formulation of topical pharmaceutical products (gels, creams). Its viscosity depends on the pH, lower at low pH and highly viscous at higher pH (Koleng *et al*., 2003).

iii. Polycaprolactone

Poly (E-caprolactone) is a biodegrable and biocompatible synthetic polymer. It is synthesized by the ring opening polymerization of E-caprolactone monomer using ammonium heptamolybdate as a catalyst (Jones, 2004; Gurlek *et al*., 2017). It is popular for controlled release systems. Polycaprolactone has received increasing interest recently as a biomaterial for medical device.

iv. Silicones or polysiloxanes

Silicones are a class of synthetic resins or mucilages with both organic and inorganic characteristics. They represent the most commercially important inorganic polymers. Silicones are synthetic mucilages made up of repeating units of siloxane, which is a chain of alternating silicon atoms and oxygen atoms, frequently combined with carbon and hydrogen or both. Their properties depends highly on the organic group attached to the silicon atom and can exist as low viscosity oil to gels, rubber and solid resins (Jones, 2004; Rahimi & Shokrolahi, 2001; Mashak and Rahimi, 2009). There is an unsual rotation around the Si-0 bond which allows the mucilage chain to be highly flexible while

maintaining the structural integrity. Also different organic group can easily be substituted along the polymer chain and this extends the properties of these polymers.

Silicones are inert and compatible with body tissues. Their pharmaceutical use is mainly in the production of a variety of medical devices such as cardiac valves, intravaginal controlled drug delivery implants, intraocular lenses and hydrocephalus shunts. Pilysiloxanes are also useful in different aesthetic and reconstructive prostheses such as ear, breast and joint prostheses (Jones, 2004; Rahimi and Shakrolahi, 2001).

v. Hydroxypropylmethylcellulose

Hydroxypropylmethylcellulose is a cellulose ether incompletely o-methylated and partly 0-2-hydroxypropylated. It is non-ionic available in many grades. This semisynthetic polymer is commonly used as a straightforwardly compressible excipient for the production of controlled release tablets in the pharmaceutical field (Jones, 2004). It has the benefit of having a high potential for drug loading (i.e. the ability to handle high drug loading levels) and is independent of pH. To control the initial drug release, it easily forms a gelatinous layer in an aqueous medium and subsequently forms a solid viscous gel to regulate further drug release. The downside, however, is that the release of drugs from its matrices does not obey time-independent kinetic, i.e. the drug is not released at a constant rate (Odeku and Fell, 2004). Hydroxypropylmethylcellulose is also used extensively in the pharmaceutical industry as a binder in tablet manufacturing, film coating of tablets and a viscosity modifying agent (Jones, 2004).

vi. Hydroxypropylcellulose

Hydroxypropylcellulose is non-polar, water-soluble cellulose ether commercially present in different molecular weights. Lower molecular weight grades of hydroxypropylcellulose are often used as binders at concentration of 2 to 8% in combination with other excipients for conventional tablet production. Higher molecular weight varieties are employed at concentrations of 20 to 30% in the pharmaceutical industry as hydrophilic matrices for controlled drug release (Jones, 2004; Picker-Freyer and Durig, 2007). Hydroxypropylcellulose also has wide application in film coating of tablets.

vii. Hydroxyethylcellulose

Hydroxyethylcellulose is a white, non-ionic, free flowing, water soluble powder. It is hydroscopic and dissolve ready in both cold and hot water. It is available in different grades. Hydroxyethylcellulose in topical and ophthalmic formulations, has extensive applications as viscosity modifying agent, in solid drug delivery forms as a controlled release matrix, binding and film coating agent. (Jones, 2004)

viii. Methylcellulose

With about 27 to 32 percent of the hydroxyl groups replaced by methoxyl groups, methylcellulose is a cellulose methylether. Methylcellulose is available in the market as different viscosity grades. It is used as an emulsifying agent, controlled drug release dosage forms, granulating agent, tablet coating material and viscosity modifier in oral and tropical formulation in the pharmaceutical industry (Jones, 2004; Allen and Luner, 2003).

2.14.3 Hydrophilic polymer

Hydrophilic polymers are categorized into three main classes (Bamiro, 2011).

i. Natural polymer
ii. Cellulose ethers
iii. Polymer of acrylic acid

Examples of these have been discussed in the two proceeding subsections.

2.15 *Irvingia* mucilage

Irvingia mucilage is obtained from the kernel or nuts of the seed of *Irvingia gabonensis* (O'Rorke) Bail (family Irvingiaceae). *Irvingia gabonensis* is also known as African bush mango or wild mango and belongs to a genus of African and South East Asian trees (Odeku and Patani, 2005, Matos *et al*., 2009 and Etta *et al*., 2014). The genus *Irvingia* has seven species which are *Irvingia gabonensis*, *Irvingia wombolu*, *Irvingia grandifolia*, *Irvingia excels*, *Irvingia malayaria*, *Irvingia smithii* and *Irvingia giarobur* (Ladipo *et al*., 1996; Etta *et al*., 2014).

Irvingia gabonensis bears edible fruits that resemble mango which are further valued due to their fat and protein rich nuts. The nuts also known as dika nuts, from which the mucilage is obtained after fat extraction are used widely in Nigeria for thickening soup because they form a thick viscous sauce base on heating (Eka, 1980; Abaelu and Akinrimisi, 1980; Onyeike *et al*., 1995; Ajuk *et al*., 1999; Odeku and Patani, 2005). The plant is commonly called ogbono (Igbo), aapon (Yoruba), mbukpabuyo (Efik), ogwi (Ibibio) (Nosiri *et al*., 2011; Etta *et al*., 2014) and okpukpa or egbene by the Izons of the Niger Delta of Nigeria.

Different parts of *Irvinga* plant have been utilized in herbal medicine for curing a variety of ailments (Lowe *et al*., 2000). Ingestion of the bark has been reported to be useful in treating hernias, yellow fever, dysentery and reducing the effect of poison. The bark is also mixed with palm oil to treat diarrhoea. The antimicrobial property of the bark helps to heal scabby skin. The boiled bark extract is known to have analgesic effect and used in relieving tooth pain (Okolo *et al*., 1995; Etta *et al*., 2014; Oloyede, 2015). The crude methanol extract of the leaves of *Irvingia gabonensis* was found to possess anti-diarrhegenic and anti-ulcer properties (Raji *et al*., 2001). The kernel or nuts and bark extract have been observed to reduce fasting blood glucose levels in both test animals and humans thus its possible usefulness in management of diabetes (Onoagbe *et al*., 1999; Ngondi *et al*., 2005 and 2006; Omonkhua and Onoagbe, 2012). Also dika nuts have been noted to be very effective in body weight reduction and controlling harmful blood cholesterol level (Ngondi et al, 2005; Etta *et al*., 2014).

Omonkhua and Onoagbe (2012) reported the relatively low liver toxicity, but sustained anti-obesity and hypoglycemic effect of the aqueous extract of the bark of *Irvingia gabonensis* on long-term oral administration in rabbits, suggesting the high likelihood of its relevance in the management of diabetes. However, Etta *et al*., (2014) cautioned that despite the beneficial effects, the consumption of dika nuts should be in moderation as the ethanolic extract of *Irvingia gabonesis* kernel was observed to have degenerative effect on the histo morphology of both the liver and testes tissue of male albino rats at high doses.

Irvinga kernel fat and the kernel residue after fat extraction have some potential industrial applications. The fat is useful in producing margarine, cooking oil, perfumes, soap, as lubricant in tablet manufacture, and suppository base (Udeala *et al*., 1980; Okorie, 1998; Odeku and Patani, 2005). The kernel residue after fat extraction, has been shown to contain polysaccharide but devoid of starch, dextrin and tanins. It retains its' viscous gum like consistency that is highly treasured in local soup making and serve as a thickener or binder in the food and pharmaceutical industry (Joseph, 1995).

Odeku and Patani (2005) investigated dika nut mucilage obtained from the kernel residue as binding agent in metronidazlole tablet formulation in comparison with official binding agent, gelatin B.P. The compressional characteristics, mechanical properties and the drug release properties were assessed. Metronidazole tablet formulations containing dika nut mucilage as binder were observed to have lower mechanical strength but longer disintegration and dissolution times. Figures 2.4, 2.5, 2.6 shows *Irvingia* tree, fruits (split apart) and the dry kernels respectively.

Figure 2.4. *Irvingia* tree by Taylor Creek, Okolobiri, Bayelsa State, Nigeria.

Figure 2.5. *Irvingia* fruits (split apart)

Figure 2.6. *Irvingia* Kernel (dried)

2.16 Ibuprofen

Ibuprofen is (2RS)-2[4-(-2-Methylpropyl) phenyl] propanoic acid, chemical formular $C_{13}H_{18}O_2$ and molecular weight 206.3. It has the following chemical structure:

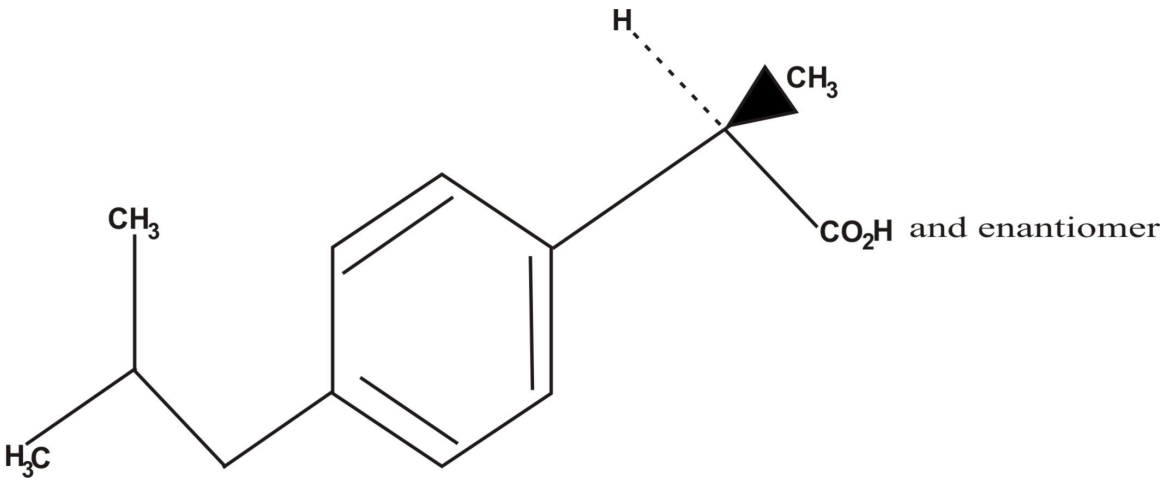


Figure 2.7. Structure of Ibuprofen

Ibuprofen is a cyclo-oxygenase inhibitor, an analgesic and a non-steroidal anti-inflammatory medication. It is a crystalline powder that is white or nearly white or colorless crystal. Ibuprofen is completely insoluble in water and is freely soluble in acetone, methanol and methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

Fifty grams of ibuprofen dissolved in 4 g/L solution of sodium hydroxide R and diluted to 100 mL with the alkaline solution, has a peak absorption of ultra violet light at 264 nm and 272 nm, within a spectral range of 240-300 nm using a spectrophotometer with a bandwidth of 1.0 nm and scanning speed of not more 50 nm/min. Ibuprofen can also be identified by infrared absorption spectrophotometry and thin-layer chromatography (The Pharmacopoiea, 2017). Two grams of ibuprofen dissolved in methanol R diluted to 20 mL with the same solvent give a clear and colourless solution. Also, 0.5 g of ibuprofen dissolved in methanol and diluted to 20 ml with the solvent give an optical rotation of -0.05^0 to + $0.05^{0..}$

CHAPTER THREE

MATERIALS AND METHODS

3.1 Materials

The materials used were ibuprofen (BASF Aktiengesell shaft, Ludwigshafen, Germany), microcrystalline cellulose (Person Pharmaceuticals Ltd, Backinghenshire England), dibasic calcium phosphate anhydrous, D1 hydrate (BDH Chemicals Ltd, Poole England) direct compressible lactose (BDH Chemicals Ltd U.K) xanthan gum (Myprotein Co Chesire, U.K), hydroxypropylmethyl cellulose (Ranbaxy Laboratories Ltd, Gurgoan, India) and ogbono (okpukpa) mucilage (from *Irvingia* kernel - dika nut, sourced from the local market at Okolobiri - Gbarain, Yenagoa, Bayelsa State Nigeria).

3.2 Extraction of *Irvingia* kernal (ogbono) mucilage

One kilogram of ogbono, the dried kernel of *Irvingia* (family Irvingiacece), was grinded to fine powder in Osterizer blender after removing the seed coat often present in small quantity. The powder was soaked with two liters of petroleum ether for 24 hours. The liquid extract was separated from the residue by decanting and squeezing the moist residue in a calico cloth. The residue was further extracted by re-soaking with petroleum ether and this was repeated until there was no more fat yield. The residue devoid of fat, containing the mucilage, was then made slurry by adding sufficient distilled water. The slurry was filtered using a clean calico cloth and the kernel mucilage obtained by precipitating with 96% v/v ethanol. The precipitated mucilage was collected by filtering the liquid out and squeezing employing calico cloth. A fraction of the mucilage was freeze dried and the other in hot air oven at 40^0C. Both mucilage samples were pulverized and saved in containers that prevent air entry for use later. The percentage yield of mucilage was calculated (Odeku and Patani, 2005).

3.3 Phytochemical assessment

The following phytochemical tests were carried out on *Irvingia* kernel mucilage: (Trease and Evans, 2009; Pathak *et al*., 2011).

3.3.1 Test for mucilage

A drop of rethemuim red solution was added to some powder of the *Irvingia* kernel and observed under optical microscope.

3.3.2 Test for phenolic compound

i. 10 mL of water and 0.1 mL of Iron (III) chloride was added to 1 g of *Irvingia* kernel mucilage powder.
ii. 10 mL of water and bromine water was added to 1 g of *Irvingia* kernel mucilage powder.

3.3.3 Test for alkaloid

Two grammes of the kernel mucilage powder was extracted using 2 mL of 10% Hydrochloric acid (HCl) on a hot water bath (100ºC) and filtered.

i. Mayer's test: Very small quantity of tetraiodomercurate (II) solution was added dropwise to about 0.5 mL of filtrate.
ii. Dragendorff's test: To about 0.5 mL of the filtrate, very small quantity of tetrapotassium pentaiodobismuth (2-) diiodide solution was added dropwise.
iii. Wagner's test: To about 0.5 mL of the filtrate very small quantity of iodine in potassium iodide solution was added in drops

3.3.4 Test for chloride

Iron (III) chloride (Ferric chloride) and 0.1M hydrochloric acid was used to hydrolyze 1 g of the *Irvingia* kernel mucilage powder by boiling for 30 minutes. 10% lead (II) ethanoate was then added.

3.3.5 Test for sulphate

Few drops of barium chloride was added to 1 g of *Irvingia* kernel mucilage powder following hydrolysis boiling with ferric chloride and 0.1M hydrochloric acid for 30 minutes

3.3.6 Test for reducing sugar

0.1 g of the mucilage powder was added to 2 mL of Fehling's solution and boiled in a hot water bath for 30 minutes.

3.3.7 Test for carbohydrate

Molisch's test: Two drops of α- naphthol was added to 2 mL dispersion containing 0.1 g of *Irvingia* kernel mucilage powder. 1 mL of concentrated tetraoxosulphate (vi) acid was carefully poured down the side of the text tube.

3.4 Physicochemical characterization of *Irvingia* kernel mucilage.

3.4.1 Elemental constituents of *Irvingia* kernel mucilage.

The determination of the elemental constituents of *Irvingia* kernel mucilage (2.0 g) was done using Atomic absorption spectrophotometer (Perkin Elmer, AAnalyst 200 AA Spectrophotometer, AAS, UK).

3.4.2 pH of *Irvingia* kernel mucilage

pH meter (pH tutor, Eutech instruments, Rajah cresent, Singapore) was used to determine the pH of 1% dispersion of *Irvingia* kernel mucilage.

3.4.3 Fourier transform infrared (FTIR) spectroscopy

The FITR spectrum of *Irvingia* kernel mucilage was recorded using Jasco FTIR spectrophotometer, Model 4100, (Jasco Corporation, Ishikawa-co, Hachioji, Tokyo, Japan). For spectroscopy, the dry powder was blended with potassium bromide (KBr) and pressed into a pellet. The analysis was carried out by scanning the sample through a wave length range of 400 to 4000 cm^{-1} (Abdulsamad *et al*., 2012; Udo *et al*., 2017).

3.4.4 Scanning electron microscopy (SEM) of *Irvingia* kernel mucilage

The SEM micrograph of the mucilage was done using JSM 6390 (JOEL, Tokyo, Japan) scanning microscope at 15 KV voltage. The process was performed by placing the powdered mucilage on an aluminum stub and coating with gold in a fine coat of ion sotter JFC – 1100 (JOEL, Tokyo, Japan) (Eddy *et al*., 2013; Odeku *et al*., 2013).

3.4.5 X - ray powder diffraction

Irvingia kernel mucilage X-ray diffraction pattern was obtained using Shimadzu X-ray diffractometer (Model XRD 6000, Kyoto, Japan). This was carried out at room temperature at 40 kv and 30 mA voltages and current respectively using copper made material and diffraction angle range of 4 to 90 with a scanning speed of 10 deg/min (Odeku *et al*., 2013).

3.4.6 Particle density determination

The liquid pycnometer method with xylene as displacement fluid was used to determine the particle densities of all samples. A 50 mL capacity pycnometer bottle was weighed empty (w). It was filled with xylene (non-solvent) to spill over, the excess wiped off and weighed again (W_1). The difference between the second (W_1) and first (W) weight was calculated (W_2). 2 g of the sample of interest was weighed (W_3) and quantitatively transferred into the pycnometer bottle filled with non-solvent, then excess liquid wiped off and the bottle weighed again (W_4). The particle density, Pt, was ascertained using the following equation (Ayorinde *et al*., 2013)

$$P_t(gcm^{-3}) = W_2W_3/50\ (W_3\text{-}W_4\text{+}W_2\text{+}W) \quad (3.1)$$

3.4.7 Loose bulk and tapped density determination

The loose bulk densities (bulk density at zero pressure) of mucilage and all batches of formulation were determined by pouring 20 g of sample at an angle of 45^0 through a funnel into a 50 ml glass measuring cylinder of diameter 24 mm (Paronen and Justin, 1983; Itiola, 1991). The loose bulk density values were obtained with the formular:

Loose bulk density,

$$\rho_0 = m/\pi r^2 h\ (gcm^{-3}) \quad (3.2)$$

Where; m = weight of sample in cylinder (g)

πr^2h(Vo) = Loose bulk volume (cm^3)

r = radius of cylinder (cm)

h = height of sample in the cylinder (cm)

The tapped density was determined by applying 100 tapps to the 20 g sample in the cylinder at a standard rate of 38 taps per minute (British Standard 1460). All assessments were carried out three times. Do, the relative density at zero pressure of all samples were gotten from the ratio of the loose bulk density (ρo) to the respective particle densities.

3.4.8 Compressibility index

Carr's compressibility index (Carr's 1965) was used to determine the compressibility index of the samples. This is expressed mathenmatically in equation 2.9 under section 2.4.3

Hausner's ratio is the ratio of the tapped density to bulk density i.e.

Hausner's ratio = tapped density / bulk density (3.3)

3.4.9 Angle of repose

The angles of repose of the various samples were determined using the fixed funnel approach. A sample of certain quantity was taken to a funnel and allowed to flow through it under the force of gravity to form a conical heap. The following equation was used to calculate the angle of repose:

$$\text{Tan } \theta = h/r \quad (3.4)$$

Where h = height of sample cone

r = radius of sample cone

The determinations were done in triplicate.

3.5 Production of tablets

3.5.1 Production of matrix tablets by direct compression

Tablets of 500 mg $\pm$ 10 mg were made from both hot air oven and freeze dried mucilage powder samples by direct compression method. Xanthan gum and hydroxypropylmethyl cellulose (HPMC) were used as standards. The weighed polymer powder of respective samples were compressed for 30 seconds at different predetermined loads in a 10.5 mm die together with flat-faced upper and lower punches using a carver hydraulic hand press (Model C, Carver Inc., Menomone falls Wisconsin, USA), fitted with a pressure gauge reading up to 2.0 metric tons. The die and punches were lubricated with 1% w/v dispersion of magnesium stearate in acetone prior to compression (Akin-Ajani *et al*., 2005).

Ibuprofen-polymer matrices were prepared from 100 g batches of formulations containing 10, 20, 30 and 50% w/w ibuprofen and respective polymers. The formulations were mixed in a mortar for five minutes. The powder mixtures were transferred into bottles then placed in a rotomixer (compound mixing machine, VSF 3843C, Forster equipment Co Ltd, Whetstone, Leicester, England), firmly secured with foam pads and mixed for another ten minutes. Tablets of 500 mg ±10 mg were made from the different batches of formulations following the procedure described above.

The tablets, after ejection, were kept in container that does not allow air entry for 24 hours over silica gel to give room for elastic recovery and hardening to occur. Afterward, their weight and dimension were determined using a metler (electronic) balance and micrometer screw gauge respectively to within ± 1.00 mg and 0.01 mm. The packing fractions of the tablets (relative densities), D, were computed using the equation (Akin-Ajani *et al*., 2005).

$$D = m/\pi r^2 hPt \ (gcm^{-3}) \qquad (3.5)$$

Where; m = weight of the tablet (g)

r = radius of the tablet (cm)

h = thickness of the tablet (cm)

Pt = particle density of the solid material (g/cm³)

Different compression pressures were used to obtain different packing fractions of the tablets.

Irvingia kernel matrix tabelts (500 mg) were also prepared by direct compression of mucilage with fixed loads on hydraulic presses with 12.5 mm flat-faced punches, the die and punches lubricated as stated earlier. The effects of drug concentration, excipieints and xanthan gum and HPMC on *Irvingia* mucilage matrices were studied by preparing 500mg±10mg matrix tablets under a compression force of 4000 kg following the procedure described above with the following modifications: drug concentration effect - matrices containing 10, 20, 30 and 50% w/w ibuprofen; excipient effect - matrices having lactose, avicel and dicalcium phosphate in the drug-mucilage-excipient ratio of 1:3:1 and xanthan gum and HPMC effect - kernel matrix tablet containing xanthan gum or HPMC in the drug-*Irvingia* mucilage-xanthan gum or HPMC ratios of 2:7:1, 2:6:2, 2:5:3, 2:4:4 and 2:0:8 (Odeku and Fell, 2004; Bamiro *et al*., 2011).

3.5.2 Production of matrix tablets by wet granulation

200g batches of 10, 20, 30, and 50% w/w ibuprofen and *Irvingia* kernel mucilage (hot air oven and freeze dried sample) mixtures were blended for 5 minutes in a Kenwood planetary mixture (model A120, Hobart Manufacturing co, U.K). The powder blends were made moist mass by adding 20 mL of distilled water. Massing was carried out for a further 5 minutes and by manually passing them through a No. 12 mesh sieve (1400 μm), wet masses were granulated. The granules were dried at 45^{o}C in the hot air oven for 18 hours and screened (re-sieved) through a mesh sieve No.16 (1000 μm), then stored in container that does not allow air entry (Akin-Ajani *et al*., 2005).

Size distribution of the batched of granules was done by analysis using standard sieve (British standard 410, 1962) of the following sizes: 12 mesh (1400 μm), 16 mesh (1000 μm), 22 mesh (710 μm), 30 mesh (500 μm), 44 mesh (355 μm), 60 mesh (250 μm) and the receiver (pan). The cleaned sieves with the receiver at the bottom were arranged in descending order of aperture size. 120 g of granules were weighed and placed on the uppermost sieve. The sieve stack was shaken with a sieve shaker for 10 minutes. The granules retained on each sieve were carefully removed with a brush and weighed. The cumulative weight percent oversize was calculated and graphs of cumulative weight percent oversize versus granule size were plotted. The mean granule size which

corresponds to the size at 50% cumulative weight percentage oversize was calculated. Granules of size 500 to 1000 μm of each batch were collected separately and kept in air - tight container for tablet production.

Tablets of 500 mg ± 10 mg were prepared from the various batches of formulation following the procedure outlined in section 3.5.1

3.5.3 Preparation of compression coated tablets for colon specific drug delivery

One hundred milligram (100 mg) ibuprofen core tablet of 8mm diameter was prepared by compressing a thorough powder mixture of 1:1 ibuprofen-avicel under a compression load of 2000 kg in Remek mini press II (Rimek Mini press II, 12 station punch machine, Karnavati Engineering Ltd, near Ahmedabad, Gujarat, India). Prior to compression, one percent dispersion of magnesium stearate in acetone was used to lubricate the die and punches. The coated tablets were produced by putting half the coating material (oven-dried and freeze-dried *Irvingia* kernel mucilage) in a 12.4 mm die, carefully positioning the core tablet in the middle and adding the remaining coating material. Then the coat was compressed to surround the core using compression load of 3500 kg (Odeku, 2005). The crushing strength and frability of the tablets were determined after allowing for elastic recovery using DBK tablet hardness tester and Combell Electronic Thermonik friability apparatus respectively as described in subsection 3.7.1 and 3.7.2.

3.6 Compression characteristics of tablets

3.6.1 Heckel plots

Heckel plots of Ln [1/(1-D)] versus applied pressure (P) in MNm^{-2} were plotted for the *Irvingia* kernel mucilage tablets and ibuprofen-mucilage matrices in comparison with those of xanthan gum and hydroxypropylmethylcellulose (HPMC). The slope and intercept accordingly were used to calculate K and A values. Py (yield pressure), is the inverse of the slope (1/k). The relative density, D_A was computed from equation (2.18) and the value of D_B i.e. the relative density of cycle of rearrangement at low pressure, was obtained from the difference between D_A and Do (equation 2.19) (Odeku and Fell, 2006; Okunlola and Odeku, 2011; Ayorinde *et al*., 2013; Ogunjimi and Alebiowu, 2014).

3.6.2 Kawakita plots

Kawakita graphs of P/C versus compression pressure P (MNm^{-2}) were gotten for the different polymers and ibuprofen-polymer matrices. The volume of polymer at zero pressure (i.e. the loose bulk volume) is obtained using the equation:

$$Vo = / \pi r^2 h \quad (cm^3) \qquad (3.6)$$

Where r = 10 ml cylinder radius

h = height of powder in cylinder.

The tablets volumes at various compression pressures, Vρ were also calculated. The volume reduction extent, C, was estimated from equation 2.21.

The values of **a** and **ab** were gotten from the intercept and slope of the graphs accordingly (Okunlola and Odeku, 2011; Ogunjimi and Alebiowu, 2014).

3.7 Mechanical properties of tablets

3.7.1 Crushing strength

Tablet crushing strength was determined using DBK tablet hardness tester (Model, EHO1, DBK instruments, Mumbai, 400060 India). The tablet was placed between the spindle and anvil, then the knob screwed to apply a diametric force on the tablet. Once the tablet split into two equal halve, the value of force (in Newton) on display on the electronic screen was recorded. For each batch, six tablets were used and the mean and standard deviation (SD) calculated and recorded (Odeku and Fell, 2006)

3.7.2 Friability

The friabilities of the different batches of tablet were assessed using Cambell electronic Thermonik friability apparatus (Model C- FTA 20, Mumbai 400 025, India). Ten tablets were weighed together with a metler balance, prior to this, their individual dimensions being determined using a micrometer screw gauge. They were then placed in the friabilator and the apparatus operated for 4 minutes at 25 revolutions per minute. The percentage weight loss (friability) on display on the screen was recorded. The test was done in triplicate and the mean and standard deviation recorded (Odeku and Fell, 2006)

3.8 Disintegration test

The disintegration times of the mucilage matrix tablets were determined in distilled water at 37 ± 0.5% using Tab-Machine, tablet disintegration tester (Tab-Machine Tablet disintegration tester Model T-TD20, Mombai 400 025 India). The tablets were place on the wire mesh just above the surface of the distilled water in the tube. The apparatus and a stop clock were started same time. The matrix tablets were kept in contact with the distilled water inside the tube. The time taken for all the matrix tablets to distingrate and pass through the wire mesh was recorded.

3.9 Dissolution test

The dissolution test on both the ibuprofen-mucilage matrices and the compression coated tablets was done using the USP XXIII basket method (Tab-Machine six stage dissolution rate test apparatus IP/BP/USP, model T.DR-6; Kshitij Innovations, Ambala, India) with 900 ml medium maintained at 37 ± 0.5^{o}C rotated at 50 revolutions per minute. The media used were 0.1M HCl (pH 1.2) first 2 hours and sorensen's phosphate buffer (pH 7.4) for the rest of the test for the ibuprofen-mucilage matrix tablets and the core tablet for coating for colon targeted drug delivery (Odeku and Fell, 2005). The media for the coated tablets was same as above for the first 2 hours, then sorensens's phosphate buffer (pH7.4) for another 3 hours and phosphate buffer saline (PBS) (pH 6.8) for the rest of the test and to imitate the gastro intestinal setting. Also included in the media was rat ceacal content. Samples (5 mls) were withdrawn at fixed intervals replacing with fresh media to maintain sink conditions. The sample was diluted and ibuprofen release ascertained using U.V Spectrophotometer at 222 mm (UV-Visible Spectrophotometer, Model U.V Pharmaspec 1700E, 23 OCE, Shimadzu Corporation, Kyoto, Japan). The test was done in triplicate and mean value obtained.

3.10 Drug release kinetics and mechanism

The data obtained from the dissolution test were fitted into the various mathematical models or kinetic equations outlined in subsection 2.12.3.2.3 to ascertain the ibuprofen release kinetics and mechanism from the ibuprofen-mucilage matrices.

3.11 Factorial experimental designs for ibuprofen matrices at relative density of 0.90

The individual and interaction effect of processing factor (denoted by F), method of preparation (M) and the concentration of ibuprofen (C) on the crushing strength and crushing strength friability ratio (CSFR) of ibuprofen-*Irvingia* kernel matrix tablets was studied using statistical principle (Woolfall, 1964; Alebiowu and Itiola, 2003).

The 2^n factorial experimental design was used where n is the number of variables, in this case three variables, thus 2^3 i.e 8. Each variables is used at both the high level (denoted by subscript H) and low level - denoted by subscript L (Alebiowu and Itiola, 2003; Alebiowu and Ojeleye, 2007).

With the above designation, the various combinations between the variables in the design were:

$F_LM_LC_L$ $F_LM_LC_H$ $F_LM_HC_H$ $F_LM_HC_L$

$F_HM_HC_H$ $F_HM_HC_L$ $F_HM_LC_L$ $F_HM_LC_H$

Where F_L= processing factor low (oven dried *Irvingia* kernel)

F_H= Processing factor high (freeze dried *Irvingia* kernel)

M_L= Method of preparation low (direct compression)

M_H= Method of preparation high (wet granulation)

C_L= Concentration of ibuprofen low (10% w/w)

C_H= Concentration of ibuprofen high (50% w/w)

The results were grouped into a number of sets in other to determine the effect each of the three variables had separately on the crushing strength and crushing strength friability ratio of the matrix tablets and also to examine if the variables acted independently or were interacting.

The effect of increasing the processing factor (F) from its “low” level to its “high” level on the crushing strength and crushing strength–friability ratio were obtained by summing all results of crushing strength (or crushing strength-friability ratio) of samples containing “high” level of F and subtracting the sum of the samples containing “low” level. That is:

¼[($F_HM_HC_H$+ $F_HM_HC_L$+$F_HM_LC_L$+$F_HM_LC_H$) –

($F_LM_LC_L$+$F_LM_LC_H$+$F_LM_HC_H$+$F_LM_HC_L$)]

Following the same pattern, the effect of increasing M and C were calculated.

For method of preparation M.

¼[($F_HM_HC_H$+ $F_HM_HC_L$+$F_LM_HC_H$+$F_LM_HC_L$) –

($F_HM_LC_L$+$F_HM_LC_H$+$F_LM_LC_L$+$F_LM_LC_H$)]

For concentration of ibuprofen C

¼[($F_HM_HC_H$+ $F_HM_LC_H$+$F_LM_LC_H$+$F_LM_HC_H$) –

($F_HM_HC_L$+$F_HM_LC_L$+$F_LM_LC_L$+$F_LM_HC_L$)]

The extent or value by which the result of the treatment departs from zero not minding whether positive or negative is a quantitative assessment of the effect of the variables (F,M or C) on the crushing strength and CSFR of the matrix tablets.

Evaluation of whether there was any interaction between two variables was done by taking the difference between the sum of the results of the combinations in which they occur together at either “high” or “low” levels and the sum of other combinations. This gives the interaction coefficient.

For processing factor (F) and method of preparation (M)

¼[($F_HM_HC_H$+ $F_HM_HC_L$+$F_LM_LC_L$+$F_LM_LC_H$) –

($F_HM_LC_L$+$F_HM_LC_H$+$F_LM_HC_H$+$F_LM_HC_L$)]

For processing factor (F) and concentration of ibuprofen(C) (F and C)

¼[($F_HM_HC_H$+ $F_HM_LC_H$+$F_LM_LC_L$+$F_LM_HC_L$) –

($F_HM_HC_L$+$F_HM_LC_L$+$F_LM_LC_H$+$F_LM_HC_H$)]

For method of preparation and concentration of ibuprofen (M and C)

¼[($F_HM_HC_H$+ $F_LM_HC_H$+$F_LM_LC_L$+$F_HM_LC_L$) –

($F_HM_HC_L$+$F_HM_LC_H$+$F_LM_HC_L$+$F_LM_LC_H$)]

There was no interaction between variables if the result is zero. When the interaction coefficient is profoundly different from zero, then the two variables involved interacted

with each other. The degree of interaction is measured by the extent this value is away from zero (Odeku and Itiola, 2003; Ogunjimi and Alebiowu, 2010 and 2016).

3.12 Statistical analysis

The results obtained from the various groups of assessments on the mucilage andibuprofen matrices were analysed with Microsoft Excel using analysis of variance (ANOVA) to ascertain any significant ($P \leq 0.05$) difference.

CHAPTER FOUR

RESULTS

4.1 Characterization of *Irvingia* kernel mucilage

4.1.1 *Irvingia gabonensis* kernel mucilage yield

The percentage yield of *Irvingia gabonensis* kernel mucilage was 43.8% w/w.

4.1.2 Phytochemical properties of *Irvingia gabonensis* kernel mucilage

The results of phytochemical properties of *Irvingia gabonensis* kernel mucilage are presented in Table 4.1. This shows that *Irvingia* mucilage contains carbohydrate, reducing sugar, mucilage and alkaloid but no chloride, sulphate and phenolic compounds.

4.1.3 Elemental constituents analysis of *Irvingia gabonensis* kernel mucilage

The elemental constituents of *Irvingia gabonensis* kernel mucilage are given in Table 4.2. From the results, *Irvingia* mucilage is free of heavy metal such as lead, copper and arsenic. This is a very desirable feature as their presence would have limited its use both pharmaceutically and in the food industry.

4.1.4 Proximate composition of *Irvingia gabonensis* kernel mucilage

The proximate compositions of *Irvingia gabonensis* kernel mucilage are displayed in Table 4.3. The result showed the presence of protein, fat, fibres and carbohydtrates. There was no meaningful difference in the percentage composition of both oven dried and freeze dried *Irvingia* mucilage.

4.1.5 pH of *Irvingia gabonensis* kernel mucilage

The pH of *Irvingia gabonensis* kernel mucilage at a temperature of 30.5^0C was 5.23 for oven dried sample and 5.80 for freeze dried sample. The drying process does not significantly affect the pH of the mucilage.

Table 4.1. Phytochemical screening of *Irvingia* kernel mucilage

Constituents	Oven dried *Irvingia*	Freeze dried *Irvingia*
Mucilage (Ruthemium red solution)	+	+
Phenolic compound	-	-
Alkaloid (Mayer,Wagner&Dragendorff's)	+	+
Chloride (10% lead acetate solution)	-	-
Sulphate (barium chloride drops)	-	-
Reducing sugar (Fehlings solution)	+	+
Carbohydrade (Molisch's test)	+	+

Table 4.2. Elemental constituents of *Irvingia* kernel mucilage

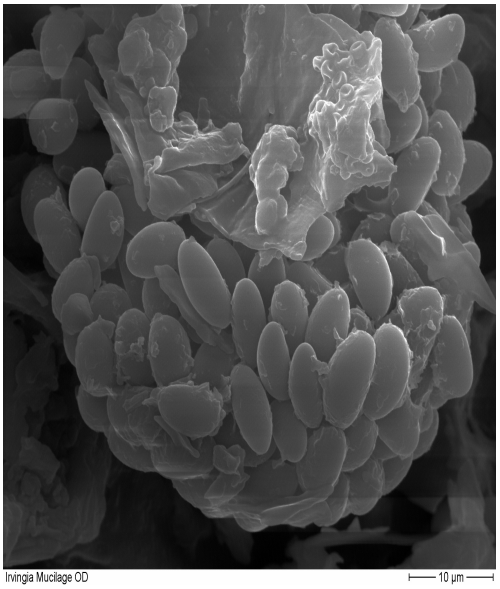
Element	Mg/100g	
	Oven dried *Irvingia*	Freeze dried *Irvingia*
Calcium(Ca)	23.54	22.88
Iron(Fe)	1.15	1.19
Magnesium(Mg)	0.33	0.27
Potassium(K)	266.77	288.50
Sodium(Na)	34.54	33.30
Zinc(Zn)	1.23	1.20
Copper(Cu)	0.00	0.00
Manganese(Mn)	1.10	1.08
Lead(Pb)	0.00	0.00
Arsenic(As)	0.00	0.00
Phosphorous(P)	333.24	321.60
Selenium(Se)	0.00	0.00
Cadmium(Cd)	0.00	0.00

Table 4.3. Proximate composition of *Irvingia* kernel mucilage

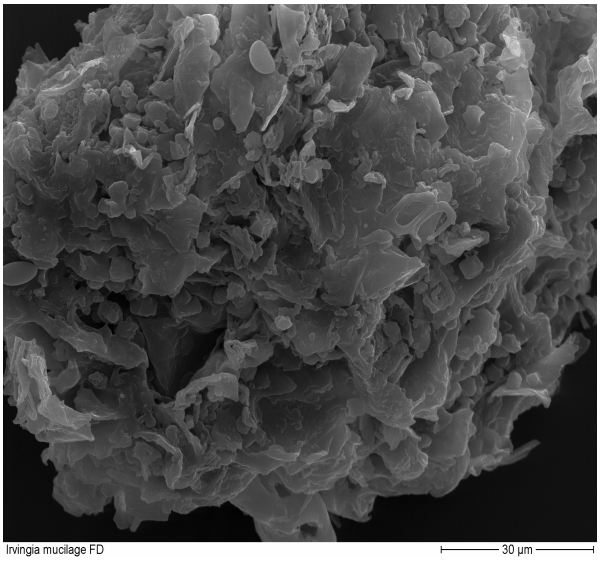
Constituent	Percentage composition (%)	
	Oven dried *Irvingia*	Freeze dried *Irvingia*
Protein	12.88	12.72
Fat	2.77	2.68
Ash	2.85	2.86
Fibre	1.34	1.35
Starch	2.39	2.68
Reducing sugar	6.65	6.95

4.1.6 Scanning electron microscopy (SEM) of *Irvingia gabonensis* kernel mucilage.

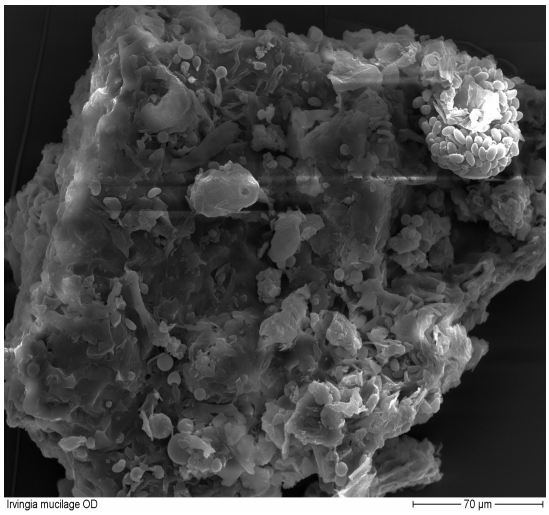
The scanning electron micrograph *Irvingia* mucilages are displayed in Plate 4.1. It shows the morphology and surface characteristics of the particles. The particles appear flat, having different shapes and look like flake.



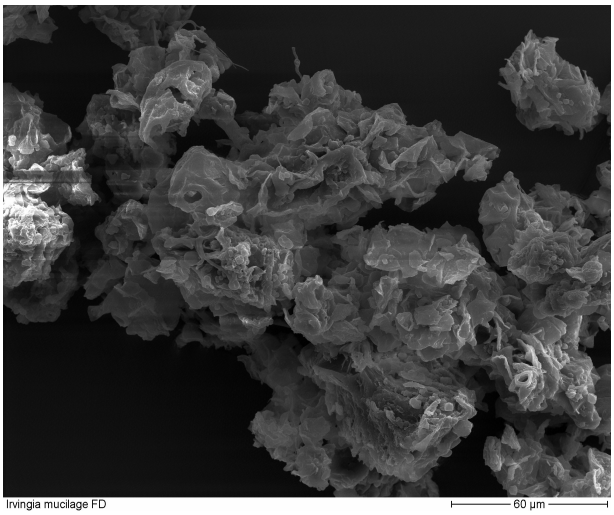
(a) SEM of oven dried *Irvingia gabonensis* kernel mucilage (10 µm)



(b) SEM of freeze dried *Irvingia gabonensis* kernel mucilage (30 µm)

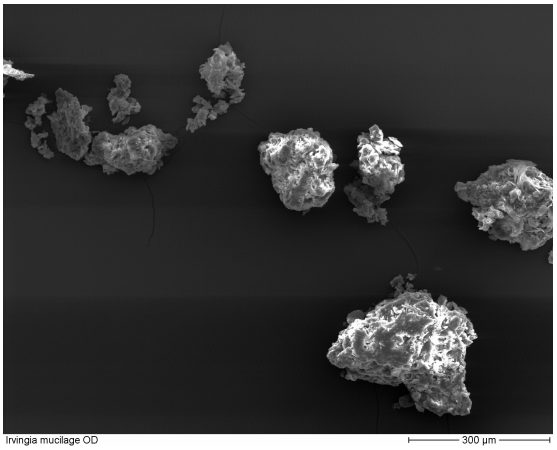


(c) SEM of oven dried *Irvingia gabonensis* kernel mucilage (70 µm)

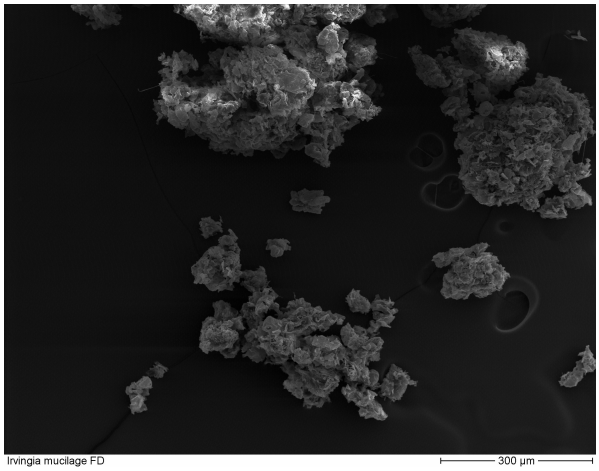


(d) SEM of freeze dried *Irvingia gabonensis* kernel mucilage (60 µm)

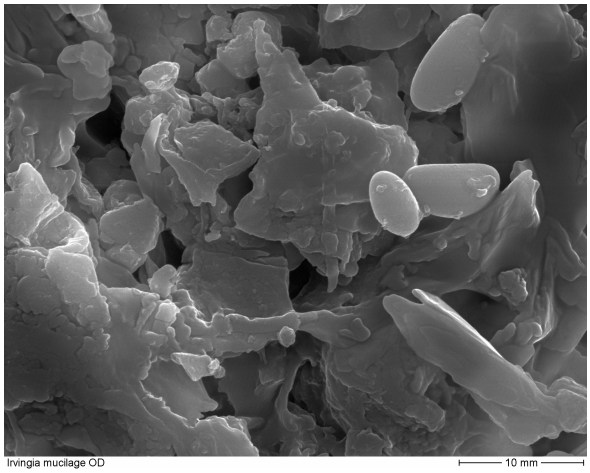
Plate 4.1. SEM of oven and freeze dried *Irvingia gabonensis* mucilage



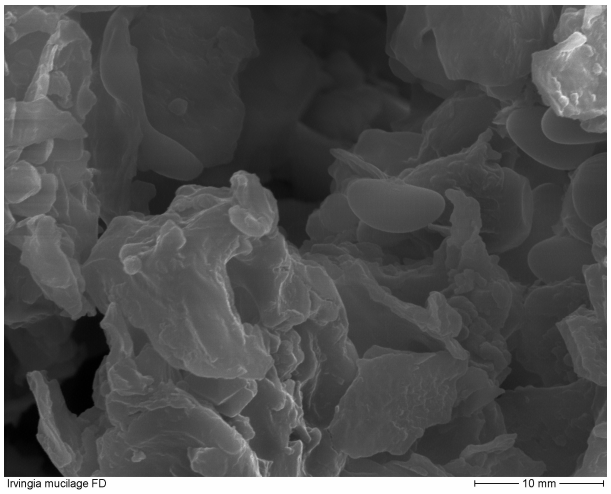
(e) SEM of oven dried *Irvingia gabonensis* kernel mucilage (300 µm)



(f) SEM of freeze dried *Irvingia gabonensis* kernel mucilage (300 µm)



(g) SEM of oven dried *Irvingia gabonensis* kernel mucilage (10 mm)



(h) SEM of freeze dried *Irvingia gabonensis* kernel mucilage (10 mm)

Plate 4.1. cont.

4.1.7 X-ray powder diffraction spectrum of *Irvingia gabonenesis* kernel mucilage

The x-ray diffraction patterns of *Irvingia gabonensis* kernel mucilage are presented in Figures 4.1 and 4.2. The result shows that *Irvingia* mucilage is slightly crystalline as shown by the several peaks.

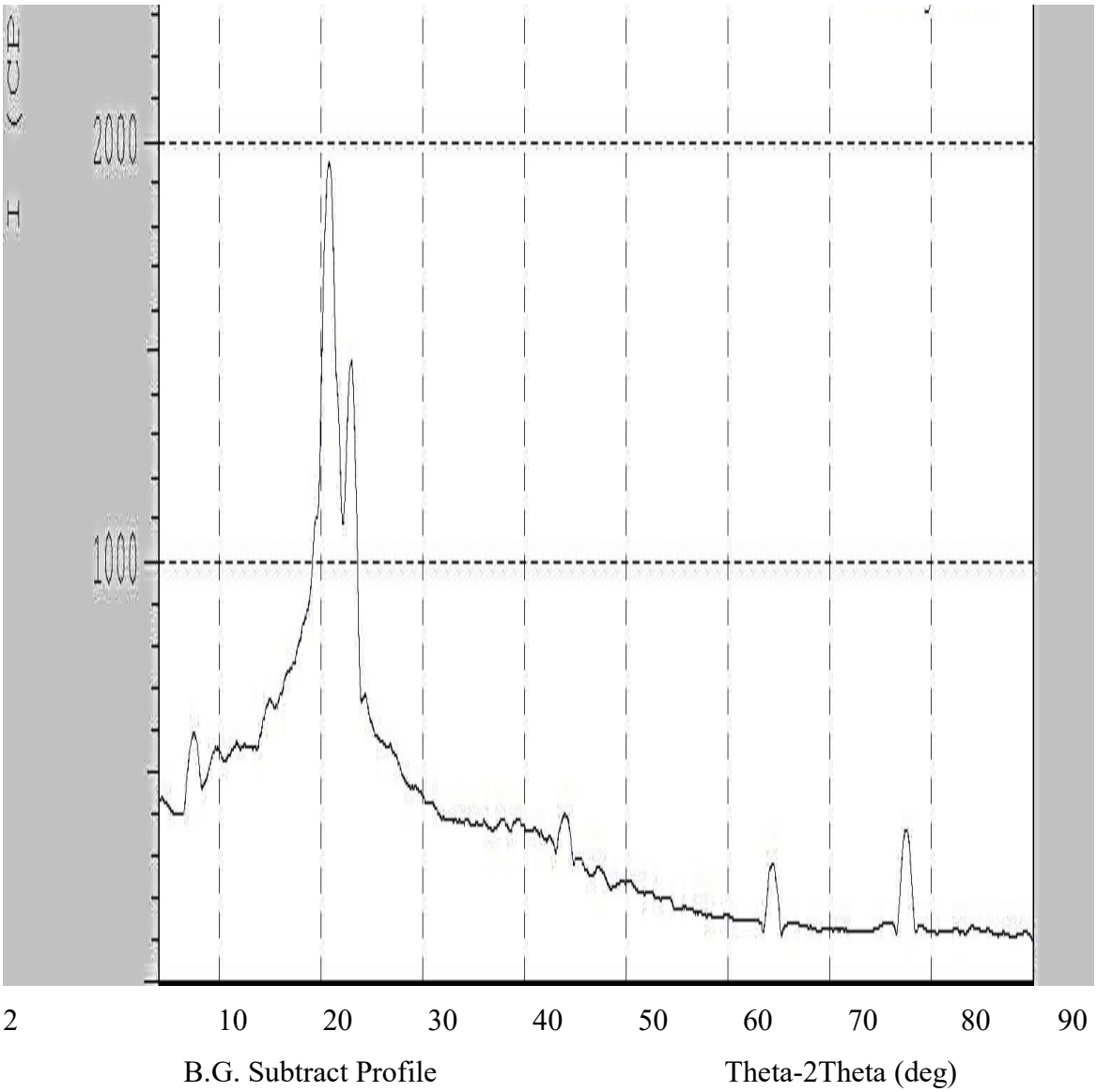


Figure 4.1. X-ray powder diffraction spectrum of oven dried *Irvingia* kernel mucilage

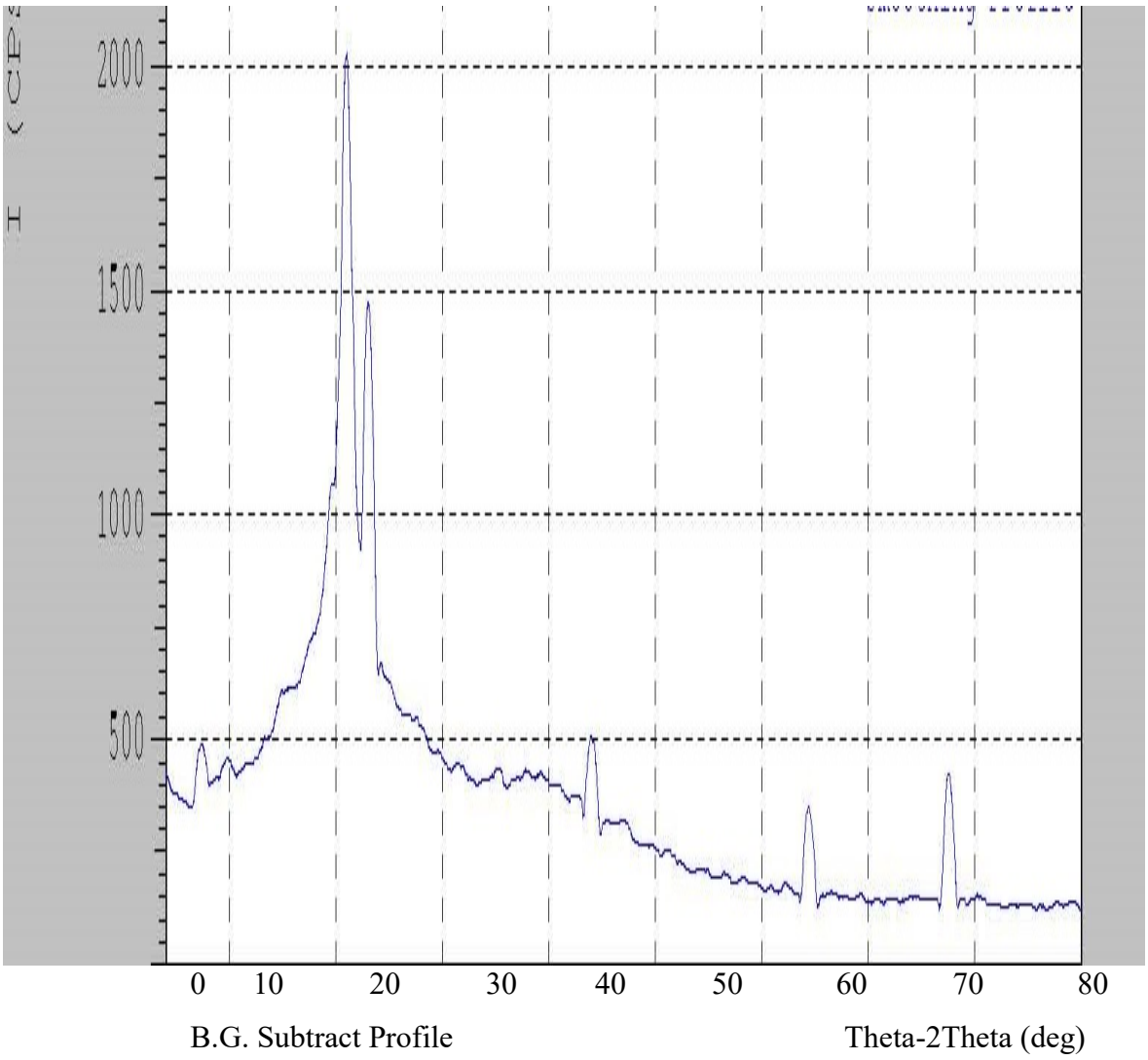


Figure 4.2. X-ray powder diffraction spectrum of freeze dried *Irvingia* kernel mucilage

4.1.8 Fourier transform infrared (FTIR) spectrum of *Irvingia gabonenesis* kernel mucilage

The Fourier transform infrared (FTIR) spectrum of *Irvingia* mucilage is presented in Figures 4.3. The assigned functional groups are shown in Tables 4.4 and 4.5. There was no significance difference in the peak of absorbances and intensities, thus functional groups in both oven and freezed dried mucilages. The drying process did not affect the structure of the mucilage.

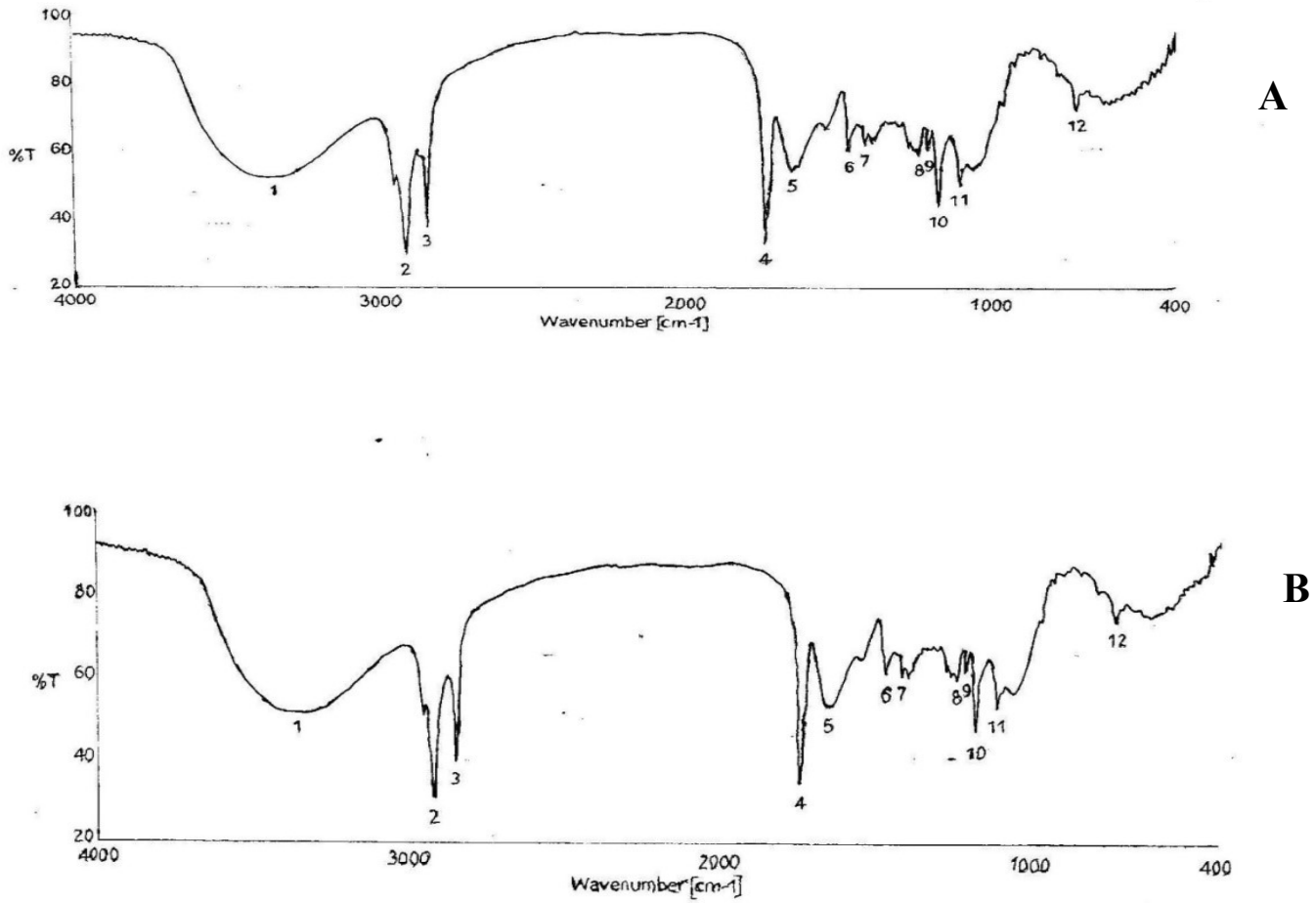


Figure 4.3. FTIR Spectrum of *Irvingia gabonensis* kernel mucilage

A = Oven dried *Irvingia* mucilage

B = Freeze dried Irvingia mucilage

Table 4.4. FTIR peaks, intensity and assigned functional groups of oven dried *Irvingia gabonensis* kernel mucilage (see Appendix I)

Peak (Cm^{-1})	Intensity	Assignment (functional group)
3351.68	51.683	O-H stretch. Alcohol
2916.81	28.805	C-H stretch. Aliphatic
2850.27	37.079	C-H stretch. Alkane
1741.41	32.566	C-O stretch. Carbonyl
1654.62	54.068	C-O stretch. Ketone / C = C stretch
1465.63	59.713	C-H scissoring and bending, alkanes
1413.57	61.487	C-H bending
1230.08	58.789	=C-O-C symetric and asymetric stretch, Ethers
1205.29	60.331	=C-O-C symetric and asymetric stretch, Ethers
1175.40	43.666	C-O stretch, carboxylic acid, ether, ester or alcohol
1105.01	50.064	C-O stretch. Carboxylic acid, ether, ester or alcohol
720.28	72.489	C-H bending

(Eddy *et al*., 2013; Michael, 2017 and Udoh *et al*., 2017.)

Table 4.5. FTIR peaks, intensity and assigned functional groups of freeze dried *Irvingia gabonensis* kernel mucilage (see Appendix II)

Peak (Cm^{-1})	Intensity	Assignment (functional group)
3358.43	50.846	O-H stretch. Alcohol
2916.81	29.418	C-H stretch. Aliphatic
2850.27	38.612	C-H stretch. Alkane
1742.37	33.918	C=O stretch. Carbonyl
1651.73	52.738	C=O stretch. Ketone / C=C stretch
1465.63	60.522	C-H Scissoring and bending, alkanes
1413.57	60.729	C-H bending
1238.08	59.968	=C-O-C symmetric & asymetric stretch, Ethers
1205.29	61.896	=C-O-C symmetric & asymetric stretch, Ethers
1175.40	40.544	C-O stretch. Carboxylic acid, ether, ester or alcohol
1105.01	53.006	C-O stretch. Carboxylic acid , ether, ester or alcohol
720.28	74.591	C-H bending

(Eddy *et al*., 2013; Michael, 2017 and Udoh *et al*., 2017.)

4.1.9 Material properties *of Irvingia gabonensis* kernel mucilage, xanthan gum and HPMC.

The results of some material properties assessment of *Irvingia* mucilage, xanthan gum and HPMC are shown in Table 4.6. The result shows that freezed dried mucilage had slightly lower Hausner's ratio, Carr's index and angle of repose values than oven dried sample. Freezed dried mucilage flow property was closely comparable to that of HPMC standard polymer.

Table 4.6. Material properties of *Irvingia* kernel mucilage, xanthan gum and hydroxypropylmethylcelulose (HPMC)

Parameter	Oven dried *Irvingia*	Freeze dried *Irvingia*	Xathan gum	HPMC
Particle density (g/cm^3)	1.203±0.07	1.233±0.03	1.509±0.05	1.294±0.04
Bulk density (g/cm^3)	0.306±0.03	0.298±0.02	0.388±0.01	0.344±0.03
Tap density (g/cm^3)	0.394±0.02	0.382±0.08	0.531±0.06	0.440±0.05
Relative density (D_0)	0.230±0.05	0.240±0.02	0.260±0.05	0.270±0.01
Hausner's ratio	1.29±0.20	1.28±0.14	1.37±0.16	1.29±1.04
Carr's index (%)	22.43±0.14	21.88±0.09	26.92±0.05	22.46±1.01
Angle of repose (°)	54.83±0.12	51.14±0.07	55.12.43±0.07	52..80 ±0.07

4.2 Compression and tablet properties of *Irvingia* mucilage

4.2.1 Heckel graphs of *Irvingia* kernel mucilage, xanthan gum and HPMC

The relative densities at various compression pressures of *Irvingia* kernel mucilage, xanthan gum and HPMC tablets prepared using direct compression are shown in Table 4.7. These values were used in constructing Heckel graphs of Ln[1/(1-D)] versus applied pressure and shown in Figure 4.4. The values of the linear region gradient 'K' and intercept of its extrapolation 'A,' were obtained. K is the converse of the mean yield pressure, P_y. The parameters derived from Heckel plots are presented in Table 4.8.

Table 4.7. Values of applied pressure (MNm^{-2}), relative density of tablet (D) and Ln[1/(1-D)] for *Irvingia* kernel mucilage, xanthan gum and HPMC

Polymer	Applied pressure (MNm^{-2})	Relative density (D)	Ln[1/(1-D)]
Oven dried *Irvingia*	14.14	0.817	1.700
	28.28	0.830	1.772
	42.42	0.842	1.845
	56.56	0.847	1.879
	70.70	0.851	1.904
	84.84	0.863	1.987
	113.13	0.876	2.086
	141.41	0.880	2.121
	169.69	0.885	2.161
Freeze dried *Irvingia*	14.14	0.808	1.652
	28.28	0.829	1.765
	42.42	0.834	1.797
	56.56	0.839	1.824
	70.70	0.845	1.867
	84.84	0.850	1.898
	113.13	0.864	1.996
	141.41	0.869	2.029
	169.69	0.879	2.114

Table 4.7 cont.

Polymer	Applied pressure (MNm^{-2})	Relative density (D)	Ln[1/(1-D)]
Xanthan gum	14.14	0.694	1.184
	28.28	0.729	1.306
	42.42	0.735	1.328
	56.56	0.737	1.334
	70.70	0.757	1.415
	84.84	0.793	1.575
	113.13	0.809	1.656
	141.41	0.833	1.787
	169.69	0.849	1.891
HPMC	14.14	0.786	1.543
	28.28	0.792	1.569
	42.42	0.796	1.588
	56.56	0.810	1.659
	70.70	0.817	1.697
	84.84	0.827	1.756
	113.13	0.834	1.796
	141.41	0.843	1.853
	169.69	0.852	1.913

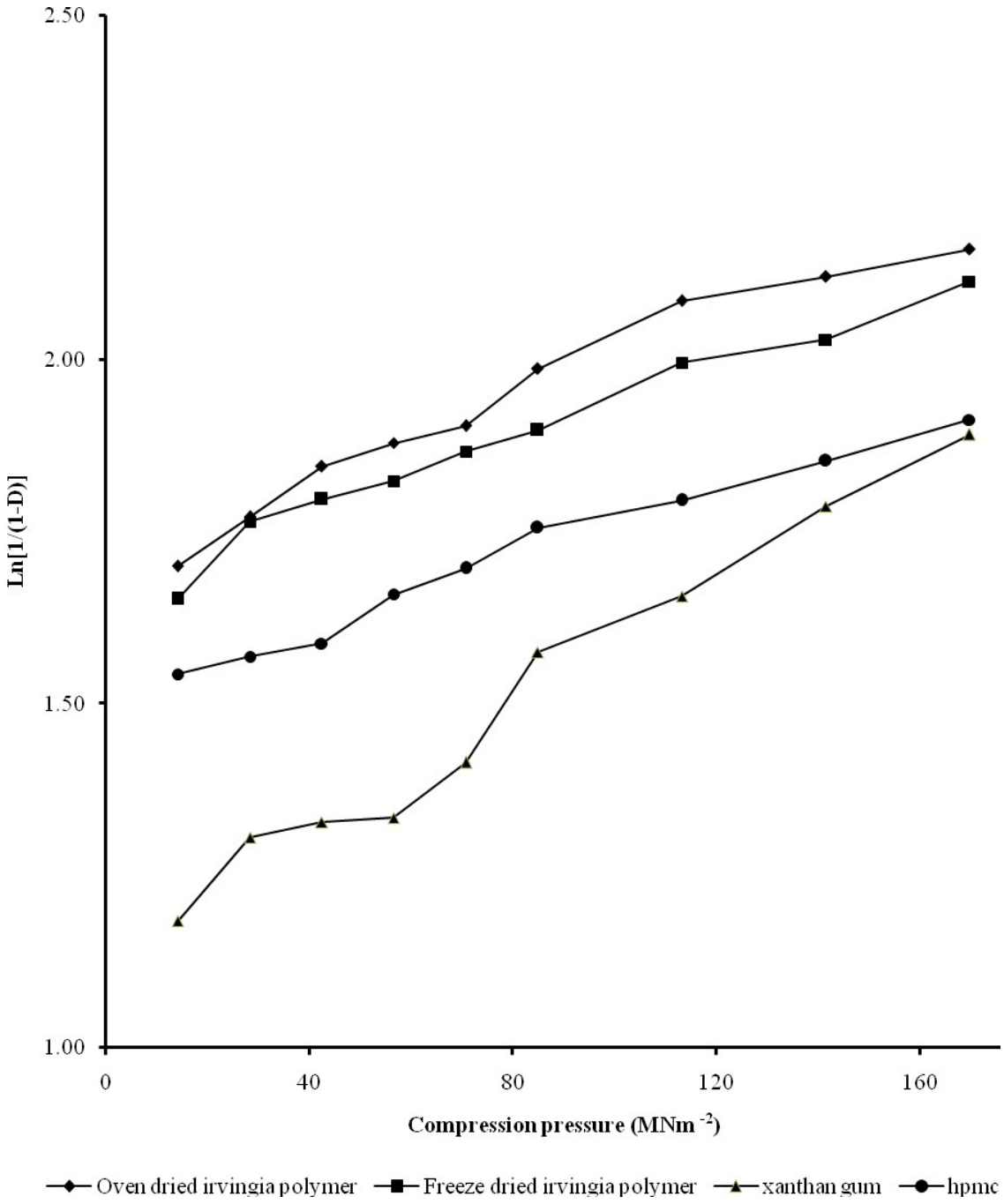


Figure 4.4. Heckel plots for *Irvingia* kernel mucilage, xanthan gum and HPMC matrices produce using direct compression.

Table 4.8. Informations obtained from Heckel and Kawakita graphs of *Irvingia* mucilage matrices produced using direct compression

Polymer		Heckel plot			Kawakita plot	
	Do	P_y (MPa)	D_A	D_B	P_k (MPa)	D_i
Oven dried *Irvingia*	0.254	333.33	0.796	0.542	1.754	0.398
Freeze dried *Irvingia*	0.242	333.33	0.803	0.561	0.313	0.332
Xanthan gum	0.257	250.00	0.678	0.421	6.265	0.423
HPMC	0.266	333.33	0.775	0.509	0.969	0.290

4.2.2 Kawakita plots of *Irvingia* kernel mucilage, xantahn gum and HPMC tablets

The values of initial bulk volume i.e volume at zero compression pressure, V_o of *Irvingia* kernel mucilage, xanthan gum and HPMC and their bulk volumes after compression (volume changed of tablets with applied pressure) V_P are given in Table 4.9. Kawakita plots of P/C against P were obtained from these values and displayed in Figure 4.5. They are straight line graphs with correlation coefficient as good as 1. The values of '**a**' and '**ab**' corresponding to the slope and intercept respectively were determined. The minimum porosity of the powder bed before compression is '**a**' while '**b**' relate to the plasticity of the material. Values of Di, the outset relative density of the formulations were obtained by subtracting '**a**' from 1 (1-**a**). P_K, a pressure term similar to P_y (both reciprocally related to plasticity) was ascertained from inverse of '**b**' values. Both D_i and P_k values are included in Table 4.8.

4.2.3 Heckel Plots of ibuprofen-*Irvingia* kernel mucilage, xanthan gum and HPMC matrices

The values of particle and granule densities of ibuprofen-mucilage mixture formulations containing 10, 20, 30 and 50% w/w ibuprofen are presented in Table 4.10. Values of loose bulk density and relative density (D_o) of the formulations for direct compression are shown in Table 4.11.

The packing fractions or relative density at different compression pressure of ibuprofen-polymer matrix tablets containing 10, 20, 30 and 50% w/w of ibuprofen and respective polymer prepared by direct compression are expressed in Table 4.12.

Table 4.9. Applied pressure (P), volume at no pressure (V_0), volume (V_P), volume decrease extent (C) and P/C for *Irvingia* kernel mucilage, xanthan gum and HPMC

Polymer	Applied pressure (MNm^{-2})	V_0	V_P	C	P/C
Oven dried *Irvingia*	14.14	1.188	0.518	0.564	25.075
	28.28		0.509	0.571	49.509
	42.42		0.503	0.576	73.604
	56.56		0.500	0.579	97.721
	70.70		0.495	0.583	121.205
	84.84		0.490	0.587	144.504
	113.13		0.483	0.594	190.562
	141.41		0.481	0.595	237.673
	169.69		0.478	0.598	283.951
Freeze dried *Irvingia*	14.14	1.426	0.492	0.656	21.593
	28.28		0.484	0.660	42.831
	42.42		0.480	0.663	63.975
	56.56		0.479	0.664	85.144
	70.70		0.478	0.665	106.391
	84.84		0.477	0.666	127.466
	113.13		0.475	0.667	169.630
	141.41		0.473	0.668	211.698
	169.69		0.468	0.672	252.660

Table 4.9. cont.

Polymer	Applied pressure (MNm^{-2})	V_0	V_P	C	P/C
Xanthan gum	14.14	0.903	0.483	0.466	30.375
	28.28		0.457	0.493	57.324
	42.42		0.454	0.497	85.388
	56.56		0.450	0.502	112.675
	70.70		0.443	0.509	138.879
	84.84		0.419	0.536	158.394
	113.13		0.411	0.545	207.738
	141.41		0.401	0.556	254.467
	169.69		0.396	0.561	302.535
HPMC	14.14	1.568	0.491	0.687	20.595
	28.28		0.487	0.689	41.036
	42.42		0.483	0.692	61.308
	56.56		0.475	0.697	81.118
	70.70		0.474	0.697	101.371
	84.84		0.472	0.699	121.389
	113.13		0.464	0.704	160.723
	141.41		0.463	0.705	200.637
	169.69		0.459	0.707	239.885

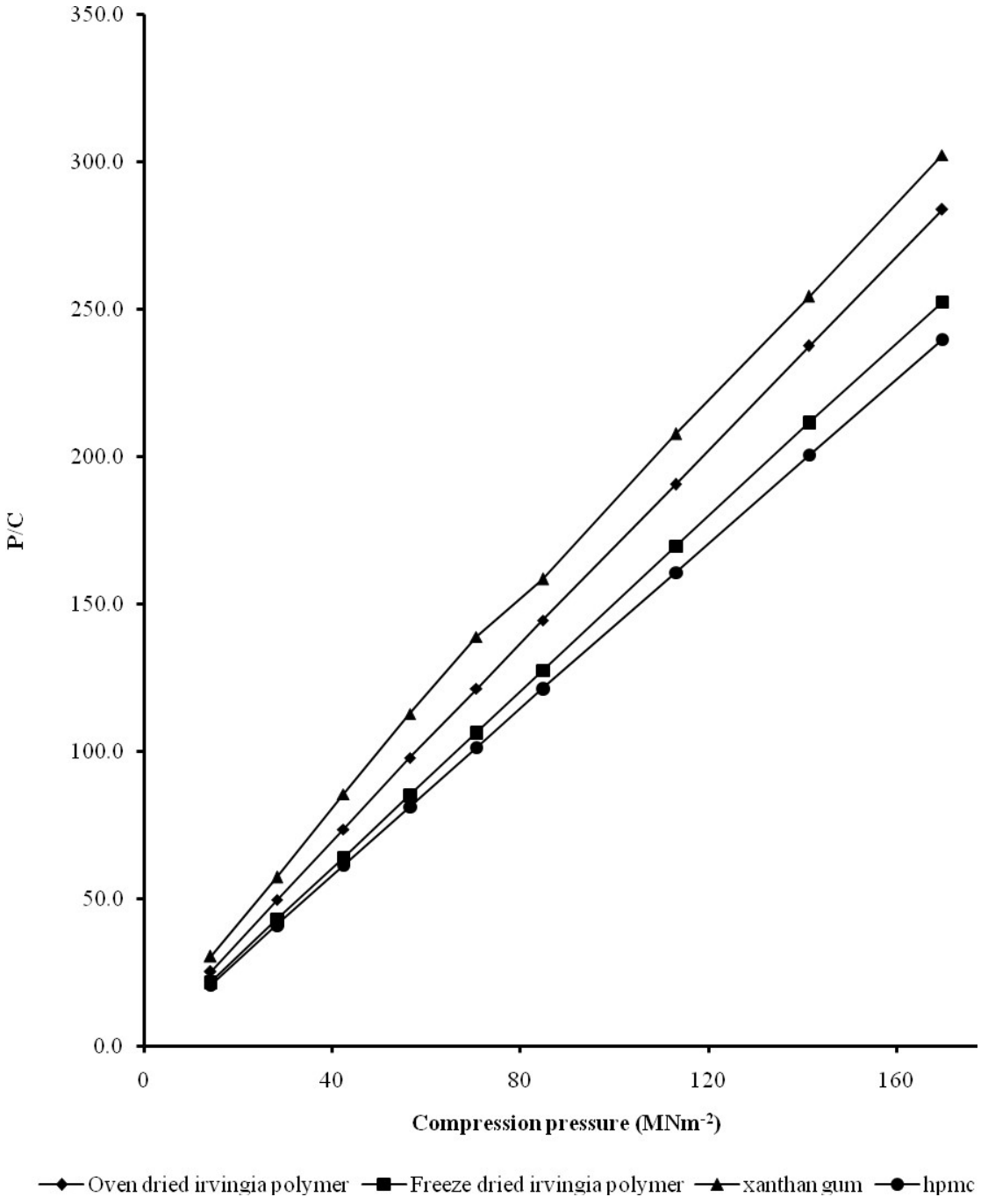


Figure 4.5. Kawakita plots for *Irvingia* kernel mucilage, xanthan gum and HPMC matrix tablets prepared by direct compression.

Table 4.10. Values of particle and granule density of ibuprofen-mucilage mixture formulations

Polymer	Ibuprofen conc. (%w/w)	Particle density (gcm^{-3})	Granule density (gcm^{-3})
Oven dried *Irvingia*	10	1.300	1.220
	20	1.230	1.181
	30	1.181	1.177
	50	1.174	1.167
Freeze dried *Irvingia*	10	1.245	1.244
	20	1.205	1.202
	30	1.202	1.198
	50	1.200	1.174
Xanthan gum	10	1.440	-
	20	1.402	-
	30	1.344	-
	50	1.328	-
HPMC	10	1.262	-
	20	1.240	-
	30	1.172	-
	50	1.167	-

Table 4.11. Values of loose bulk density (gcm^{-3}) and relative density (D_0) of ibuprofen-mucilage mixtures for direct compression

Polymer	Ibuprofen conc. (%w/w)	Loose bulk density (gcm^{-3})	Relative density (D_0)
Oven dried *Irvingia*	10	0.298	0.229
	20	0.275	0.223
	30	0.252	0.214
	50	0.242	0.206
Freeze dried *Irvingia*	10	0.291	0.234
	20	0.263	0.218
	30	0.257	0.214
	50	0.252	0.210
Xanthan gum	10	0.365	0.254
	20	0.344	0.247
	30	0.302	0.243
	50	0.291	0.237
HPMC	10	0.255	0.202
	20	0.247	0.199
	30	0.231	0.197
	50	0.226	0.194

Table 4.12. Values of applied pressure (MNm^{-2}), relative density of tablet (D) and Ln[1/(1-D)] for ibuprofen matrices made using direct compression approach

Polymer	Conc. of ibuprofen (%w/w)	Applied pressure (MNm^{-2})	Relative density (D)	Ln[1/(1-D)]
Oven dried *Irvingia*	10	14.14	0.840	1.836
		28.28	0.847	1.880
		42.42	0.856	1.939
		56.56	0.865	2.004
		70.70	0.876	2.084
		84.84	0.887	2.183
		113.13	0.896	2.259
		141.41	0.906	2.360
		169.69	0.911	2.424
	20	14.14	0.884	2.153
		28.28	0.891	2.220
		42.42	0.898	2.287
		56.56	0.902	2.324
		70.70	0.916	2.467
		84.84	0.926	2.607
		113.13	0.929	2.640
		141.41	0.932	2.690
		169.69	0.936	2.755
	30	14.14	0.893	2.254
		28.28	0.902	2.319
		42.42	0.907	2.377
		56.56	0.914	2.449
		70.70	0.921	2.537
		84.84	0.927	2.616
		113.13	0.932	2.681
		141.41	0.938	2.781
		169.69	0.944	2.880

Table 4.12. cont.

Polymer	Conc. of ibuprofen (%w/w)	Applied pressure (MNm^{-2})	Relative density (D)	Ln[1/(1-D)]
Oven dried *Irvingia*	50	14.14	0.919	2.509
		28.28	0.923	2.560
		42.42	0.926	2.607
		56.56	0.933	2.702
		70.70	0.939	2.802
		84.84	0.945	2.901
		113.13	0.949	2.968
		141.41	0.953	3.061
		169.69	0.958	3.167
Freeze dried *Irvingia*	10	14.14	0.835	1.802
		28.28	0.842	1.847
		42.42	0.855	1.934
		56.56	0.862	1.983
		70.70	0.868	2.025
		84.84	0.871	2.047
		113.13	0.875	2.082
		141.41	0.879	2.115
		169.69	0.885	2.166
	20	14.14	0.866	2.012
		28.28	0.878	2.101
		42.42	0.891	2.214
		56.56	0.904	2.342
		70.70	0.912	2.430
		84.84	0.920	2.522
		113.13	0.927	2.624
		141.41	0.933	2.702
		169.69	0.935	2.734

Table 4.12. cont.

Polymer	Conc. of ibuprofen (%w/w)	Applied pressure (MNm^{-2})	Relative density (D)	Ln[1/(1-D)]
Freeze dried *Irvingia*	30	14.14	0.875	2.083
		28.28	0.884	2.155
		42.42	0.892	2.222
		56.56	0.907	2.374
		70.70	0.913	2.445
		84.84	0.924	2.577
		113.13	0.929	2.642
		141.41	0.935	2.737
		169.69	0.941	2.834
	50	14.14	0.889	2.197
		28.28	0.899	2.290
		42.42	0.904	2.343
		56.56	0.913	2.445
		70.70	0.926	2.601
		84.84	0.934	2.717
		113.13	0.939	2.802
		141.41	0.944	2.886
		169.69	0.946	2.918
Xanthan gum	10	14.14	0.735	1.327
		28.28	0.744	1.362
		42.42	0.759	1.422
		56.56	0.773	1.482
		70.70	0.782	1.522
		84.84	0.789	1.555
		113.13	0.811	1.668
		141.41	0.837	1.813
		169.69	0.850	1.894

Table 4.12. cont.

Polymer	Conc. of ibuprofen (%w/w)	Applied pressure (MNm^{-2})	Relative density (D)	Ln[1/(1-D)]
Xanthan gum	20	14.14	0.753	1.396
		28.28	0.764	1.444
		42.42	0.767	1.455
		56.56	0.781	1.518
		70.70	0.797	1.596
		84.84	0.811	1.666
		113.13	0.821	1.721
		141.41	0.841	1.840
		169.69	0.855	1.929
	30	14.14	0.780	1.513
		28.28	0.788	1.552
		42.42	0.796	1.587
		56.56	0.810	1.660
		70.70	0.818	1.705
		84.84	0.827	1.756
		113.13	0.848	1.882
		141.41	0.869	2.029
		169.69	0.882	2.136
	50	14.14	0.799	1.604
		28.28	0.808	1.648
		42.42	0.820	1.712
		56.56	0.825	1.745
		70.70	0.838	1.820
		84.84	0.850	1.898
		113.13	0.865	2.005
		141.41	0.884	2.158
		169.69	0.894	2.242

Table 4.12. cont.

Polymer	Conc. of ibuprofen (%w/w)	Applied pressure (MNm^{-2})	Relative density (D)	Ln[1/(1-D)]
HPMC	10	14.14	0.806	1.639
		28.28	0.816	1.695
		42.42	0.818	1.705
		56.56	0.822	1.727
		70.70	0.825	1.744
		84.84	0.830	1.773
		113.13	0.845	1.867
		141.41	0.852	1.911
		169.69	0.859	1.961
	20	14.14	0.809	1.653
		28.28	0.818	1.706
		42.42	0.821	1.720
		56.56	0.824	1.740
		70.70	0.829	1.763
		84.84	0.833	1.787
		113.13	0.849	1.891
		141.41	0.852	1.908
		169.69	0.858	1.952
	30	14.14	0.840	1.834
		28.28	0.848	1.883
		42.42	0.856	1.935
		56.56	0.862	1.981
		70.70	0.866	2.011
		84.84	0.869	2.036
		113.13	0.875	2.081
		141.41	0.878	2.105
		169.69	0.883	2.147

Table 4.12. cont.

Polymer	Conc. of ibuprofen (%w/w)	Applied pressure (MNm^{-2})	Relative density (D)	Ln[1/(1-D)]
HPMC	50	14.14	0.842	1.844
		28.28	0.851	1.904
		42.42	0.858	1.953
		56.56	0.865	2.004
		70.70	0.871	2.046
		84.84	0.872	2.057
		113.13	0.881	2.128
		141.41	0.889	2.200
		169.69	0.898	2.284

Heckel plots of Ln[1/(1-D)] against compression pressure were gotten from these values and representative Heckel plots of 20%, 50% w/w exhibited in Figures 4.6 and 4.7. Values of K and A, the gradient of the straight line region and the intercept of its extrapolation respectively were obtained. The mean yield values, P_y were determined as the reciprocal of K. The parameters derived from the Heckel graphs are shown in Table 4.13.

4.2.4 Kawakita plots of ibuprofen-*Irvingia* kernel mucilage, xanthan gum and HPMC matrices

The initial bulk volume at zero applied pressure, Vo of ibuprofen-mucilage formulations (i.e ibuprofen-*Irvingia* kernel mucilage, ibuprofen-xanthan gum and ibuprofen-HPMC) and the bulk volume after compression, V_P which is volume change of tablets with applied pressure of the formulations are presented in Table 4.14. These values were used in plotting kawakita graphs of P/C versus P and representative kawakita plots for 20% & 50% w/w ibuprofen-mucilage are displayed in Figures 4.8 and 4.9. The values of **a** and **ab** representing the slope and intercept respectively of the straight line plots were determined. The start relative density of the formulations, D_i, were obtained as the difference between 1 and **a** (i.e 1-**a**). P_k which is conversely related to plasticity is the inverse of the values of **b**. The values of $D_1$and P_K are contained in Table 4.13.

4.3 Mechanical properties and drug release

4.3.1 Friability of *Irvingia* kernel mucilage, xanthan gum and HPMC tablets

The values of friability at different relative density (packing fraction) of *Irvingia* kernel mucilage, xanthan gum and HPMC tablets prepared by direct compression are given in Table 4.15.

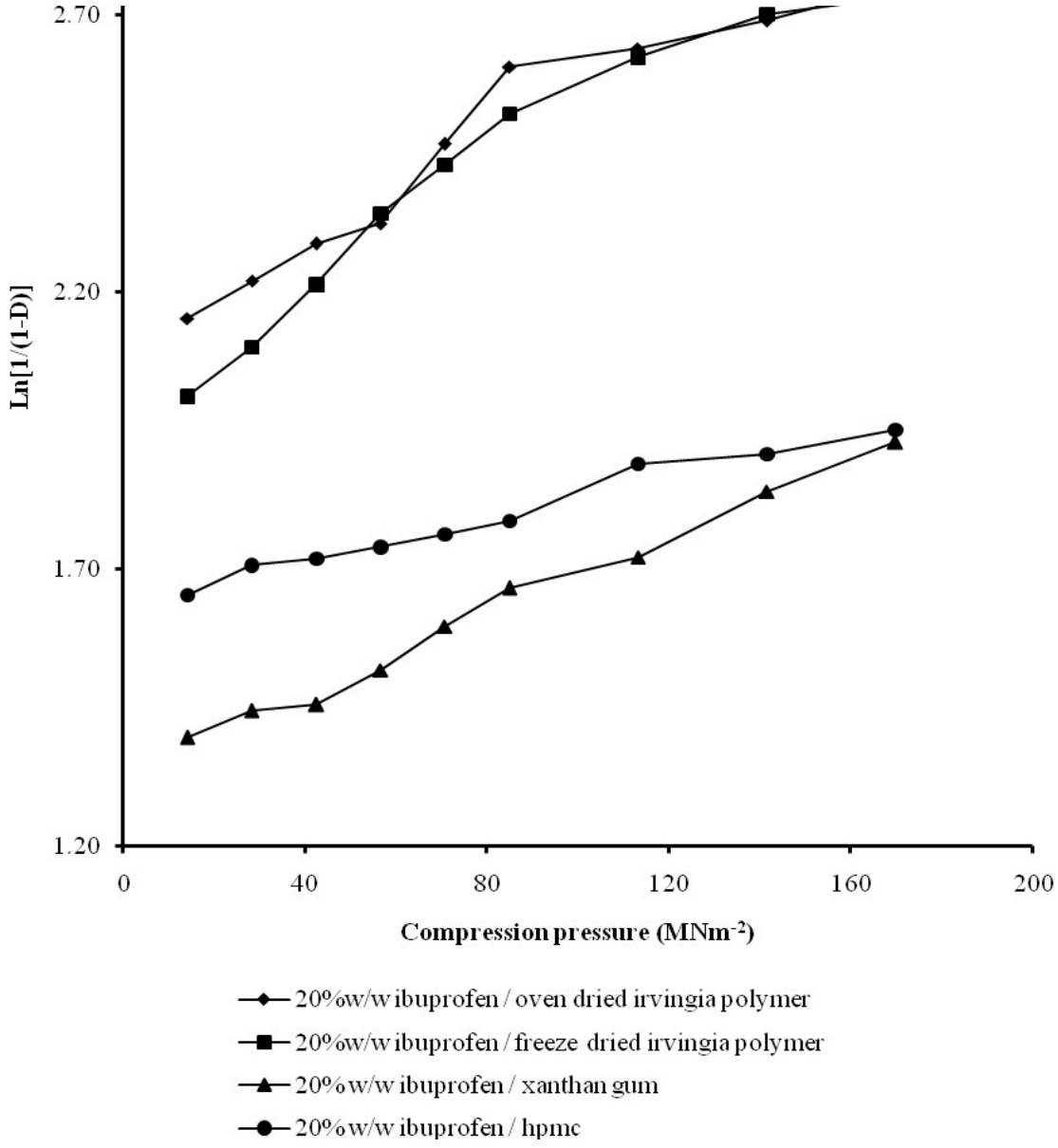


Figure 4.6. Heckel plots for *Irvingia* kernel mucilage, xathan gum and HPMC matrix tablet containing 20% w/w ibuprofen prepared by direct compression

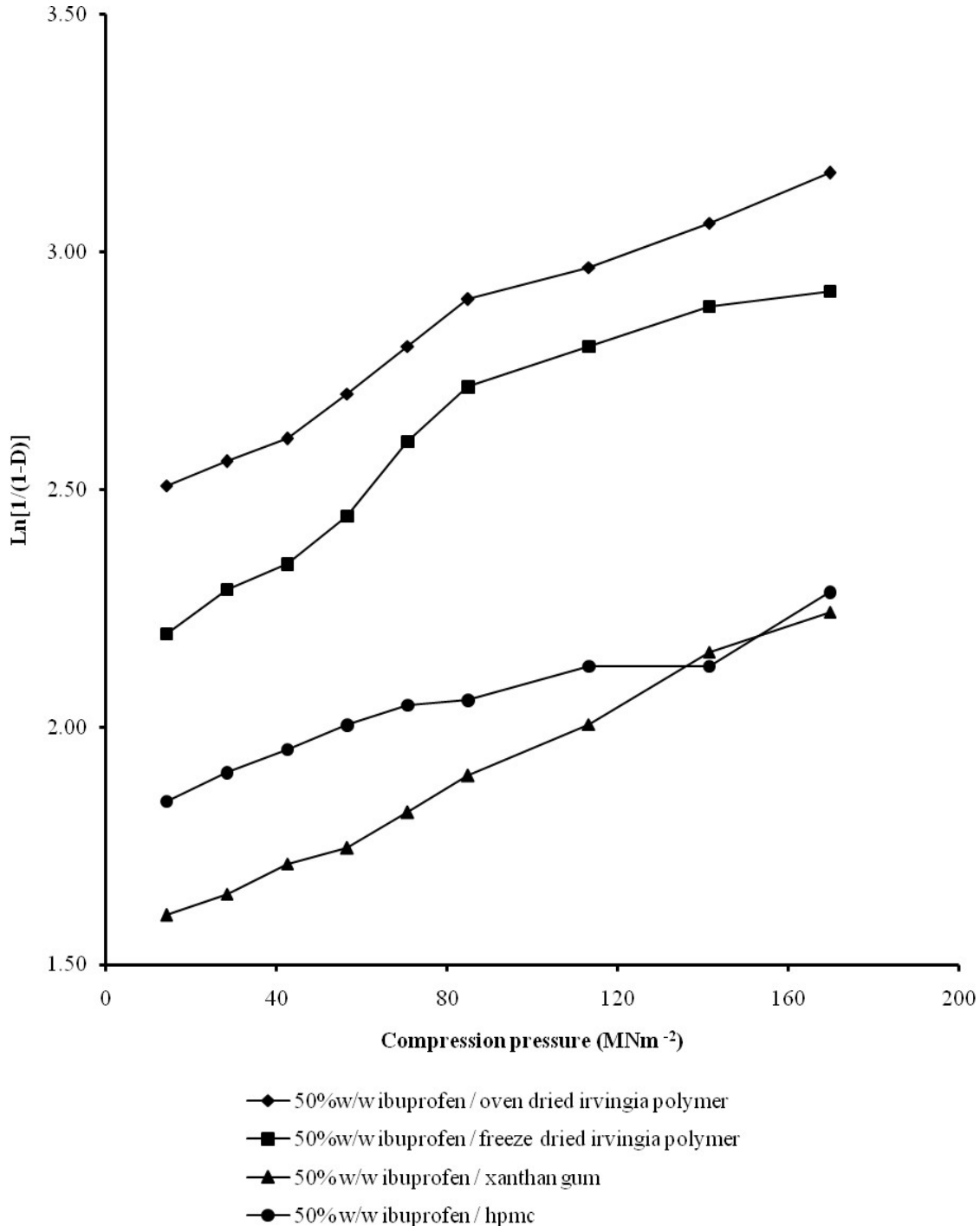


Figure 4.7. Heckel plots for *Irvingia* kernel mucilage, xathan gum and HPMC matrix tablet containing 50% w/w ibuprofen prepared by direct compression

Table 4.13. Variables obtained from Heckel and Kawakita graphs of ibuprofen-polymer mixture formulations

Polymer	Conc. of Ibuprofen (%)	Direct compression						Wet granulation					
		Heckel plot				Kawakita plot		Heckel plot				Kawakita plot	
		D_0	P_y (MPa)	D_A	D_B	P_K (MPa)	Di	D_0	P_y (MPa)	D_A	D_B	P_K (MPa)	Di
Oven dried *Irvingia*	10	0.229	333.33	0.820	0.591	1.638	0.427	0.215	243.90	0.815	0.576	0.821	0.342
	20	0.223	384.62	0.860	0.637	1.376	0.412	0.213	256.41	0.858	0.627	0.803	0.321
	30	0.214	454.55	0.883	0.669	0.799	0.372	0.207	270.27	0.880	0.666	0.647	0.300
	50	0.206	909.09	0.903	0.697	0.254	0.323	0.198	357.14	0.900	0.706	0.366	0.292
Freeze dried *Irvingia*	10	0.234	250.00	0.832	0.598	1.325	0.392	0.224	204.08	0.829	0.606	0.855	0.300
	20	0.218	263.16	0.872	0.654	1.152	0.363	0.209	227.27	0.867	0.649	0.815	0.290
	30	0.214	333.33	0.890	0.676	1.133	0.350	0.201	285.71	0.884	0.670	0.813	0.280
	50	0.210	500.00	0.905	0.695	1.047	0.337	0.195	312.50	0.897	0.687	0.747	0.271
Xanthan Gum	10	0.254	454.55	0.774	0.520	3.266	0.432	-	-	-	-	-	-
	20	0.247	526.32	0.794	0.547	1.808	0.386	-	-	-	-	-	-
	30	0.243	526.32	0.898	0.655	1.299	0.373	-	-	-	-	-	-
	50	0.237	555.56	0.905	0.668	1.299	0.366	-	-	-	-	-	-
HPMC	10	0.202	370.37	0.801	0.599	0.334	0.293	-	-	-	-	-	-
	20	0.199	400.00	0.809	0.610	0.439	0.285	-	-	-	-	-	-
	30	0.197	625.00	0.838	0.641	0.399	0.279	-	-	-	-	-	-
	50	0.194	666.67	0.840	0.646	0.460	0.270	-	-		-	-	-

Table 4.14. **A**pplied pressure (P), volume at zero pressure (V_0), volume (V_P), volume decrease extent (C) and P/C for ibuprofen matrices made using direct compression method

Polymer	Conc. of Ibuprofen (%w/w)	Applied Pressure (MNm^{-2})	V_0	V_P	C	P/C
Oven dried *Irvingia*	10	14.14	1.045	0.479	0.542	26.10
		28.28		0.476	0.544	51.96
		42.42		0.471	0.549	77.24
		56.56		0.467	0.553	102.22
		70.70		0.465	0.555	127.39
		84.84		0.461	0.559	151.69
		113.13		0.455	0.565	200.35
		141.41		0.443	0.566	249.70
		169.69		0.431	0.569	298.33
	20	14.14	1.083	0.477	0.560	25.27
		28.28		0.474	0.562	50.28
		42.42		0.470	0.566	74.89
		56.56		0.466	0.569	99.34
		70.70		0.461	0.575	123.03
		84.84		0.454	0.580	146.24
		113.13		0.453	0.581	194.69
		141.41		0.451	0.583	242.47
		169.69		0.450	0.584	290.43
	30	14.14	1.169	0.471	0.597	23.67
		28.28		0.468	0.600	47.17
		42.42		0.465	0.602	70.47
		56.56		0.464	0.603	93.73
		70.70		0.463	0.604	117.02
		84.84		0.462	0.605	140.28
		113.13		0.460	0.607	186.40
		141.41		0.457	0.609	232.05
		169.69		0.452	0.613	276.78

Table 4.14. cont.

Polymer	Conc. of Ibuprofen (%w/w)	Applied Pressure (MNm^{-2})	V_0	V_P	C	P/C
Oven dried *Irvingia*	50	14.14	1.256	0.467	0.628	22.51
		28.28		0.465	0.629	44.93
		42.42		0.464	0.630	67.30
		56.56		0.463	0.631	89.63
		70.70		0.462	0.632	111.89
		84.84		0.461	0.633	134.14
		113.13		0.460	0.634	178.43
		141.41		0.454	0.638	221.59
		169.69		0.450	0.642	264.48
Freeze dried *Irvingia*	10	14.14	1.126	0.478	0.576	24.55
		28.28		0.468	0.584	48.40
		42.42		0.464	0.588	72.18
		56.56		0.460	0.592	95.57
		70.70		0.458	0.593	119.21
		84.84		0.454	0.597	142.16
		113.13		0.451	0.599	188.79
		141.41		0.450	0.601	235.48
		169.69		0.444	0.605	280.30
	20	14.14	1.213	0.473	0.610	23.18
		28.28		0.468	0.614	46.04
		42.42		0.464	0.618	68.68
		56.56		0.459	0.622	90.98
		70.70		0.455	0.625	113.12
		84.84		0.453	0.626	135.47
		113.13		0.450	0.629	179.98
		141.41		0.449	0.630	224.46
		169.69		0.443	0.635	267.33

Table 4.14. cont.

Polymer	Conc. of Ibuprofen (%w/w)	Applied Pressure (MNm^{-2})	V_0	V_P	C	P/C
Freeze dried *Irvingia*	30	14.14	1.256	0.469	0.627	22.56
		28.28		0.464	0.631	44.83
		42.42		0.462	0.632	67.10
		56.56		0.459	0.635	89.11
		70.70		0.457	0.637	111.07
		84.84		0.453	0.639	132.74
		113.13		0.452	0.640	176.64
		141.41		0.446	0.645	219.30
		169.69		0.442	0.649	261.66
	50	14.14	1.300	0.470	0.638	22.16
		28.28		0.468	0.640	44.19
		42.42		0.463	0.644	65.89
		56.56		0.459	0.646	87.49
		70.70		0.456	0.649	108.88
		84.84		0.450	0.653	129.89
		113.13		0.447	0.656	172.51
		141.41		0.446	0.657	215.20
		169.69		0.443	0.659	257.54
Xanthan gum	10	14.14	0.950	0.474	0.501	28.20
		28.28		0.468	0.508	55.67
		42.42		0.464	0.512	82.90
		56.56		0.457	0.520	108.86
		70.70		0.452	0.524	134.81
		84.84		0.447	0.530	160.23
		113.13		0.437	0.541	209.29
		141.41		0.423	0.555	255.01
		169.69		0.417	0.562	302.20

Table 4.14. cont.

Polymer	Conc. of Ibuprofen (%w/w)	Applied Pressure (MNm^{-2})	V_0	V_P	C	P/C
Xanthan gum	20	14.14	1.093	0.471	0.569	24.84
		28.28		0.466	0.574	49.31
		42.42		0.461	0.578	73.42
		56.56		0.455	0.583	96.97
		70.70		0.450	0.588	120.17
		84.84		0.446	0.592	143.34
		113.13		0.435	0.602	187.90
		141.41		0.422	0.614	230.43
		169.69		0.416	0.620	273.91
	30	14.14	1.140	0.469	0.589	24.03
		28.28		0.464	0.593	47.71
		42.42		0.460	0.597	71.10
		56.56		0.453	0.603	93.85
		70.70		0.448	0.607	116.52
		84.84		0.443	0.611	138.82
		113.13		0.434	0.620	182.57
		141.41		0.420	0.631	224.00
		169.69		0.415	0.636	266.87
	50	14.14	1.188	0.467	0.607	23.29
		28.28		0.462	0.611	46.30
		42.42		0.458	0.614	69.04
		56.56		0.451	0.620	91.18
		70.70		0.446	0.624	113.27
		84.84		0.441	0.629	135.01
		113.13		0.431	0.637	177.51
		141.41		0.417	0.649	217.98
		169.69		0.413	0.652	260.11

Table 4.14. cont.

Polymer	Conc. of Ibuprofen (%w/w)	Applied Pressure (MNm^{-2})	V_0	V_P	C	P/C
HPMC	10	14.14	1.616	0.492	0.696	20.33
		28.28		0.483	0.701	40.34
		42.42		0.482	0.702	60.44
		56.56		0.480	0.703	80.44
		70.70		0.477	0.705	100.35
		84.84		0.474	0.707	120.11
		113.13		0.470	0.709	159.58
		141.41		0.468	0.710	199.04
		169.69		0.466	0.711	238.55
	20	14.14	1.663	0.494	0.703	20.12
		28.28		0.490	0.705	40.09
		42.42		0.487	0.707	59.96
		56.56		0.485	0.709	79.81
		70.70		0.483	0.710	99.65
		84.84		0.481	0.711	119.40
		113.13		0.479	0.712	158.90
		141.41		0.478	0.713	198.38
		169.69		0.476	0.714	237.65
	30	14.14	1.711	0.499	0.708	19.96
		28.28		0.495	0.711	39.79
		42.42		0.489	0.714	59.39
		56.56		0.487	0.715	79.10
		70.70		0.485	0.716	98.69
		84.84		0.484	0.717	118.37
		113.13		0.483	0.718	157.60
		141.41		0.481	0.719	196.74
		169.69		0.479	0.720	235.75

Table 4.14. cont.

Polymer	Conc. of Ibuprofen (%w/w)	Applied Pressure (MNm^{-2})	V_0	V_P	C	P/C
HPMC	50	14.14	1.758	0.501	0.715	19.78
		28.28		0.495	0.718	39.36
		42.42		0.491	0.720	58.88
		56.56		0.487	0.723	78.24
		70.70		0.483	0.725	97.49
		84.84		0.482	0.726	116.91
		113.13		0.480	0.727	155.68
		141.41		0.478	0.728	194.24
		169.69		0.477	0.729	232.93

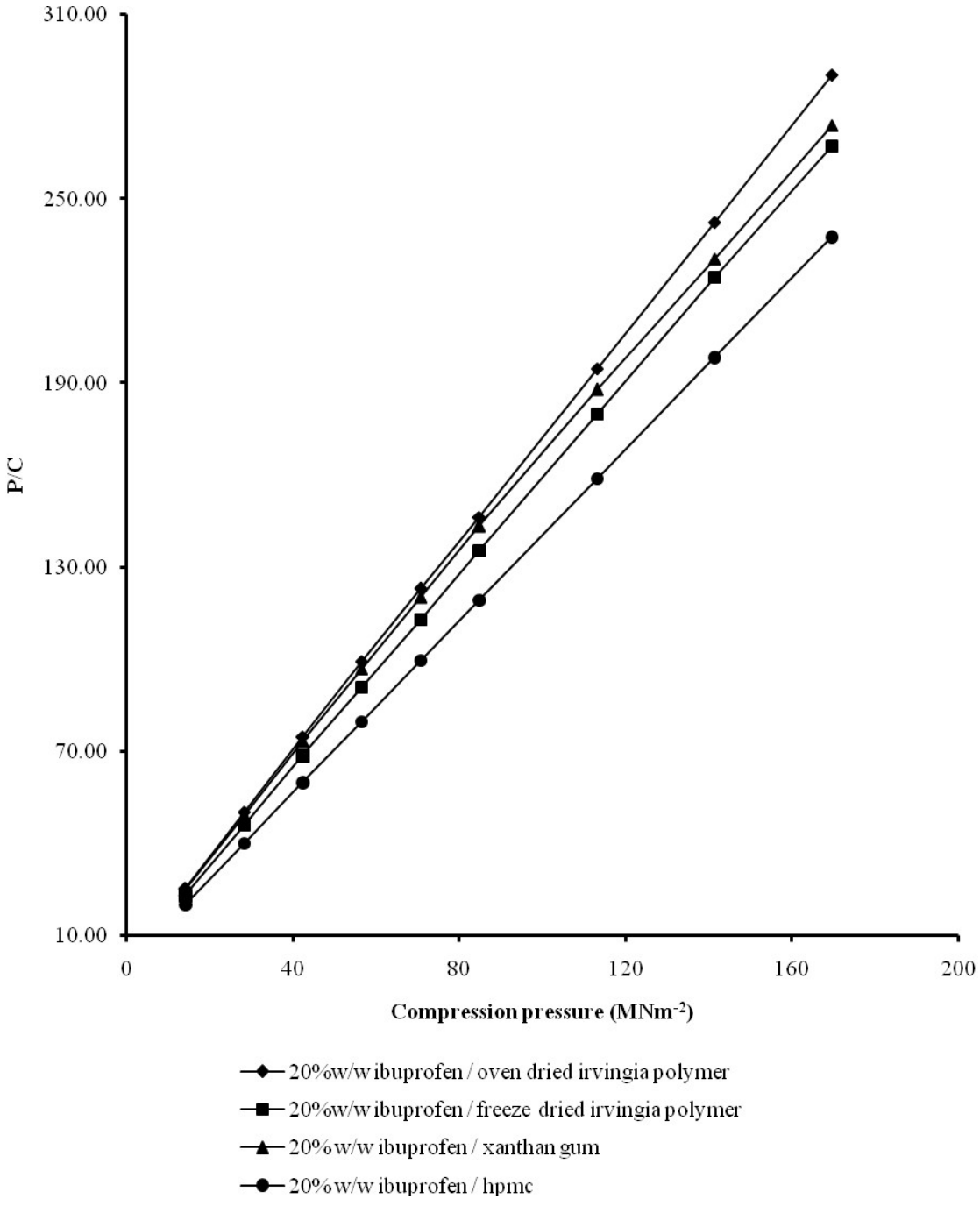


Figure 4.8. Kawakita plots for *Irvingia* kernel mucilage, xanthan gum and HPMC matrix tablet containing 20% w/w ibuprofen prepared by direct compression

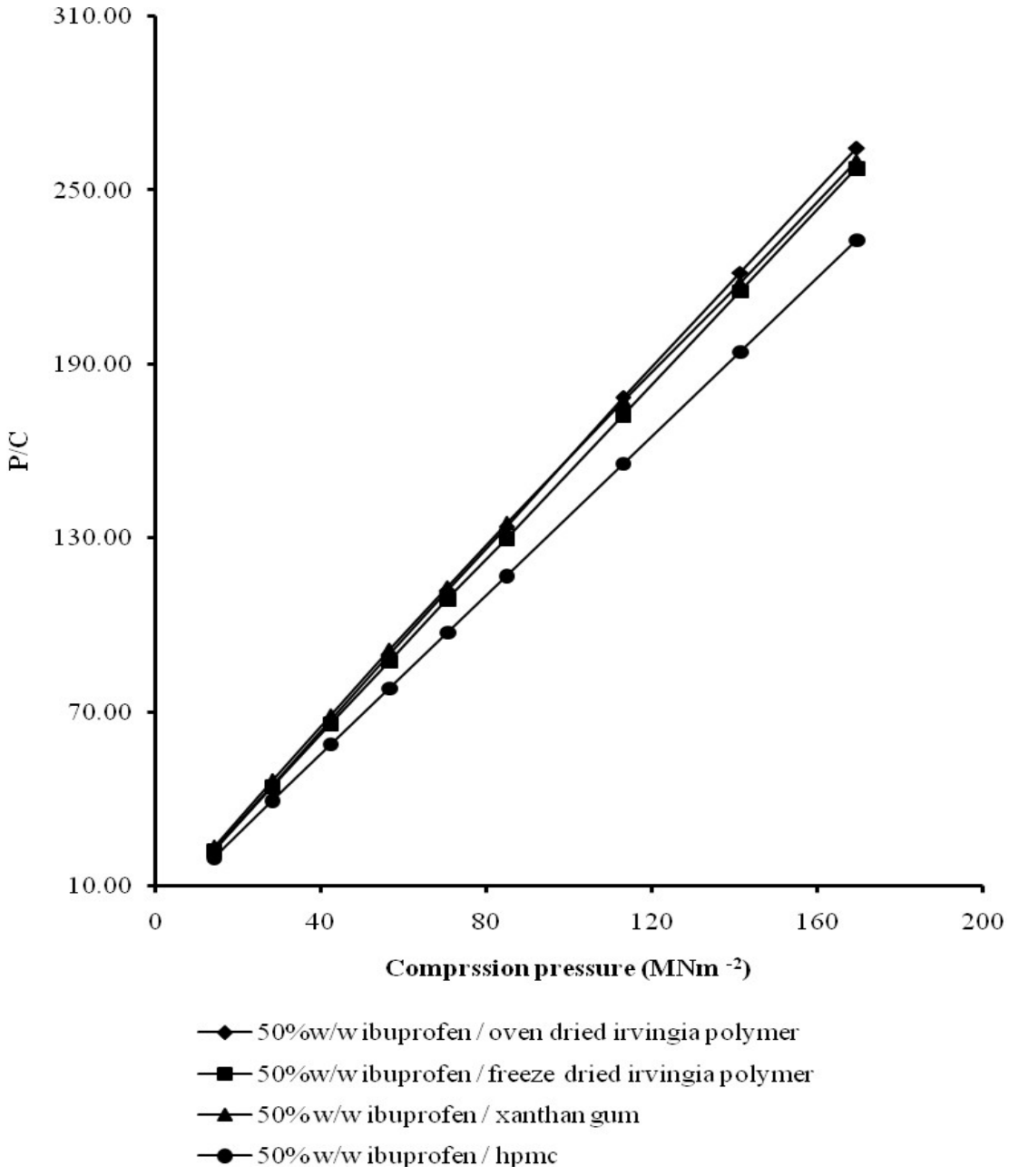


Figure 4.9. Kawakita plots for *Irvingia* kernel mucilage, xanthan gum and HPMC matrix tablet containing 50% w/w ibuprofen prepared by direct compression

Table 4.15. Values of friability of *Irvingia* kernel mucilage, xanthan gum and HPMC at different relative densities

Polymer	Relative density (D)	Friability (%)
Oven dried *Irvingia*	0.842	0.77±0.02
	0.851	0.65±0.09
	0.861	0.61±0.03
	0.874	0.53±0.01
	0.886	0.41±0.03
Freeze dried *Irvingia*	0.829	0.68±0.11
	0.840	0.54±0.03
	0.848	0.44±0.03
	0.863	0.35±0.04
	0.881	0.27±0.01
Xanthan gum	0.733	0.15±0.07
	0.758	0.13±0.01
	0.808	0.06±0.03
	0.826	0.04±0.03
	0.850	0.01±0.01
HPMC	0.783	0.13± 0.01
	0.795	0.11± 0.01
	0.810	0.05± 0.04
	0.829	0.00± 0.00
	0.853	0.00± 0.00

Plots of friability against relative density for these mucilage tablets are shown in Figure 4.10. Values of friability at packing fraction 0.85 are expressed in Table 4.16.

4.3.2 Crushing strength of *Irvingia* kernel mucilage, xanthan gum and HPMC

The crushing strength values at different relative density (packing fraction) of *Irvingia* kernel mucilage, xanthan gum and HPMC tablets prepared by direct compression are stated in Table 4.17. Graph of crushing strength versus relative density of *Irvingia* kernel mucilage is displayed in Figure 4.11. The values of crushing strength and crushing strength/friability ratio (CS/FR) at relative density 0.85 are included in Table 4.16.

4.3.3 Friability of ibuprofen-*Irvingia* kernel mucilage, xanthan gum and HPMC matrices

The value of friability at different relative density (packing fraction) of ibuprofen-mucilage matrices containing 10, 20, 30 and 50% w/w of ibuprofen and respective mucilage prepared by direct compression are shown in Table 4.18. Representative plots of friability against (packing fraction) for 20 and 50% w/w ibuprofen-mucilage matrices are presented in Figures 4.12 and 4.13. Values of friability at relative density 0.85 and 0.90 of the ibuprofen-mucilage matrices are given in Tables 4.19 and 4.20 respectively.

4.3.4 Crushing strength of ibuprofen-*Irvingia* kernel mucilage, xanthan gum and HPMC matrices

The crushing strength values at different relative density of ibuprofen-*Irvingia* kernel mucilage, xanthan gum and HPMC matrices containing 10, 20, 30 and 50% w/w of ibuprofen and the different mucilage prepared by direct compression are stated in Table 4.21.

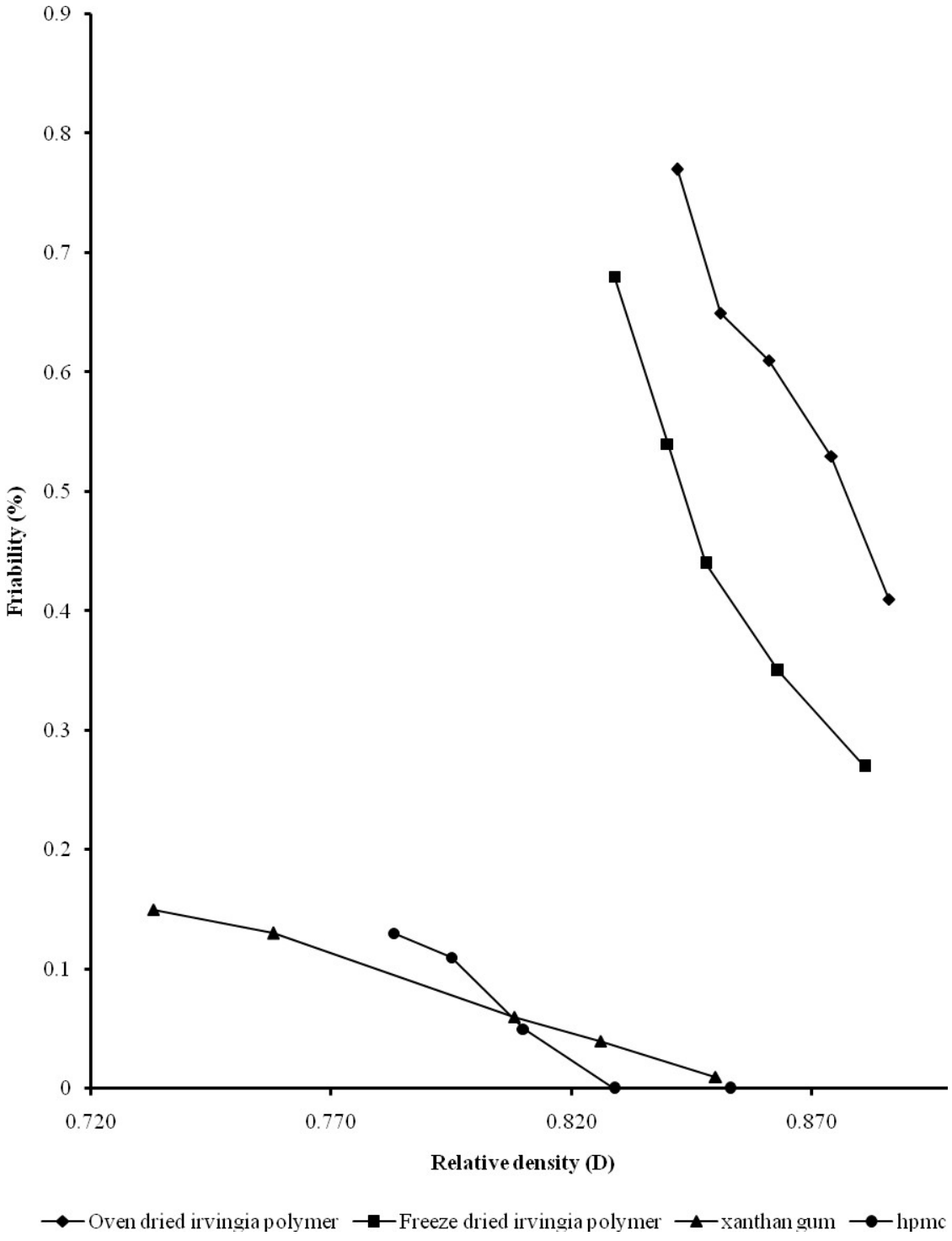


Figure 4.10. Plots of friability versus relative density (D) for *Irvingia* kernel mucilage, xanthan gum and HPMC matrix tablets produced using direct compression.

Table 4.16. Values of friability (FR), crushing strength (CS) and CSFR of *Irvingia* kernel mucilage, xanthan gum and HPMC at relative density of 0.85

Polymer	Crushing strength (N)	Friability (%)	CSFR
Oven dried *Irvingia*	55.70	0.60	92.83
Freeze dried *Irvingia*	92.00	0.38	242.12
Xanthan gum	ND	0.01	-
HPMC	ND	0.00	-

ND: Not determined – tablet remain intact at maximum crushing strength of test instrument.

Table 4.17. Values of crushing strength of *Irvingia* kernel mucilage, xanthan gum and HPMC at different relative densities

Polymer	Relative density (D)	Crushing strength (N)
Oven dried *Irvingia*	0.837	48.70±1.17
	0.848	55.65±1.20
	0.856	58.05±3.01
	0.879	63.95±0.61
	0.887	65.70±2.81
Freeze dried *Irvingia*	0.826	70.30±4.81
	0.837	83.50±2.12
	0.846	89.20±0.28
	0.865	93.30±1.41
	0.882	102.30±1.13
Xanthan gum	0.727	484.95±0.35
	0.748	ND
	0.791	ND
	0.810	ND
	0.847	ND
HPMC	0.788	490.00± 2.83
	0.804	ND
	0.811	ND
	0.828	ND
	0.858	ND

ND: Not determined – tablet remain intact at maximum crushing strength of test instrument.

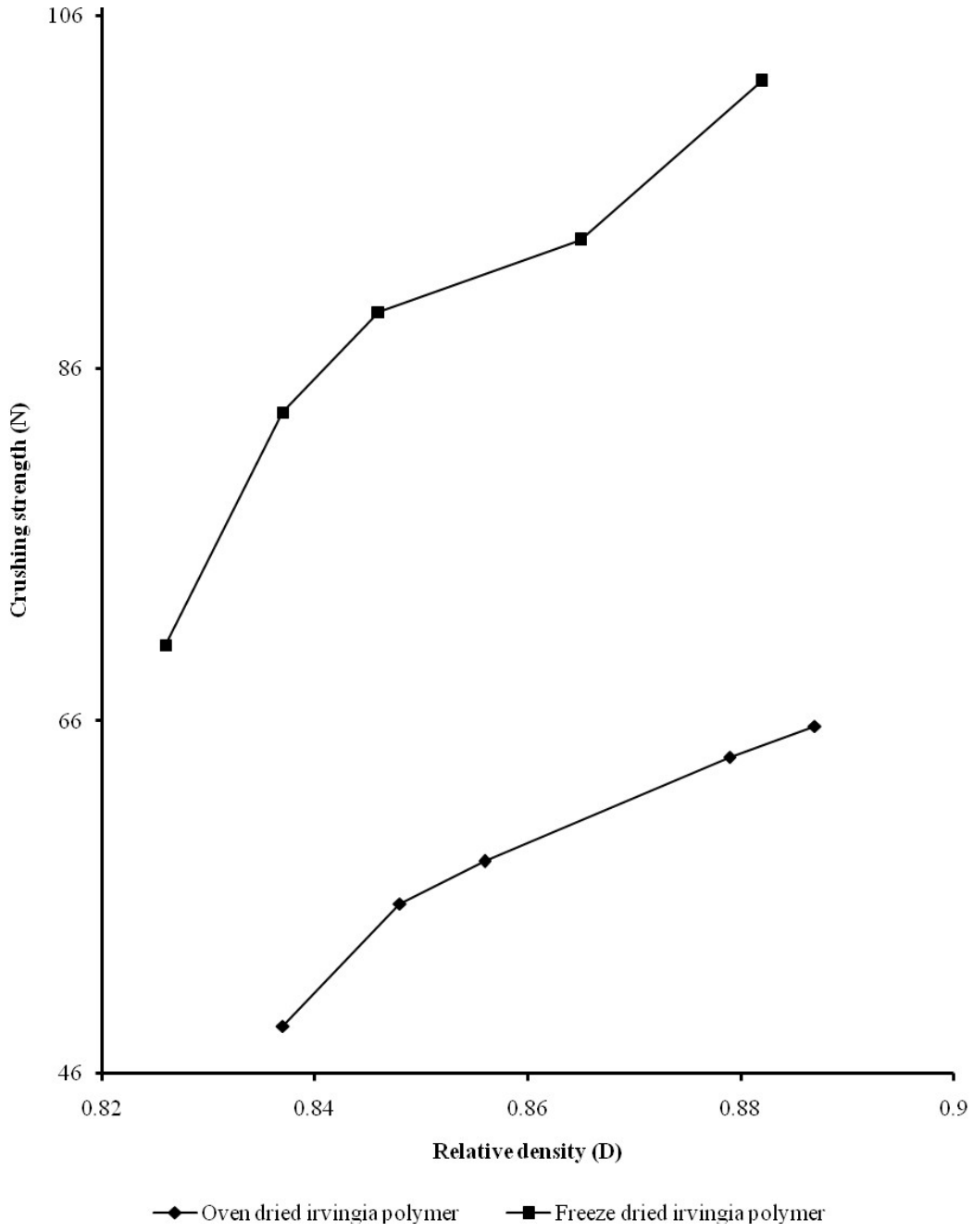


Figure 4.11. Plots of crushing strength versus relative density (D) for *Irvingia* kernel mucilage tablet prepared by direct compression

Table 4.18. Values of friability of ibuprofen matrix tablets at different relative densities prepared by direct compression method

Polymer	Conc. Of ibuprofen (% w/w)	Relative density (D)	Friability (%)
Oven dried *Irvingia*	10	0.845	0.79 ± 0.01
		0.866	0.76 ± 0.02
		0.885	0.65 ± 0.01
		0.896	0.61 ± 0.03
		0.910	0.54 ±0.02
	20	0.894	0.86 ± 0.02
		0.904	0.83 ± 0.03
		0.925	0.73 ± 0.03
		0.929	0.68 ± 0.01
		0.937	0.66 ± 0.01
	30	0.902	0.95 ± 0.03
		0.914	0.89 ± 0.02
		0.928	0.87 ± 0.01
		0.933	0.84 ± 0.03
		0.947	0.78 ± 0.02
	50	0.922	1.33 ±0.07
		0.931	1.06 ± 0.02
		0.943	0.92 ± 0.02
		0.950	0.90 ± 0.01
		0.961	0.86 ± 0.02
Freeze dried *Irvingia*	10	0.842	0.71 ± 0.02
		0.862	0.67 ± 0.02
		0.871	0.59 ± 0.01
		0.880	0.56 ± 0.02
		0.888	0.43 ±0.06
	20	0.875	0.78 ± 0.02
		0.904	0.75 ± 0.04
		0.924	0.66 ± 0.02
		0.927	0.61 ± 0.02
		0.935	0.57 ± 0.02

Table 4.18. cont.

Polymer	Conc. Of ibuprofen (% w/w)	Relative density (D)	Friability (%)
Freeze dried *Irvingia*	30	0.884	0.86 ± 0.03
		0.907	0.81 ± 0.01
		0.921	0.78 ± 0.03
		0.930	0.76 ± 0.01
		0.939	0.72 ± 0.02
	50	0.899	0.95 ±0.02
		0.914	0.93 ± 0.03
		0.930	0.86 ± 0.04
		0.939	0.82 ± 0.03
		0.945	0.75 ± 0.01
Xanthan gum	10	0.745	0.25 ± 0.07
		0.774	0.21 ± 0.05
		0.802	0.12 ± 0.06
		0.812	0.09 ± 0.01
		0.849	0.05 ±0.02
	20	0.772	0.43 ± 0.01
		0.781	0.35 ± 0.05
		0.809	0.33 ± 0.02
		0.823	0.27 ± 0.02
		0.856	0.14 ± 0.01
	30	0.790	0.51 ± 0.03
		0.811	0.47 ± 0.01
		0.830	0.44 ± 0.01
		0.849	0.40 ± 0.03
		0.879	0.34 ± 0.01
	50	0.799	0.60 ±0.16
		0.822	0.57 ± 0.15
		0.854	0.51 ± 0.09
		0.868	0.44 ± 0.08
		0.895	0.42 ± 0.12

Table 4.18. cont.

Polymer	Conc. Of ibuprofen (% w/w)	Relative density (D)	Friability (%)
HPMC	10	0.818	0.15 ± 0.01
		0.823	0.12 ± 0.02
		0.826	0.07 ± 0.04
		0.838	0.04 ± 0.01
		0.846	0.01 ± 0.01
	20	0.817	0.24 ± 0.01
		0.825	0.21 ± 0.02
		0.832	0.15 ± 0.02
		0.847	0.12 ± 0.01
		0.858	0.06 ± 0.05
	30	0.850	0.40 ± 0.03
		0.864	0.38 ± 0.02
		0.870	0.36 ± 0.02
		0.875	0.30 ± 0.01
		0.887	0.26 ± 0.02
	50	0.852	0.47 ±0.03
		0.870	0.42 ± 0.03
		0.873	0.37 ± 0.00
		0.884	0.31 ± 0.01
		0.897	0.28 ± 0.02

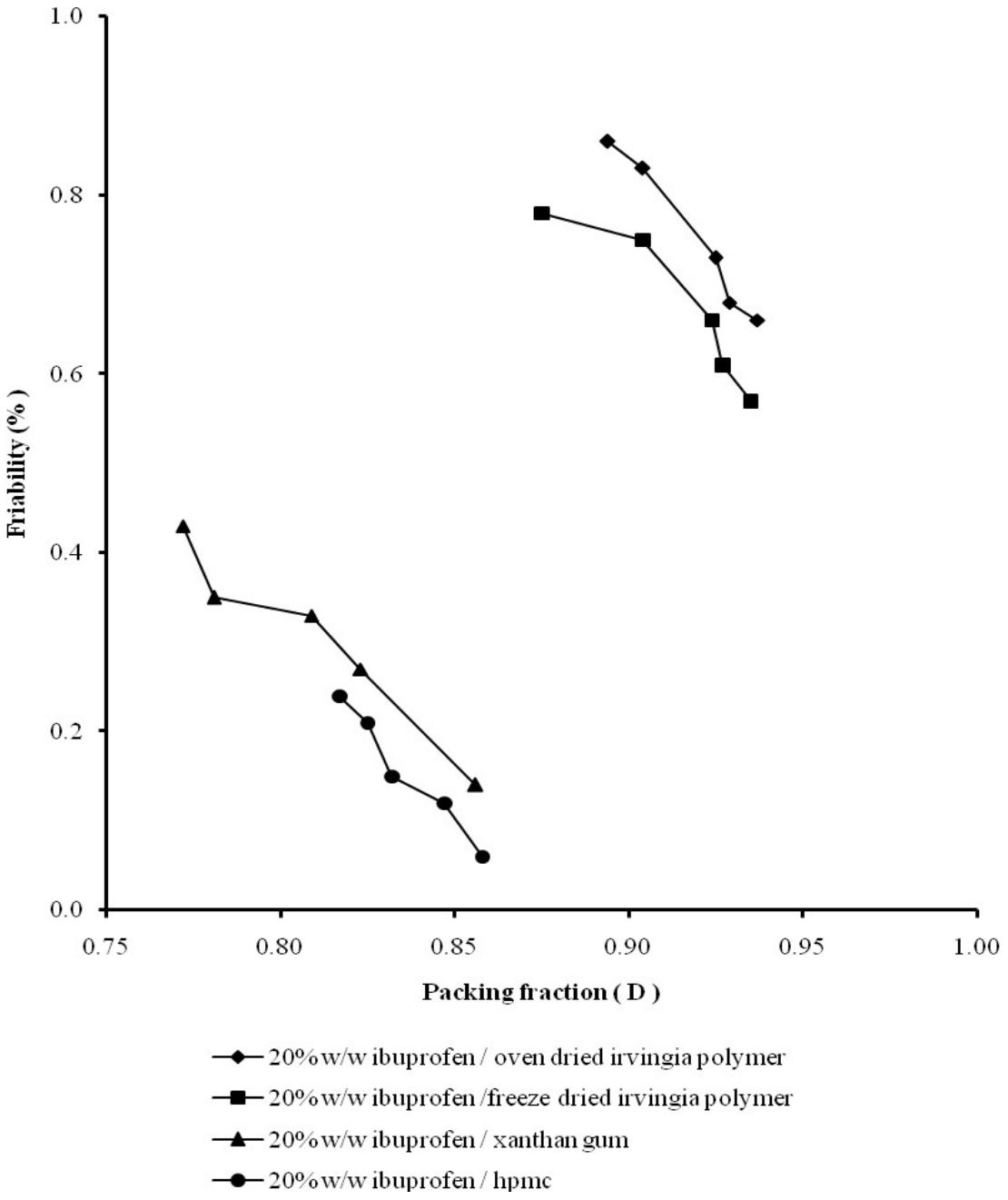


Figure 4.12. Friability versus packing fraction plot for *Irvingia* kernel mucilage, xanthan gum and HPMC matrix tablet containing 20% w/w ibuprofen prepared by direct compression

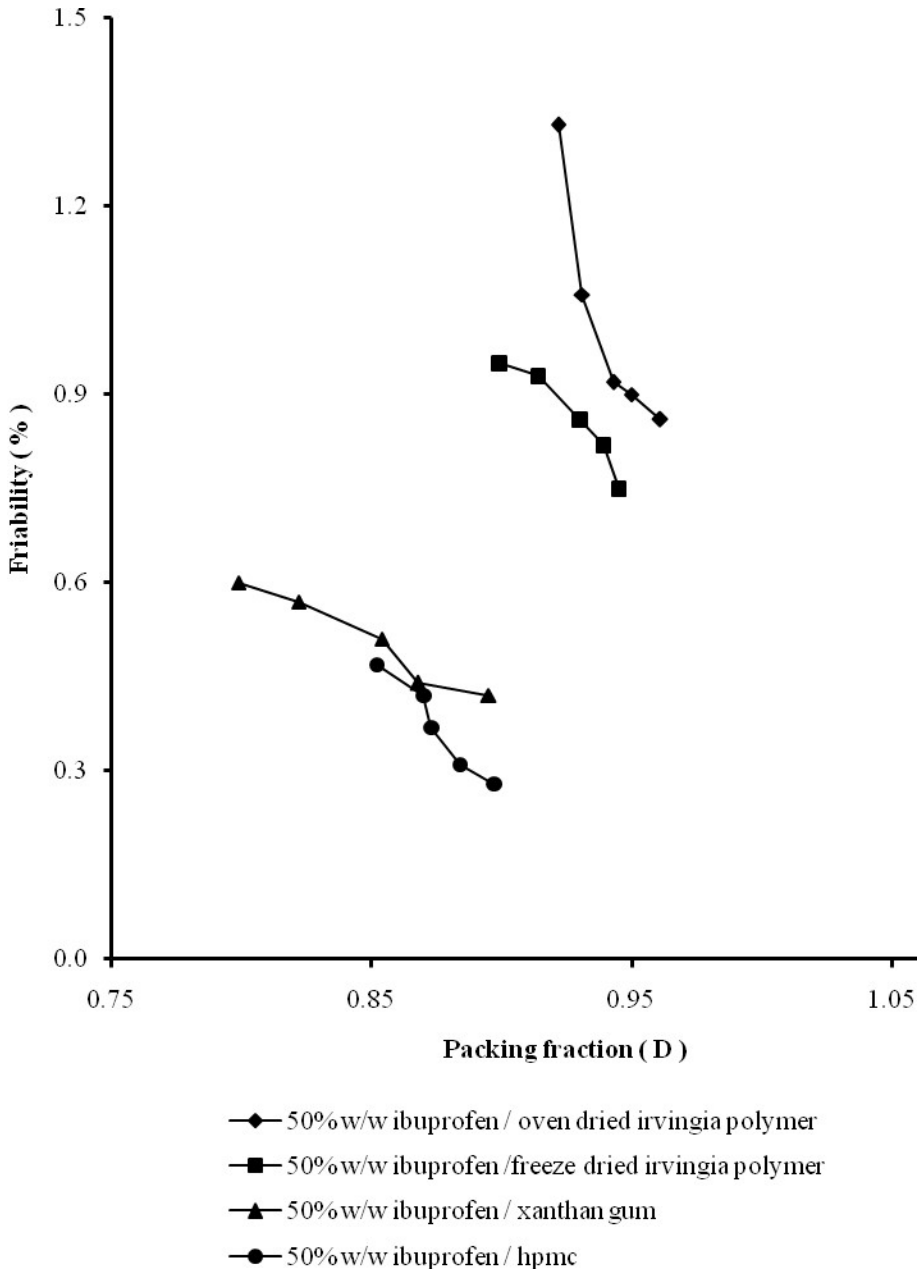


Figure 4.13. Friability versus packing fraction plot for *Irvingia* kernel mucilage, xanthan gum and HPMC matrix tablet containing 50% w/w ibuprofen prepared by direct compression

Table 4.19. Values of friability (FR), crushing strength (CS) and CSFR of ibuprofen matrix tablets at relative density of 0.85 prepared by direct compression

Polymer	Ibuprofen Conc.	Crushing strength (N)	Friability (%)	CSFR
Oven dried *Irvingia*	10	47.50	0.74	63.33
	20	21.00	0.98	21.43
	30	17.00	1.28	13.28
	50	11.00	1.80	6.11
Freeze dried *Irvingia*	10	75.50	0.59	127.97
	20	66.00	0.75	88.00
	30	52.00	0.87	59.77
	50	34.00	1.05	32.38
Xanthan gum	10	340.00	0.05	6800.00
	20	290.00	0.16	1812.50
	30	250.00	0.40	625.00
	50	197.00	0.51	386.27
HPMC	10	348.00	0.00	Undefined
	20	316.00	0.12	2633.33
	30	272.00	0.33	824.24
	50	228.00	0.37	616.22

Table 4.20. Values of friability (FR), crushing strength (CS) and CSFR of ibuprofen matrix tablets at relative density of 0.90 prepared by direct compression

Polymer	Ibuprofen Conc.	Crushing strength (N)	Friability (%)	CSFR
Oven dried *Irvingia*	10	60.00	0.58	103.45
	20	46.00	0.84	54.76
	30	37.55	0.95	39.53
	50	34.90	1.33	26.24
Freeze dried *Irvingia*	10	108.00	0.36	300.00
	20	65.00	0.76	85.53
	30	59.50	0.82	72.56
	50	47.00	0.95	49.47
Xanthan gum	10	360.00	0.00	Undefined
	20	310.00	0.00	Undefined
	30	272.00	0.00	Undefined
	50	229.00	0.42	545.24
HPMC	10	380.00	0.00	Undefined
	20	350.00	0.00	Undefined
	30	290.00	0.00	Undefined
	50	240.00	0.00	Undefined

Table 4.21. Values of crushing strength of ibuprofen matrix tablets at different relative densities produced using direct compression method

Polymer	Conc. Of ibuprofen (% w/w)	Relative density (D)	Crushing strength (N)
Oven dried *Irvingia*	10	0.846	45.90 ± 0.63
		0.864	54.40 ± 0.42
		0.888	55.70 ± 0.28
		0.897	60.54 ± 0.42
		0.913	62.80 ± 0.99
	20	0.893	41.15 ± 0.40
		0.903	48.21 ± 0.61
		0.918	53.89 ± 0.55
		0.929	55.27 ± 0.54
		0.938	59.96 ± 0.23
	30	0.900	37.55 ± 0.98
		0.913	43.53 ± 0.16
		0.926	50.43 ± 0.49
		0.932	52.32 ± 0.28
		0.946	57.00 ± 1.27
	50	0.922	34.90 ± 1.56
		0.932	43.30 ± 0.85
		0.942	46.73 ± 0.72
		0.949	48.18 ± 0.91
		0.960	52.67 ± 1.71
Freeze dried *Irvingia*	10	0.842	68.22 ± 1.15
		0.861	74.34 ± 0.79
		0.873	78.24 ± 0.93
		0.879	81.70 ± 0.42
		0.888	96.27 ± 1.37
	20	0.887	60.26 ± 0.61
		0.904	66.95 ± 0.78
		0.922	73.82 ± 0.26
		0.926	79.25 ± 0.64
		0.936	86.40 ± 1.64

Table 4.21. cont.

Polymer	Conc. Of ibuprofen (% w/w)	Relative density (D)	Crushing strength (N)
Freeze dried *Irvingia*	30	0.884	54.83 ± 0.61
		0.906	60.95 ± 2.04
		0.923	65.55 ± 1.29
		0.932	70.75 ± 1.34
		0.942	76.67 ± 0.55
	50	0.898	46.04 ± 0.52
		0.912	53.96 ± 0.34
		0.933	57.69 ± 0.69
		0.942	63.47 ± 0.81
		0.947	67.02 ± 0.31
Xanthan gum	10	0.746	282.80 ± 0.92
		0.774	290.80 ± 1.56
		0.790	304.48 ± 0.24
		0.813	329.00 ± 0.84
		0.848	336.00 ± 0.65
	20	0.767	136.15 ± 0.74
		0.780	240.10 ± 1.56
		0.808	256.23 ± 0.24
		0.822	277.15 ± 0.35
		0.857	293.30 ± 1.56
	30	0.789	185.70 ± 1.13
		0.812	205.65 ± 1.77
		0.829	249.35 ± 0.07
		0.848	253.15 ± 0.78
		0.880	262.80 ± 0.57
	50	0.798	167.55 ± 2.47
		0.827	180.50 ± 4.38
		0.853	199.60 ± 2.26
		0.866	219.20 ± 0.28
		0.893	225.95 ± 0.92

Table 4.21. cont.

Polymer	Conc. Of ibuprofen (% w/w)	Relative density (D)	Crushing strength (N)
HPMC	10	0.817	328.01 ± 0.42
		0.825	330.00 ± 0.20
		0.831	336.00 ± 0.62
		0.835	340.40 ± 0.82
		0.853	348.28 ± 0.44
	20	0.820	280.80 ± 8.63
		0.825	290.35 ± 4.31
		0.835	299.95 ± 6.01
		0.844	314.45 ± 3.18
		0.854	318.30 ± 0.35
	30	0.846	242.75 ± 4.31
		0.863	267.70 ± 2.55
		0.873	273.20 ± 2.26
		0.880	279.50 ± 1.56
		0.886	281.45 ± 6.01
	50	0.849	201.25 ± 5.44
		0.867	209.95 ± 1.77
		0.874	230.50 ± 4.24
		0.886	234.70 ± 3.96
		0.897	239.90 ± 6.51

Representative graphs of crushing strength versus packing fraction (relative desnsity) for 20% and 50% w/w ibuprofen-polymer matrices are displayed in Figure 4.14 and 4.15. Crushing strength values at relative density 0.85 and 0.90 of ibuprofen-polymer matrices are included in Tables 4.19 and 4.20 respectively.

4.3.5 Effect of drug concentration on the mechanical and drug release properties of ibuprofen-polymer matrices

The results of drug concentration effect on the tablet strength and drug release properties of ibuprofen-polymer matrices are shown in Table 4.22. Representative plots of the effect of drug concentration on the drug release profile of ibuprofen from ibuprofen-polymer matrices containing 20 and 50% w/w ibuprofen are presented in the Figures 4.16, 4.17 and 4.18.

4.3.6 Effect of excipient on the mechanical and drug release properties of ibuprofen-polymer matrices

The values of excipient effect on the tablet strength and drug release profile of ibuprofen-polymer matrix tablets are given in Table 4.23

4.3.7 Effect of polymer kind on the mechanical properties and drug release profile of ibuprofen-*Irvingia* kernel mucilage matrices

The results of mucilage type effect on the mechanical properties and drug release profile of ibuprofen-*Irvingia* kernel mucilage are presented in Table 4.24 and 4.25. Representative plots for the effect of polymer type on ibuprofen release profile from oven and freezed dried *Irvingia* kernel mucilage containing 20% and 40% w/w of xanthan gum and HPMC are displayed in Figures 4.19 and 4.20.

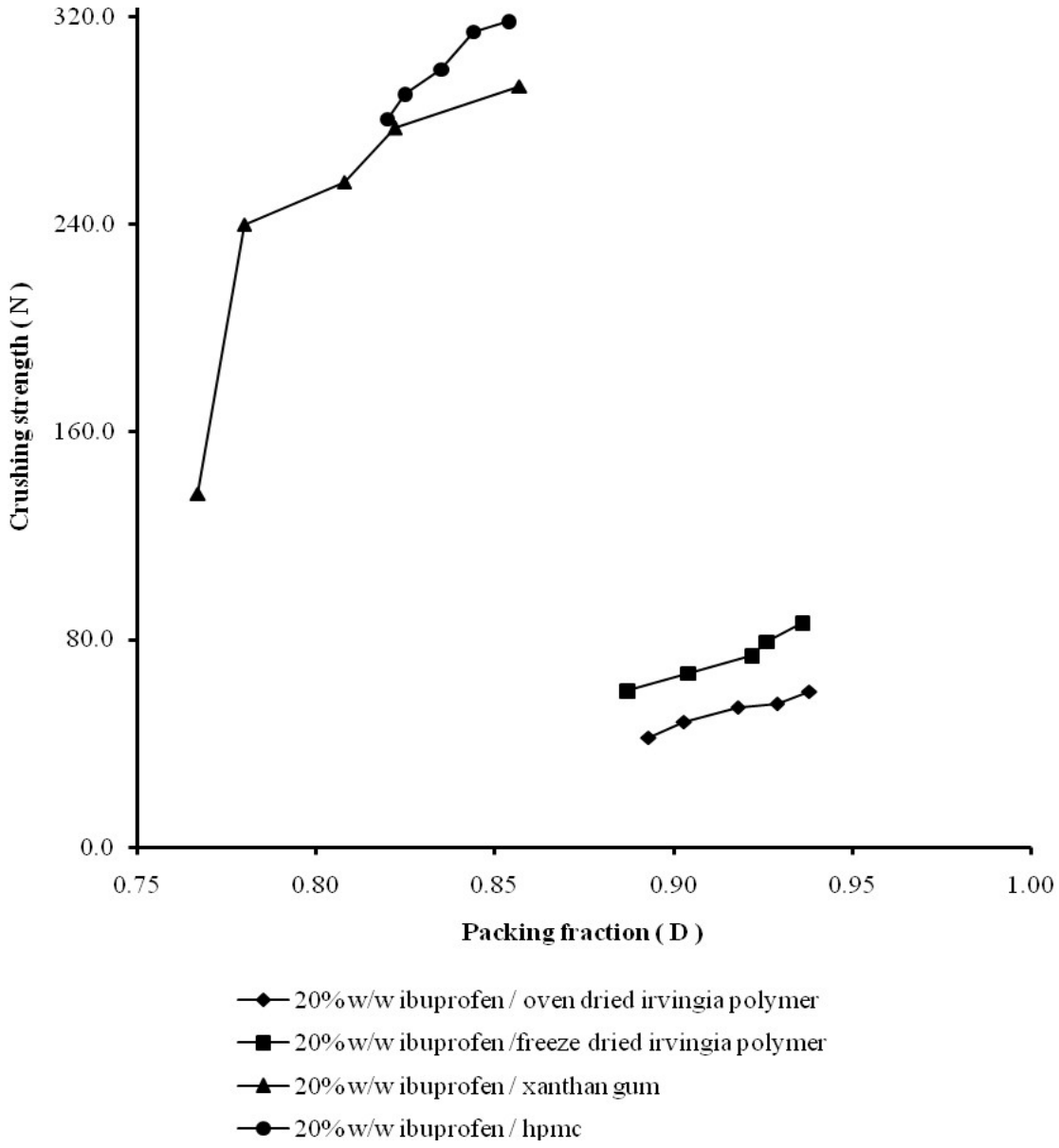


Figure 4.14. Crushing strength versus packing fraction plot for *Irvingia* kernel mucilage, xanthan gum and HPMC matrix tablet containing 20% w/w ibuprofen prepared by direct compression.

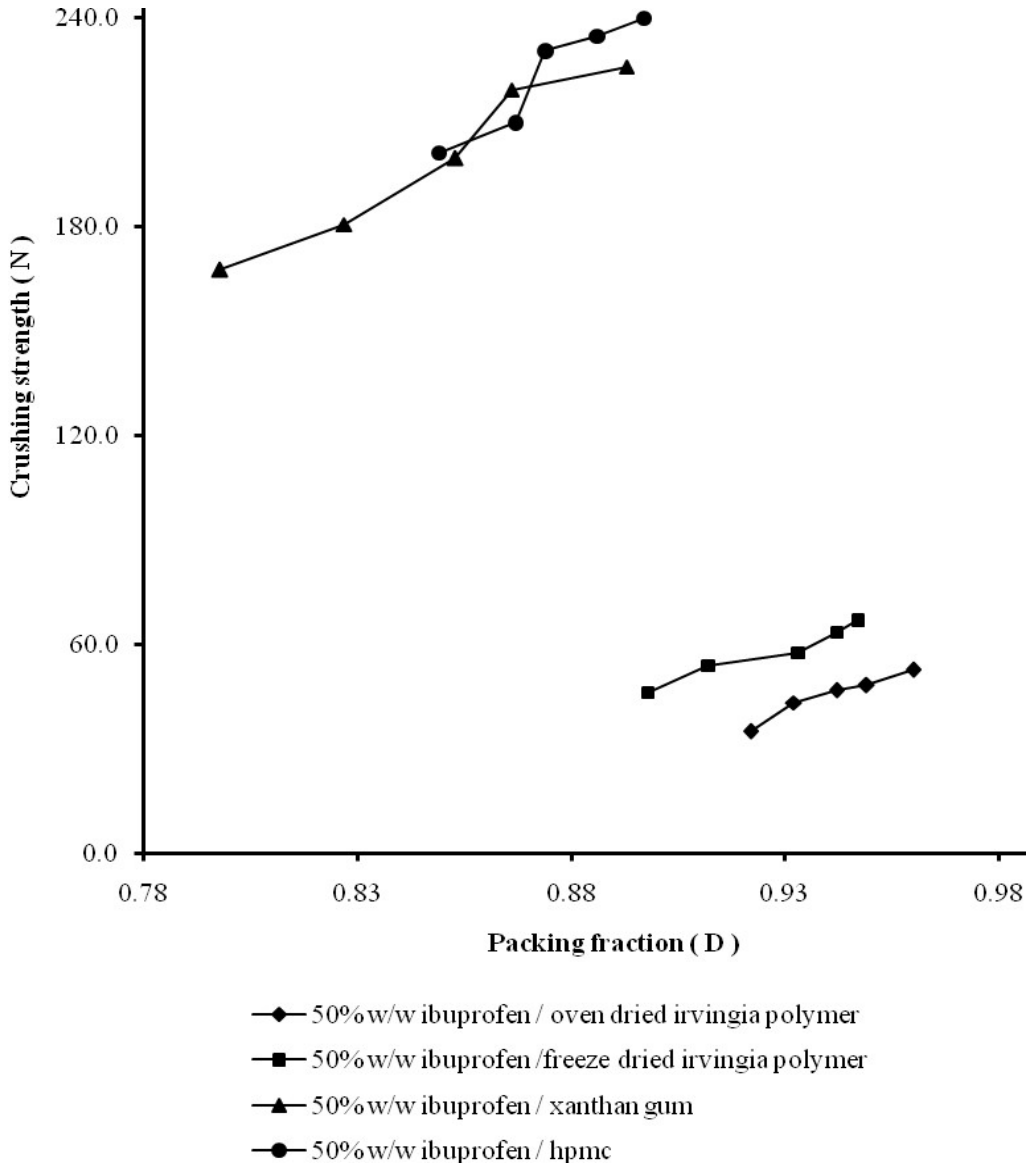


Figure 4.15. Crushing strength versus packing fraction plot for *Irvingia* kernel mucilage, xanthan gum and HPMC matrices containing 50% w/w ibuprofen made using direct compression.

Table 4.22. Drug concentration effect on the mechanical and drug release properties of ibuprofen matrices

Polymer	Ibuprofen Conc.(%w/w)	Crushing strength (N)	Friability (%)	CSFR	t_{25}(h)
Oven dried	10	15.33±0.15	0.87±0.00	17.62	3.25
Irvingia	20	10.00±0.26	0.94±0.03	10.64	2.30
	30	8.67±0.35	1.06±0.07	8.18	1.90
	50	7.33±0.25	2.79±0.47	2.63	1.05
Freeze dried	10	18.33±0.46	0.74±0.00	24.47	3.60
Irvingia	20	12.00±0.36	0.82±0.07	14.63	3.40
	30	9.00±0.10	0.89±0.08	10.11	2.70
	50	8.67±0.31	1.66±0.20	5.22	1.95
Xanthan gum	10	73.67±0.56	0.20±0.00	368.35	5.75
	20	55.66±0.97	0.34±0.03	163.74	4.20
	30	52.33±0.38	0.35±0.33	149.51	3.90
	50	47.00±0.89	0.42±0.42	111.90	3.65
HPMC	10	91.33±0.64	0.00±0.00	91.33	3.70
	20	69.68±0.25	0.24±0.00	290.29	2.70
	30	60.00±0.40	0.28±0.15	214.29	2.25
	50	54.69±0.42	0.34 ±0.07	160.79	1.80

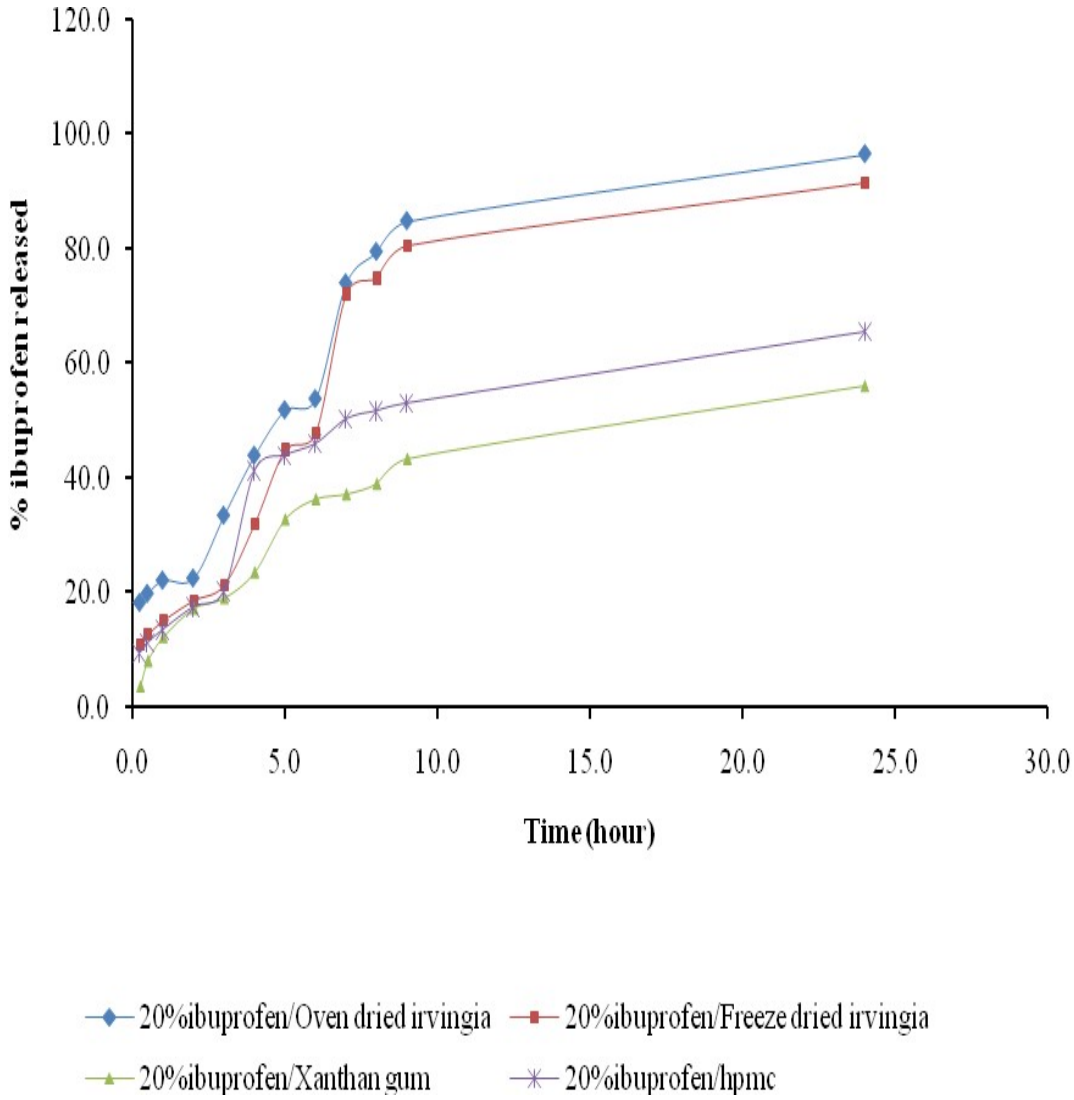


Figure 4.16. Release profile of ibuprofen from *Irvingia* kernel mucilage, xanthan gum and HPMC matrices containing 20% w/w ibuprofen

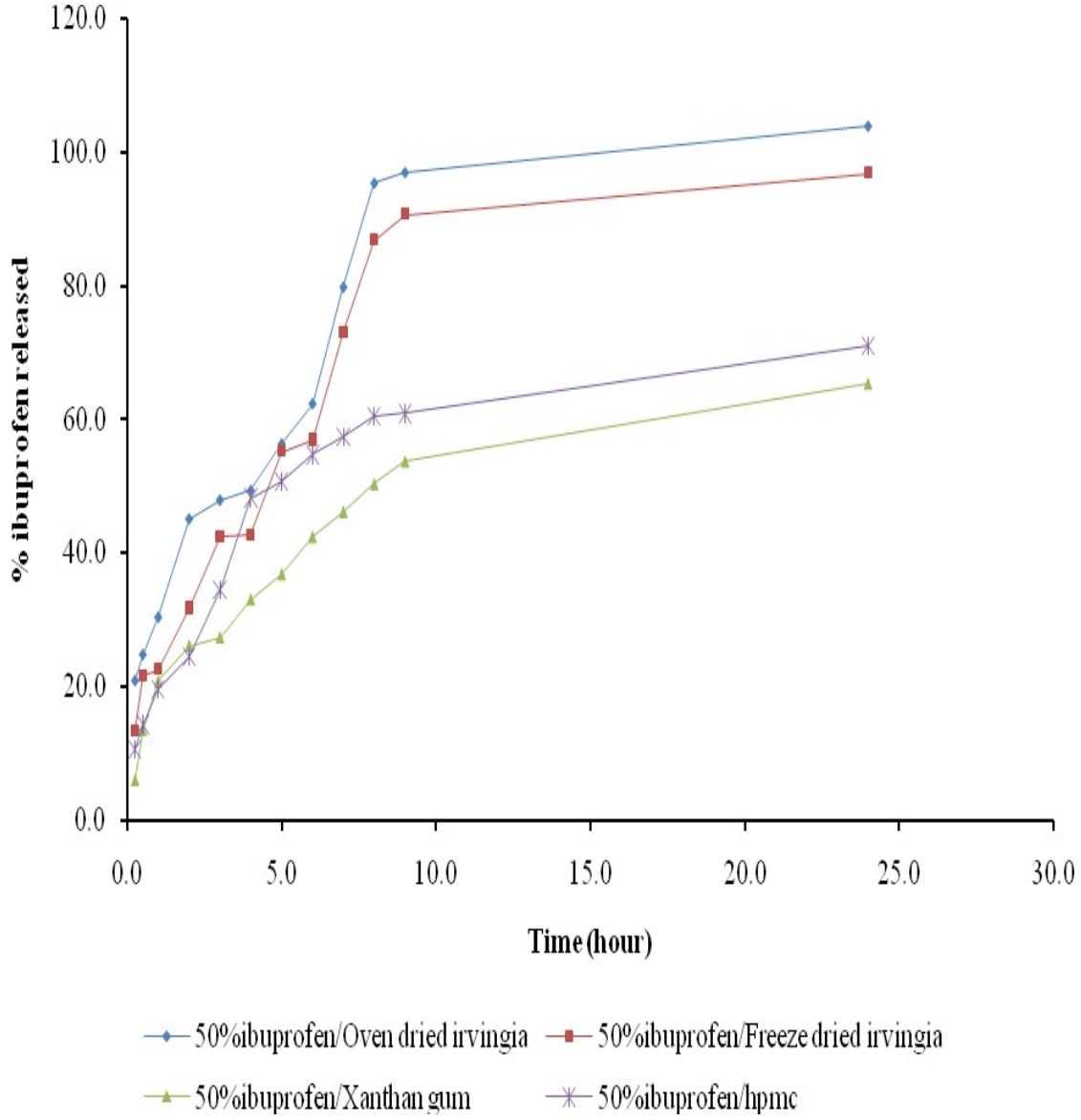


Figure 4.17. Release profile of ibuprofen from *Irvingia* kernel mucilage, xanthan gum and HPMC matrices containing 50% w/w ibuprofen

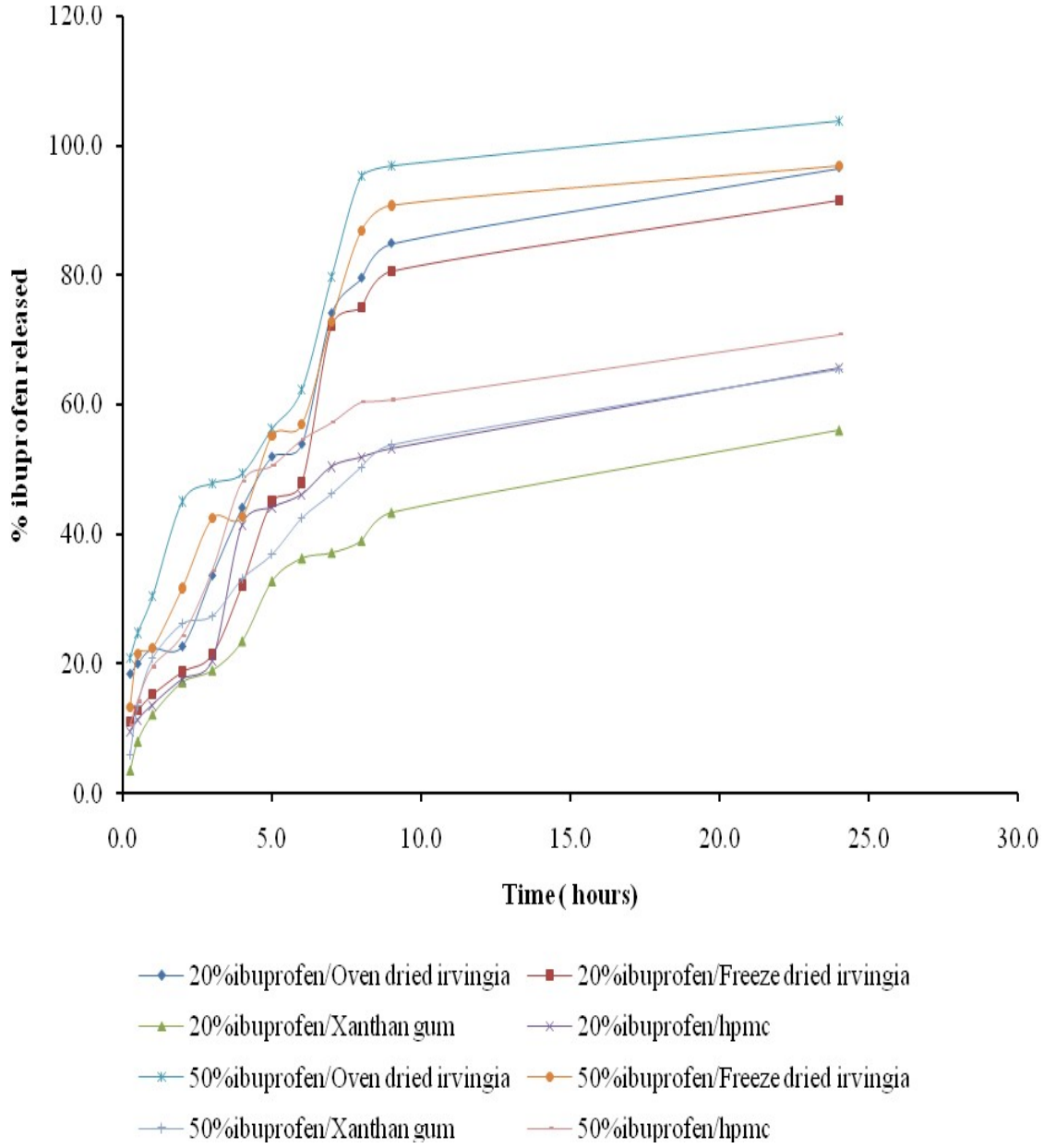


Figure 4.18. Concentration effect on the drug release profile of ibuprofen-*Irvingia* kernel mucilage, xanthan gum and HPMC matrices

Table 4.23. Effect of excipient on the mechanical and drug release properties of ibuprofen matrices

Polymer	Composition (drug- mucilage-excipient)	Crushing strength (N)	Friability (%)	CSFR	t_{25}(h)	t_{50}(h)
Oven dried *Irvingia*	1:3:1 Avicel	41.00±0.46	0.40±0.05	102.50	0.50	2.2
	1:3:1 Lactose	45.00±0.75	0.36±0.04	125.00	0.55	2.4
	1:3:1 Dicalcium Phosphate	51.67±0.80	0.35±0.03	147.62	0.85	2.8
Freeze dried *Irvingia*	1:3:1 Avicel	44.00±0.43	0.38±0.03	115.79	0.70	3.15
	1:3:1 Lactose	53.00±0.66	0.32±0.04	165.63	0.70	3.30
	1:3:1 Dicalcium Phosphate	63.33±0.32	0.27±0.02	234.57	2.20	3.50
Xanthan gum	1:3:1 Avicel	73.06±0.78	0.21±0.14	347.62	4.75	5.67
	1:3:1 Lactose	78.00±0.26	0.18±0.02	433.33	4.70	5.67
	1:3:1 Dicalcium Phosphate	83.67±0.40	0.14±0.06	597.62	4.80	5.85
HPMC	1:3:1 Avicel	87.33±0.85	0.13±0.04	671.77	4.30	5.65
	1:3:1 Lactose	90.20±0.76	0.09±0.00	1003.67	4.20	5.75
	1:3:1 Dicalcium Phosphate	98.67±0.31	0.00±0.00	98.67	4.65	5.85

Table 4.24. Effect of polymer on the mechanical and drug release properties of ibuprofen-*Irvingia* kernel mucilage matrix tablets

Polymer	*Irvingia* mucilage	Composition (drug- *Irvingia* mucilage-HPMC)	Crushing Strength (N)	Friability (%)	CSFR	t_{25}(hr)	t_{50}(h)	% drug released after 9 h
HPMC	Oven dried *Irvingia*	2:7:1	25.00±0.40	0.88±0.18	28.41	1.18	4.0	68.96
		2:6:2	14.00±0.60	4.67±0.11	3.00	1.20	4.4	66.16
		2:5:3	12.00±0.80	4.85±0.18	2.47	1.33	6.1	64.95
		2:4:4	17.50±1.66	1.95±0.10	8.97	1.38	6.6	60.93
	Freeze dried *Irvingia*	2:7:1	26.33±0.21	0.83±0.03	31.73	1.10	4.2	67.99
		2:6:2	19.67±0.97	1.97±0.24	9.98	1.30	5.5	66.04
		2:5:3	17.33±0.70	2.19±0.25	7.91	1.40	6.4	61.91
		2:4:4	18.67±0.31	2.03±0.04	9.20	1.55	7.3	58.38

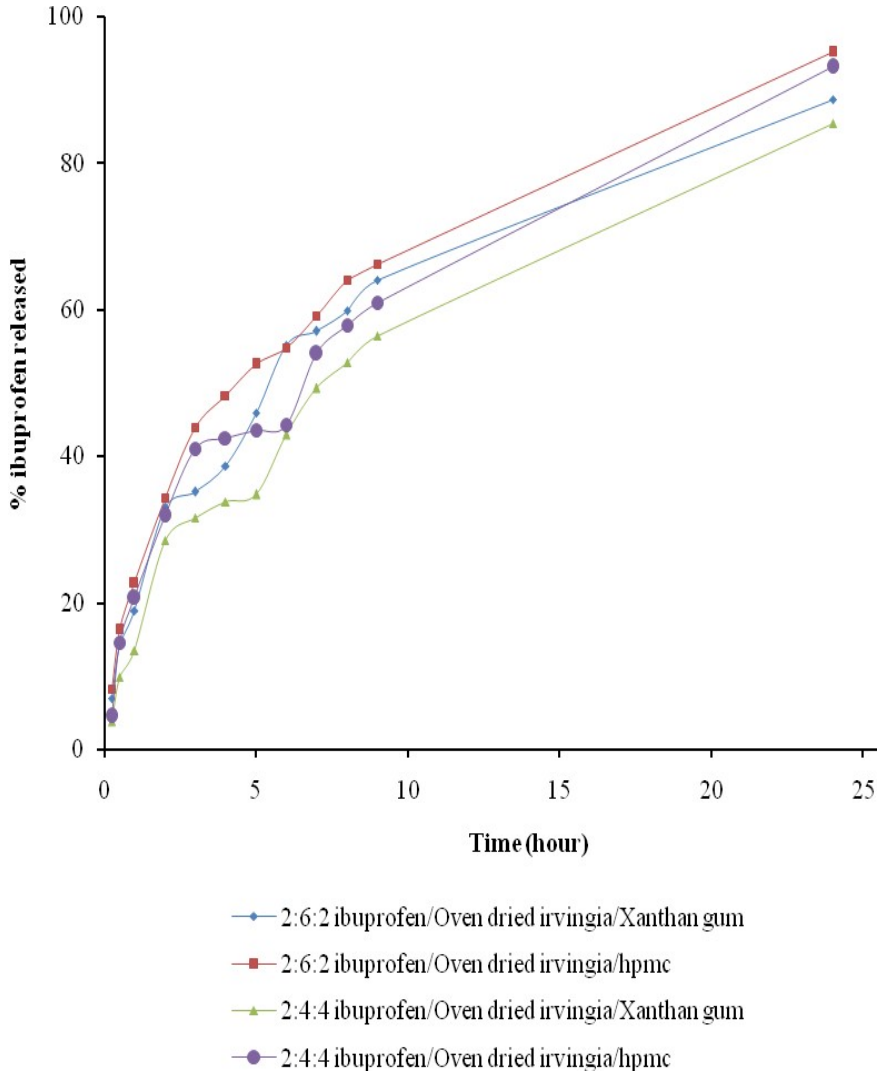


Figure 4.19. Effect of polymer type on drug release profile of ibuprofen-oven dried *Irvingia* kernel matrices

Table 4.25. Effect of polymer on the mechanical and drug release properties of ibuprofen-*Irvingia* kernel mucilage matrix tablets

Polymer	*Irvingia* mucilage	Composition (drug-*Irvingia* mucilage-Xanthan gum)	Crushing Strength (N)	Friability (%)	CSFR	t_{25}(h)	t_{50}(h)	% drug released after 9 h
Xanthan gum	Oven dried	2:7:1	17.00±0.36	0.76±0.00	22.37	1.30	4.4	66.89
	Irvingia	2:6:2	12.33±0.50	1.33±0.14	9.27	1.50	5.4	64.09
		2:5:3	8.00±0.35	0.78±0.02	10.26	1.70	6.5	58.26
		2:4:4	14.67±0.31	1.80±0.17	8.15	1.80	7.2	56.43
	Freeze dried *Irvingia*	2:7:1	18.67±0.15	0.27±0.07	69.14	1.30	5.3	65.92
		2:6:2	13.00±0.40	0.56±0.00	23.21	1.50	5.7	62.92
		2:5:3	10.33±0.25	0.43±0.01	24.03	1.60	7.0	56.07
		2:4:4	15.34±0.57	1.04±0.03	14.74	1.80	7.8	55.34

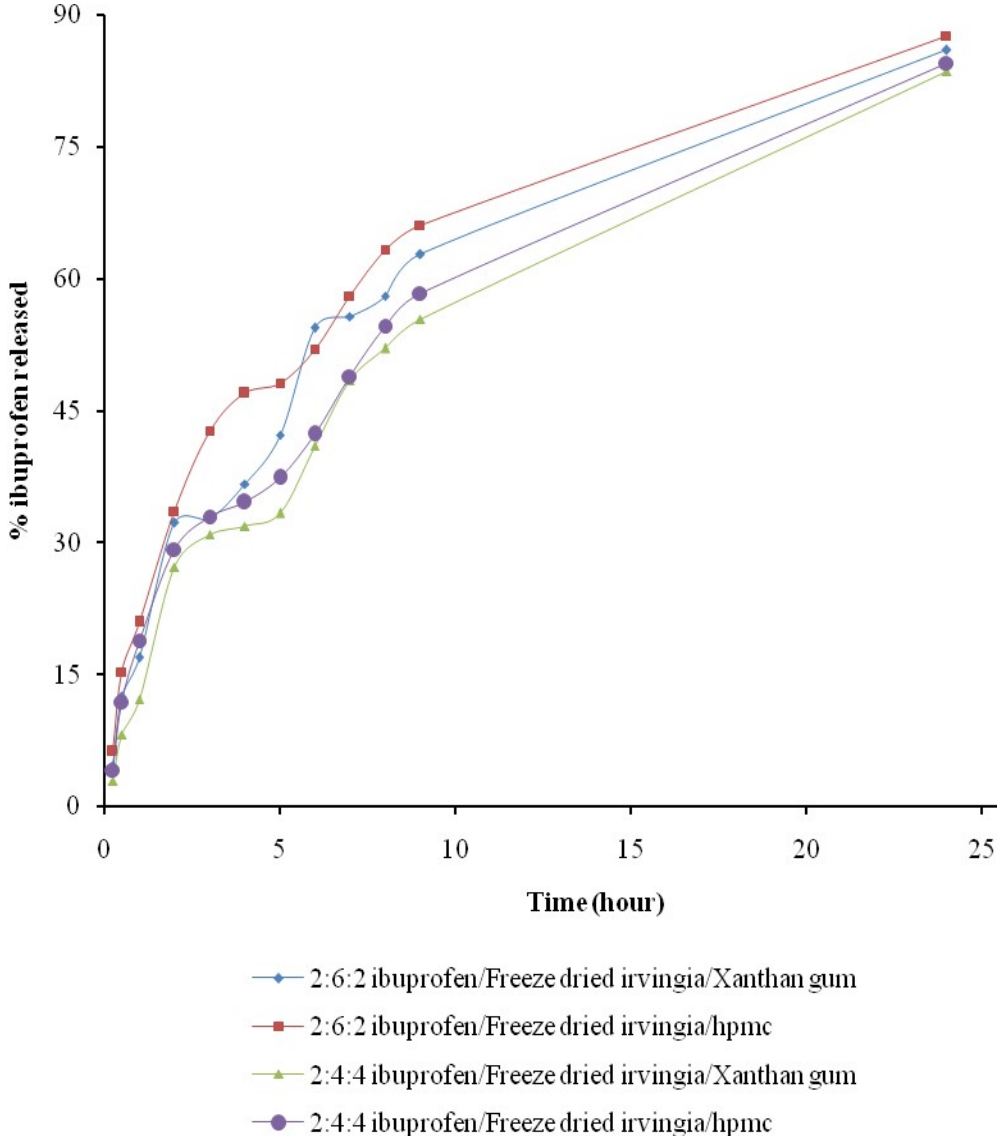


Figure 4.20. Effect of polymer type on drug release profile of ibuprofen-freeze dried *Irvingia* kernel matrices

4.3.8 Drug release parameters

The drug release parameters of ibuprofen-polymer matrices containing various concentrations of ibuprofen and different tablet excipients from various release models are shown in Tables 4.26 and 4.27. The release parameters of ibuprofen-*Irvingia* kernel mucilage matrices containing HPMC and xanthan gun from different drug release models are given in Tables 4.28 and 4.29.

4.4 *Irvingia* kernel mucilage as matrix system for wet granulation

The results of granule size distribution for ibuprofen-oven dried *Irvingia* mucilage formulations composing of 10, 20, 30 and 50% w/w ibuprofen are given in Table 4.30. Plot of cumulative weight percent oversize against granule size for these formulations is displayed in Figure 4.21. Values of granule size distribution of ibuprofen-freeze dried *Irvingia* kernel mucilage formulations are presented in Table 4.31. The plot of cumulative weight percent oversize versus granule size for these formulations is shown in Figure 4.22. Results of the mean granule sizes of the different formulations of ibuprofen and *Irvingia* kernel mucilage (oven and freeze dried) are stated in Table 4.32 while Figure 4.23 show graph of ibuprofen concentration versus mean granule size of the ibuprofen-*Irvingia* kernel mucilage granules.

The granules densities of ibuprofen-*Irvingia* kernel mucilage formulations are included in Table 4.10. Values of the loose bulk densities and relative density (D_o) of the formulations are presented in Table 4.33

Table 4.26. Release parameters of ibuprofen-polymer matrix formulations containing different concentration of ibuprofen obtained from different release models

Polymer	Ibuprofen Conc.	Zero Order		First Order		Higuchi		Hixson Crowell		Korsemeyer Release Exponent		
	(%w/w)	$k_o(h^{-1})$	r^2	K	r^2	k_h	r^2	k	r^2	k	r^2	N
Oven dried	10	3.74	0.685	0.05	0.855	22.17	0.842	1.33	0.850	0.53	0.882	1.28
Irvingia	20	3.69	0.722	0.06	0.947	21.74	0.877	1.16	0.862	0.44	0.882	1.41
	30	3.75	0.719	0.08	0.972	22.14	0.876	1.16	0.868	0.43	0.891	1.43
	50	2.94	0.680	0.03	0.764	17.66	0.858	1.03	0.913	0.40	0.939	1.42
Freeze dried	10	3.77	0.688	0.04	0.822	22.17	0.833	1.38	0.841	0.57	0.880	1.21
Irvingia	20	3.83	0.705	0.05	0.875	22.58	0.853	1.36	0.856	0.56	0.890	1.25
	30	3.83	0.711	0.05	0.900	22.67	0.870	1.34	0.889	0.54	0.920	1.30
	50	3.01	0.631	0.03	0.662	18.38	0.823	1.18	0.906	0.48	0.934	1.32
Xanthan gum	10	2.06	0.843	0.03	0.898	11.81	0.957	1.22	0.968	0.67	0.980	0.86
	20	1.93	0.712	0.01	0.778	11.78	0.910	1.16	0.972	0.59	0.956	1.03
	30	1.96	0.679	0.01	0.740	12.09	0.889	1.12	0.968	0.56	0.951	1.10
	50	1.69	0.690	0.01	0.751	10.38	0.900	0.99	0.968	0.49	0.937	1.12
HPMC	10	1.91	0.670	0.01	0.713	11.73	0.867	1.01	0.939	0.47	0.952	1.16
	20	1.90	0.466	0.01	0.512	12.79	0.729	1.10	0.891	0.49	0.891	1.25
	30	1.92	0.461	0.01	0.508	13.02	0.725	1.10	0.895	0.48	0.895	1.28
	50	1.55	0.439	0.01	0.477	10.70	0.717	0.10	0.916	0.47	0.905	1.26

Table 4.27. Release parameters of ibuprofen-polymer matrix formulations containing different tablet excipients obtained from different release models

Polymer	Composition (drug-mucilage-excipient) 1:3:1	Zero order		First Order		Higuchi		Hixson Crowell		Korsemeyer Release Exponent		
		$k_o(h^{-1})$	r^2	K	r^2	k_h	r^2	k	r^2	K	r^2	N
Oven dried *Irvingia*	Avicel	3.37	0.785	0.08	0.982	22.37	0.950	1.36	0.988	0.49	0.988	1.49
	Lactose	3.47	0.688	0.08	0.946	22.64	0.887	1.36	0.962	0.49	0.949	1.48
	Dicalcium Phosphate	3.40	0.698	0.08	0.929	23.20	0.888	1.55	0.954	0.58	0.946	1.34
Freeze dried *Irvingia*	Avicel	2.77	0.608	0.09	0.941	17.34	0.828	0.82	0.923	0.26	0.890	1.72
	Lactose	3.66	0.652	0.11	0.973	23.61	0.860	1.34	0.938	0.46	0.915	1.52
	Dicalcium Phosphate	3.44	0.519	0.95	0.958	22.09	0.748	1.19	0.861	0.40	0.851	1.58
Xanthan gum	Avicel	4.45	0.664	0.06	0.911	27.93	0.810	2.45	0.872	1.22	0.908	0.60
	Lactose	4.69	0.614	0.07	0.843	29.50	0.754	2.51	0.779	1.22	0.813	0.56
	Dicalcium Phosphate	4.58	0.588	0.06	0.739	29.01	0.733	2.49	0.782	1.22	0.827	0.57
HPMC	Avicel	4.49	0.625	0.07	0.831	28.46	0.779	2.37	0.877	1.14	0.916	0.71
	Lactose	4.45	0.623	0.08	0.874	28.52	0.793	2.25	0.883	1.01	0.913	0.86
	Dicalcium Phosphate	4.54	0.597	0.06	0.756	28.89	0.749	2.38	0.820	1.12	0.864	0.78

Table 4.28. Release parameters of ibuprofen-*Irvingia* mucilage matrices containing HPMC obtained from different release models

Irvingia Mucilage	Composition (drug-*Irvingia* mucilage-HPMC)	Zero Order		First Order		Higuchi		Hixson Crowell		Korsemeyer Release Exponent		
		$k_o(h^{-1})$	r^2	K	r^2	k_h	r^2	k	r^2	K	r^2	N
	HPMC											
Oven dried	2:7:1	3.37	0.782	0.05	0.995	20.01	0.964	1.24	0.993	0.50	0.972	1.37
Irvingia	2:6:2	3.37	0.805	0.05	0.993	19.81	0.974	1.26	0.997	0.52	0.974	1.34
	2:5:3	3.40	0.824	0.05	0.993	19.80	0.976	1.30	0.990	0.55	0.963	1.29
	2:4:4	3.37	0.850	0.05	0.986	19.34	0.978	1.33	0.977	0.59	0.928	1.24
Freeze dried	2:7:1	3.09	0.738	0.04	0.963	18.70	0.943	1.25	0.981	0.53	0.936	1.34
Irvingia	2:6:2	3.14	0.759	0.04	0.967	18.81	0.952	1.29	0.988	0.56	0.951	1.29
	2:5:3	3.12	0.799	0.03	0.964	18.31	0.959	1.28	0.983	0.56	0.958	1.25
	2:4:4	3.15	0.852	0.03	0.987	18.06	0.981	1.31	0.982	0.61	0.944	1.18

Table 4.29. Release parameters of ibuprofen-*Irvingia* mucilage matrices containing xanthan gum obtained from different release models

Irvingia Mucilage	Composition (drug-*Irvingia* mucilage-xanthan gum)	Zero Order		First Order		Higuchi		Hixson Crowell		Korsemeyer Release Exponent		
		$k_o(h^{-1})$	r^2	K	r^2	k_h	r^2	k	r^2	K	r^2	N
	Xanthan gum											
Oven dried	2:7:1	3.19	0.763	0.04	0.977	19.08	0.957	1.26	0.996	0.53	0.993	1.32
Irvingia	2:6:2	3.27	0.803	0.04	0.984	19.19	0.969	1.29	0.991	0.55	0.974	1.30
	2:5:3	3.23	0.850	0.04	0.992	18.61	0.983	1.27	0.986	0.56	0.975	1.24
	2:4:4	3.27	0.859	0.03	0.991	18.69	0.984	1.39	0.987	0.67	0.961	1.12
Freeze dried	2:7:1	3.15	0.761	0.04	0.966	18.85	0.954	1.32	0.987	0.58	0.945	1.27
Irvingia	2:6:2	3.25	0.790	0.04	0.970	19.14	0.960	1.38	0.984	0.62	0.951	1.20
	2:5:3	3.21	0.825	0.03	0.980	18.64	0.973	1.40	0.984	0.66	0.942	1.14
	2:4:4	3.25	0.854	0.03	0.987	18.62	0.980	1.45	0.986	0.71	0.955	1.07

Table 4.30. Size distribution of ibuprofen - oven dried *Irvingia* kernel mucilage granules

Sieve size (μm)	Cumulative weight % oversize			
Conc. of ibuprofen	10	20	30	50
1400	18.70	13.16	31.15	15.04
1000	47.06	38.98	50.42	46.83
710	65.33	58.99	70.62	72.07
500	78.81	78.12	80.69	85.29
355	86.95	87.26	88.01	92.20
250	94.59	94.63	94.93	96.31
0	100.00	100.00	100.00	100.00

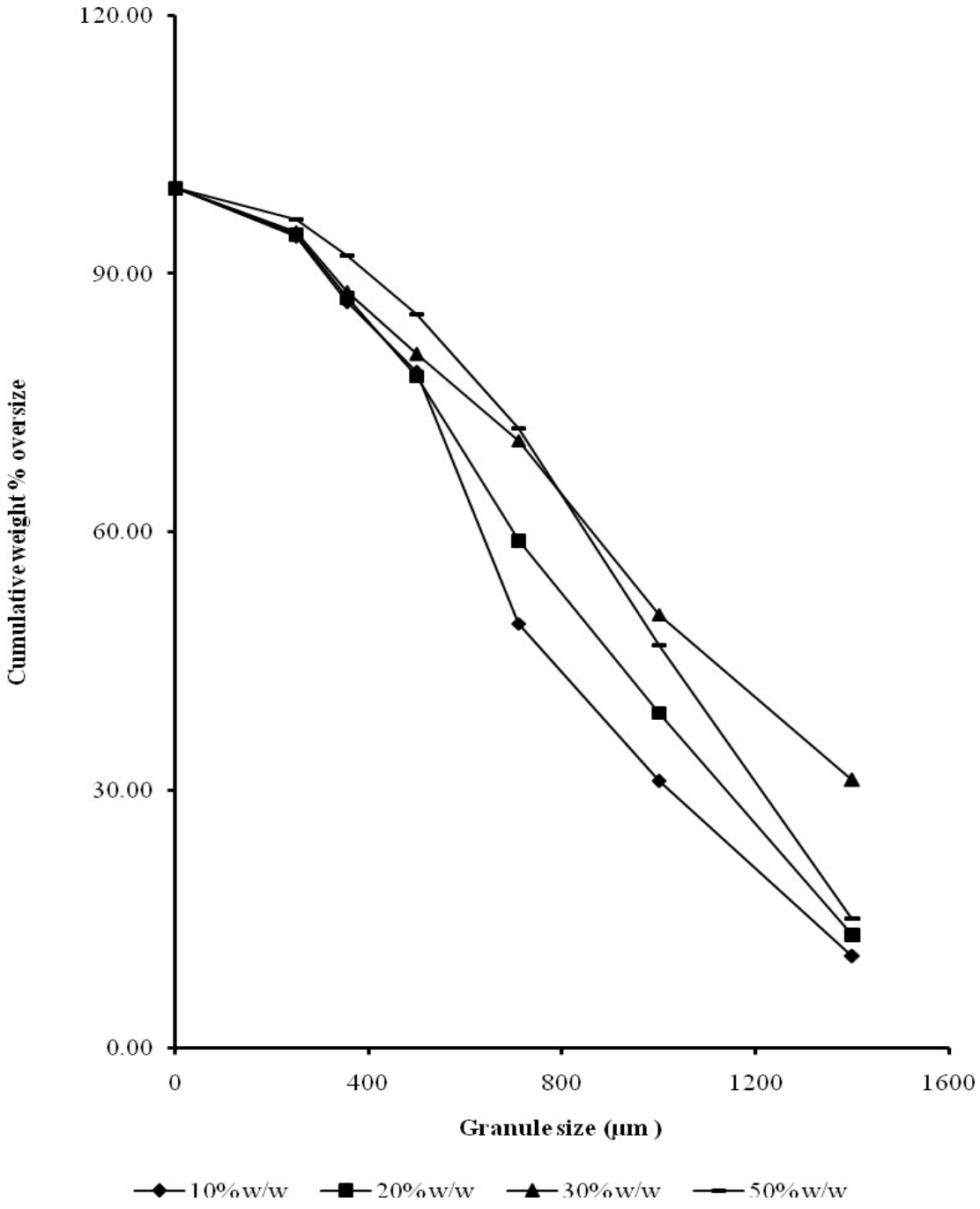


Figure 4.21. Cumulative weight % oversize versus granule size plots for oven dried *Irvingia* kernel mucilage granules containing different concentrations of ibuprofen

Table 4.31. Size distribution of ibuprofen-freeze dried *Irvingia* kernel mucilage granules

Sieve size (μm)	Cumulative weight % oversize			
Conc. of ibuprofen	10	20	30	50
1400	6.34	13.68	19.99	26.28
1000	33.01	46.23	52.12	56.62
710	52.02	63.84	66.23	70.65
500	66.88	76.60	77.36	81.73
355	78.27	84.99	88.98	88.71
250	89.66	92.20	91.15	93.74
0	100.00	100.00	100.00	100.00

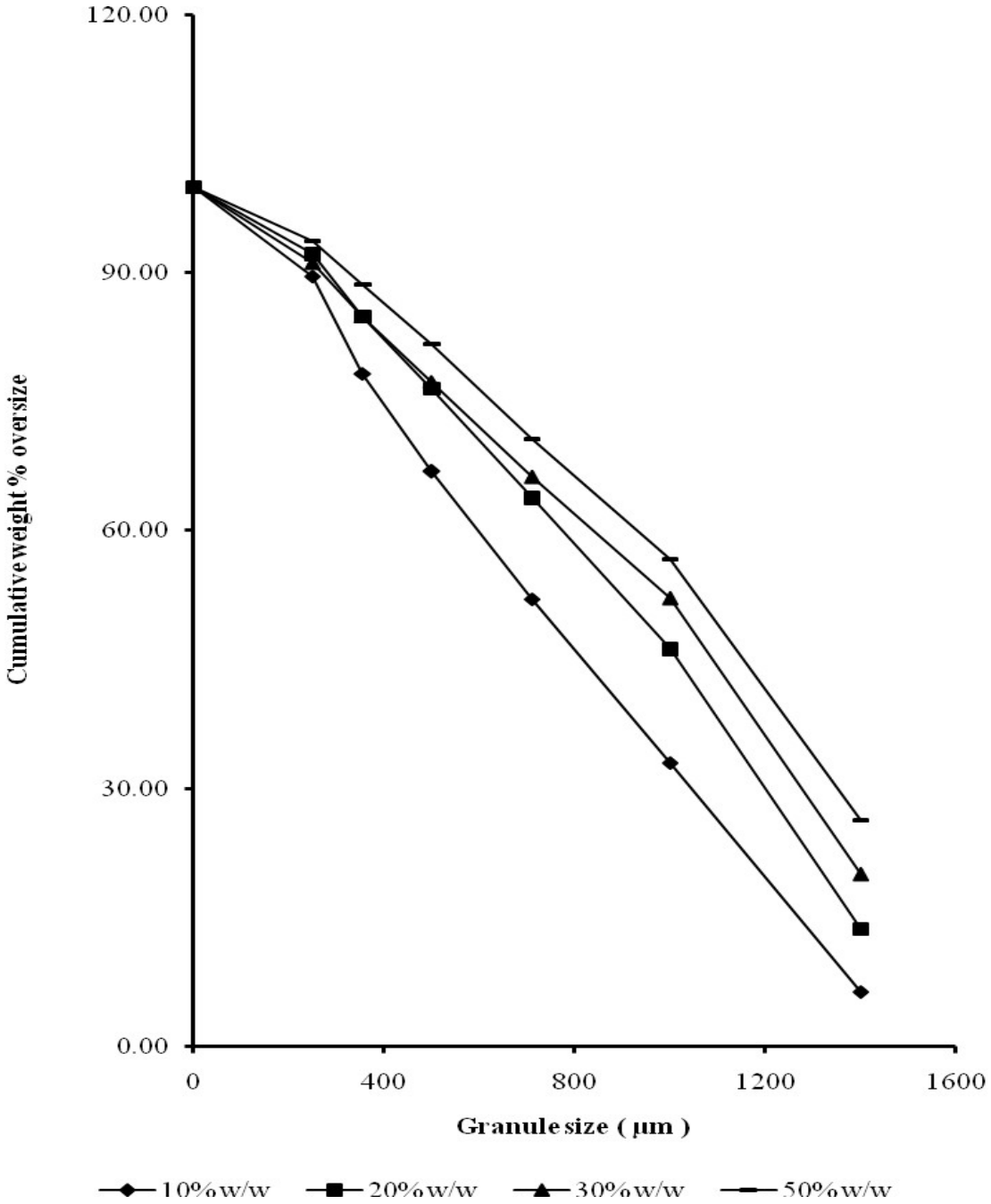


Figure 4.22. Cumulative weight % oversize versus granule size plots for freeze dried *Irvingia* kernel mucilage granules containing different concentrations of ibuprofen

Table 4.32. Mean granule size (G) for ibuprofen - *Irvingia* kernel mucilage granules

Mucilage	Conc. of Ibuprofen	Mean granule size (G) (μm)
Oven dried *Irvingia*	10	700
	20	820
	30	1000
	50	960
Freeze dried *Irvingia*	10	720
	20	920
	30	1020
	50	1090

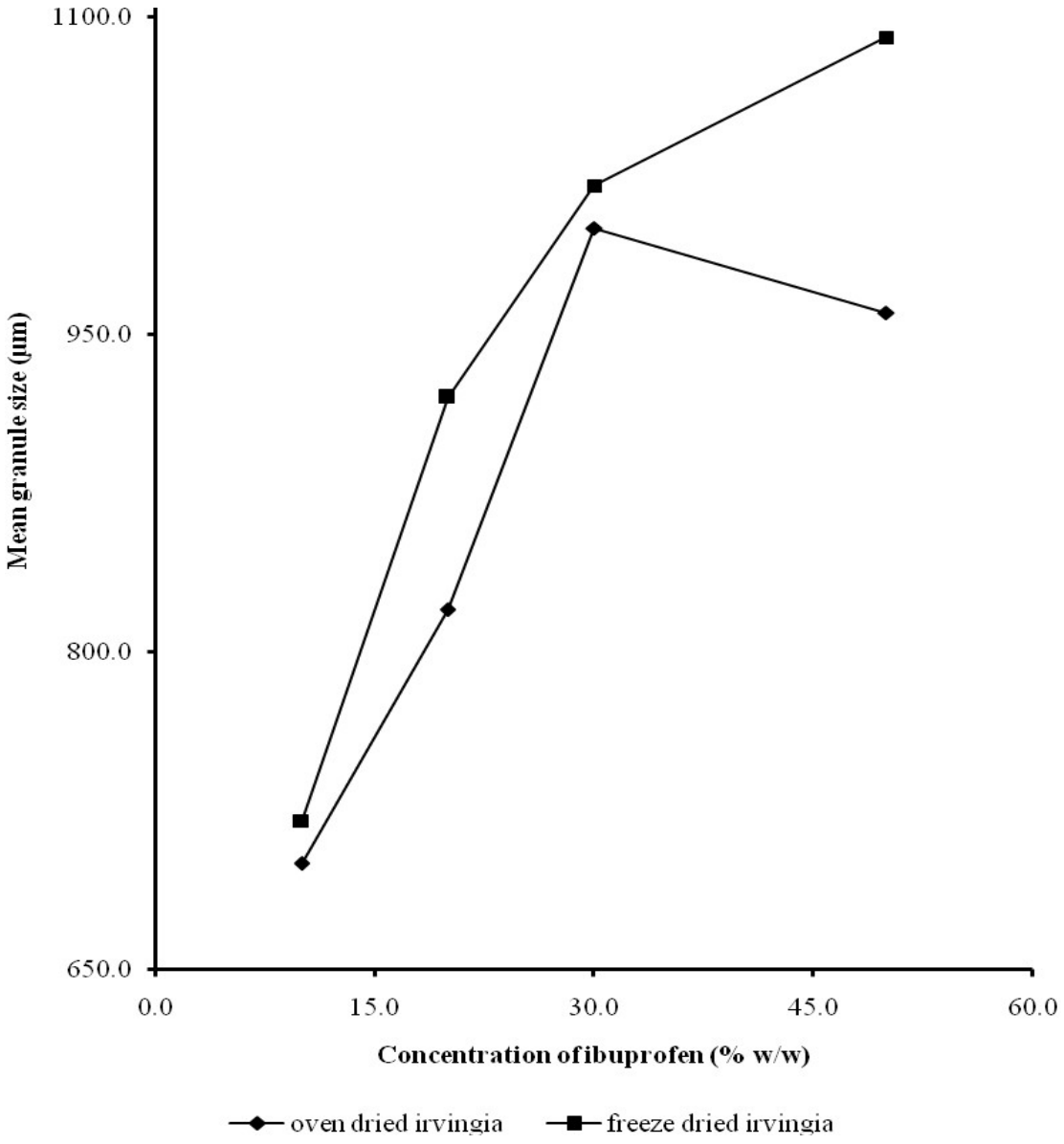


Figure 4.23 Concentration of ibuprofen versus mean granule size plots for *Irvingia* kernel mucilage granules containing different concentration of ibuprofen

Table 4.33. Values of loose bulk density (gcm^{-3}) and relative density (D_0) of ibuprofen - mucilage mixtures for wet granulation

Mucilage	Ibuprofen conc. (%w/w)	Loose bulk density (gcm^{-3})	Relative density (D_0)
Oven dried *Irvingia*	10	0.269	0.215
	20	0.257	0.213
	30	0.250	0.207
	50	0.237	0.198
Freeze dried *Irvingia*	10	0.284	0.222
	20	0.257	0.209
	30	0.247	0.201
	50	0.235	0.195
Xanthan gum	10	-	-
	20	-	-
	30	-	-
	50	-	-
HPMC	10	-	-
	20	-	-
	30	-	-
	50	-	-

4.4.1 Compressional characteristics of ibuprofen-*Irvingia* kernel mucilage matrices prepared by wet granulation

The relative densities (packing fraction) of ibuprofen-*Irvingia* kernel mucilage matrices at different compression pressure prepared by wet granulation are shown in Table 4.34. These results were used for Heckel plots of Ln[1/(1-D)] versus compression pressure. Representative Heckel plots for 20% and 50% w/w ibuprofen-*Irvingia* kernel mucilage formulations are displayed in Figures 4.24, 4.25, 4.26 and 4.27. The values of K and A, being the slope of the linear region and the intercept of its extrapolation respectively were determined. The mean yield values, $P_y$were calculated as the reciprocal of K. The paramaters gathered from these Heckel graphs are included in Table 4.13.

The results of the bulk volume at zero applied pressure, V_o of ibuprofen-*Irvingia* kernel mucilage formulations and the volume after compression, V_p, that is volume change of the matrix tablets of the formulations with compression pressure are stated in Table 4.35. The values were use for Kawakita plots of P/C against P and representative Kawakita plots for 20% and 50% w/w ibuprofen-*Irvingia* kernel mucilage are presented in Figures 4.28 and 4.29.

The values of the slope and intercept **a** and **ab** respectively of the straight line graphs were determined. The outset relative densities of the formulations, D_i, were computed by subtracting the values of **a** from 1 (i.e 1-**a**). P_k values of the formulations were derived as the inverse of values of **b**. Both values of D_i and P_k of the ibuprofen-*Irvingia* kernel matrices produced using wet granulation are included in Table 4.13.

Table 4.34. Values of applied pressure (MNm^{-2}), relative density of tablet (D) and Ln[1/(1-D)] for ibuprofen matrices produced using wet granulation process

Mucilage	Conc. of ibuprofen (%w/w)	Applied pressure (MNm^{-2})	Relative density (D)	Ln[1/(1-D)]
Oven dried *Irvingia*	10	14.14	0.815	1.686
		28.28	0.822	1.723
		42.42	0.832	1.784
		56.56	0.835	1.804
		70.70	0.841	1.841
		84.84	0.851	1.906
		113.13	0.866	2.011
		141.41	0.877	2.099
		169.69	0.884	2.151
	20	14.14	0.842	1.842
		28.28	0.849	1.893
		42.42	0.859	1.959
		56.56	0.867	2.017
		70.70	0.891	2.217
		84.84	0.897	2.275
		113.13	0.905	2.356
		141.41	0.909	2.399
		169.69	0.916	2.472
	30	14.14	0.865	2.005
		28.28	0.874	2.069
		42.42	0.879	2.110
		56.56	0.887	2.183
		70.70	0.893	2.235
		84.84	0.906	2.370
		113.13	0.913	2.438
		141.41	0.916	2.482
		169.69	0.925	2.590

Table 4.34. cont.

Mucilage	Conc. of ibuprofen (%w/w)	Applied pressure (MNm^{-2})	Relative density (D)	Ln[1/(1-D)]
Oven dried *Irvingia*	50	14.14	0.885	2.159
		28.28	0.895	2.252
		42.42	0.898	2.284
		56.56	0.907	2.375
		70.70	0.914	2.453
		84.84	0.921	2.533
		113.13	0.922	2.555
		141.41	0.925	2.584
		169.69	0.927	2.614
Freeze dried *Irvingia*	10	14.14	0.804	1.627
		28.28	0.809	1.654
		42.42	0.819	1.711
		56.56	0.824	1.740
		70.70	0.838	1.822
		84.84	0.845	1.862
		113.13	0.856	1.937
		141.41	0.863	1.986
		169.69	0.870	2.043
	20	14.14	0.830	1.771
		28.28	0.837	1.817
		42.42	0.846	1.870
		56.56	0.856	1.940
		70.70	0.875	2.075
		84.84	0.889	2.200
		113.13	0.898	2.278
		141.41	0.901	2.312
		169.69	0.905	2.351

Table 4.34. cont.

Mucilage	Conc. of ibuprofen (%w/w)	Applied pressure (MNm^{-2})	Relative density (D)	Ln[1/(1-D)]
Freeze dried *Irvingia*	30	14.14	0.854	1.922
		28.28	0.859	1.961
		42.42	0.866	2.007
		56.56	0.875	2.077
		70.70	0.879	2.115
		84.84	0.894	2.243
		113.13	0.898	2.285
		141.41	0.903	2.334
		169.69	0.908	2.391
	50	14.14	0.869	2.035
		28.28	0.879	2.110
		42.42	0.883	2.146
		56.56	0.893	2.231
		70.70	0.899	2.292
		84.84	0.906	2.361
		113.13	0.910	2.413
		141.41	0.913	2.445
		169.69	0.917	2.483

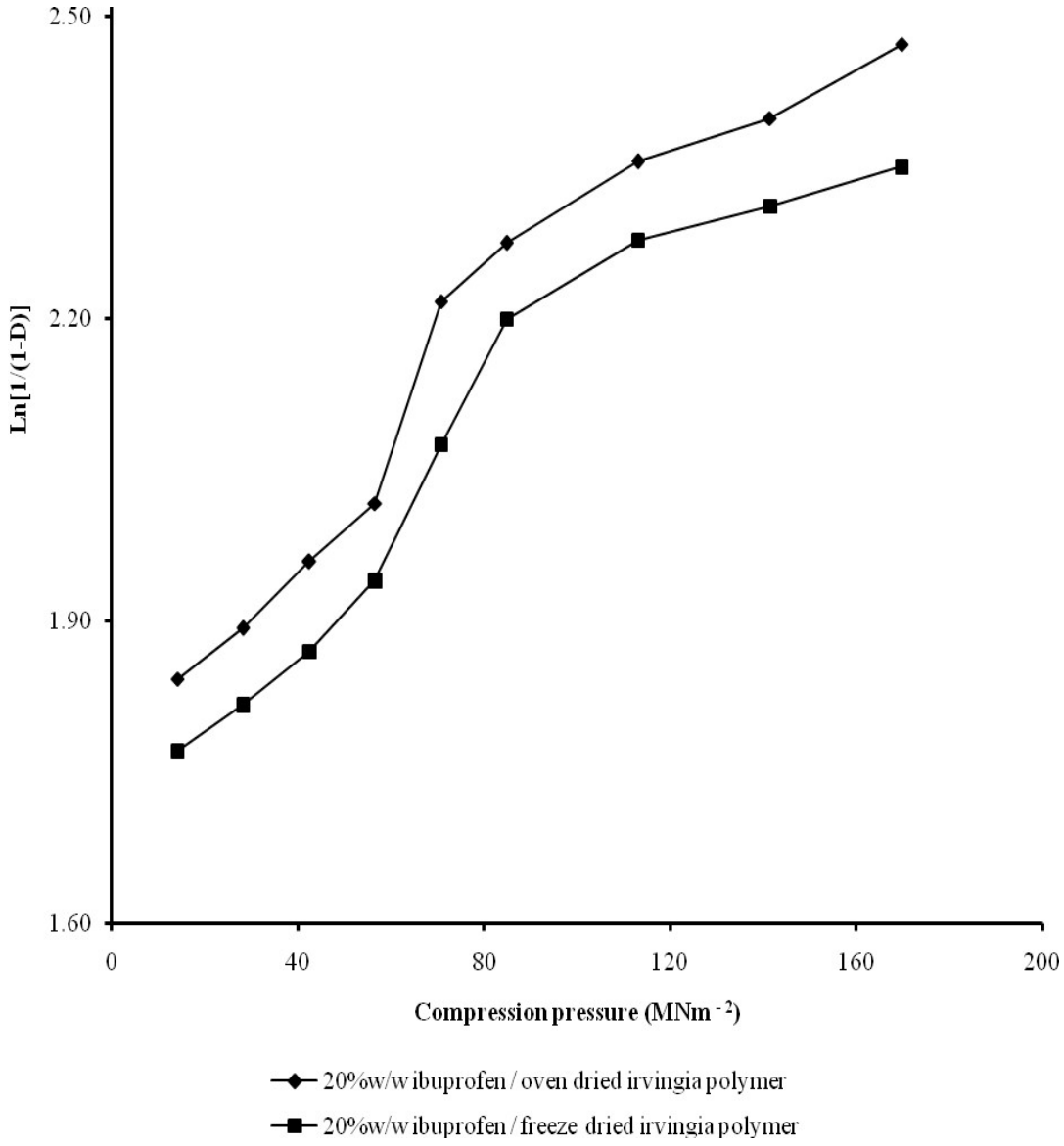


Figure 4.24. Heckel plots for *Irvingia* kernel mucilage matrix tablets containing 20% w/w ibuprofen prepared by wet granulation

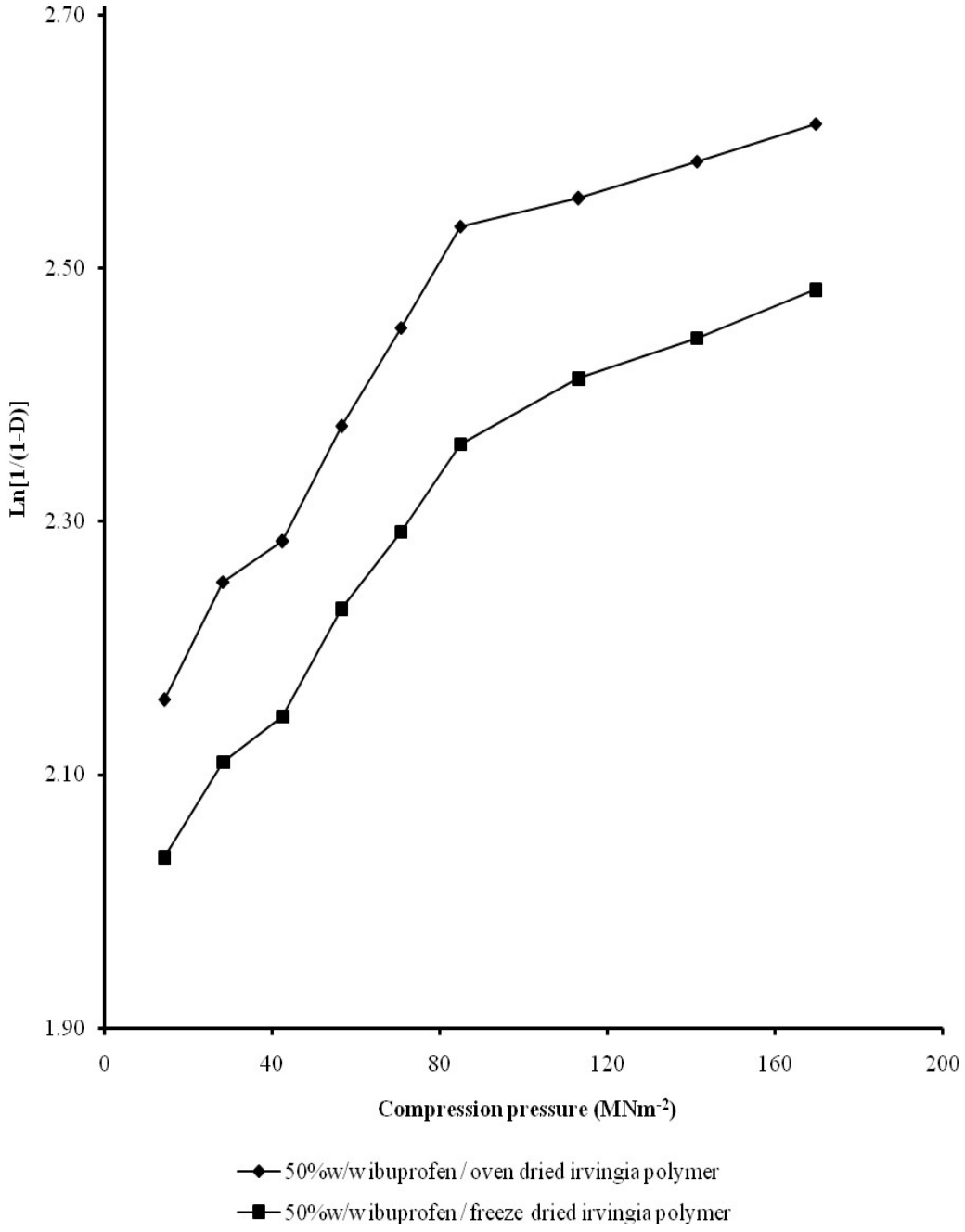


Figure 4.25. Heckel plots for *Irvingia* kernel mucilage matrix tablets containing 50% w/w ibuprofen prepared by wet granulation

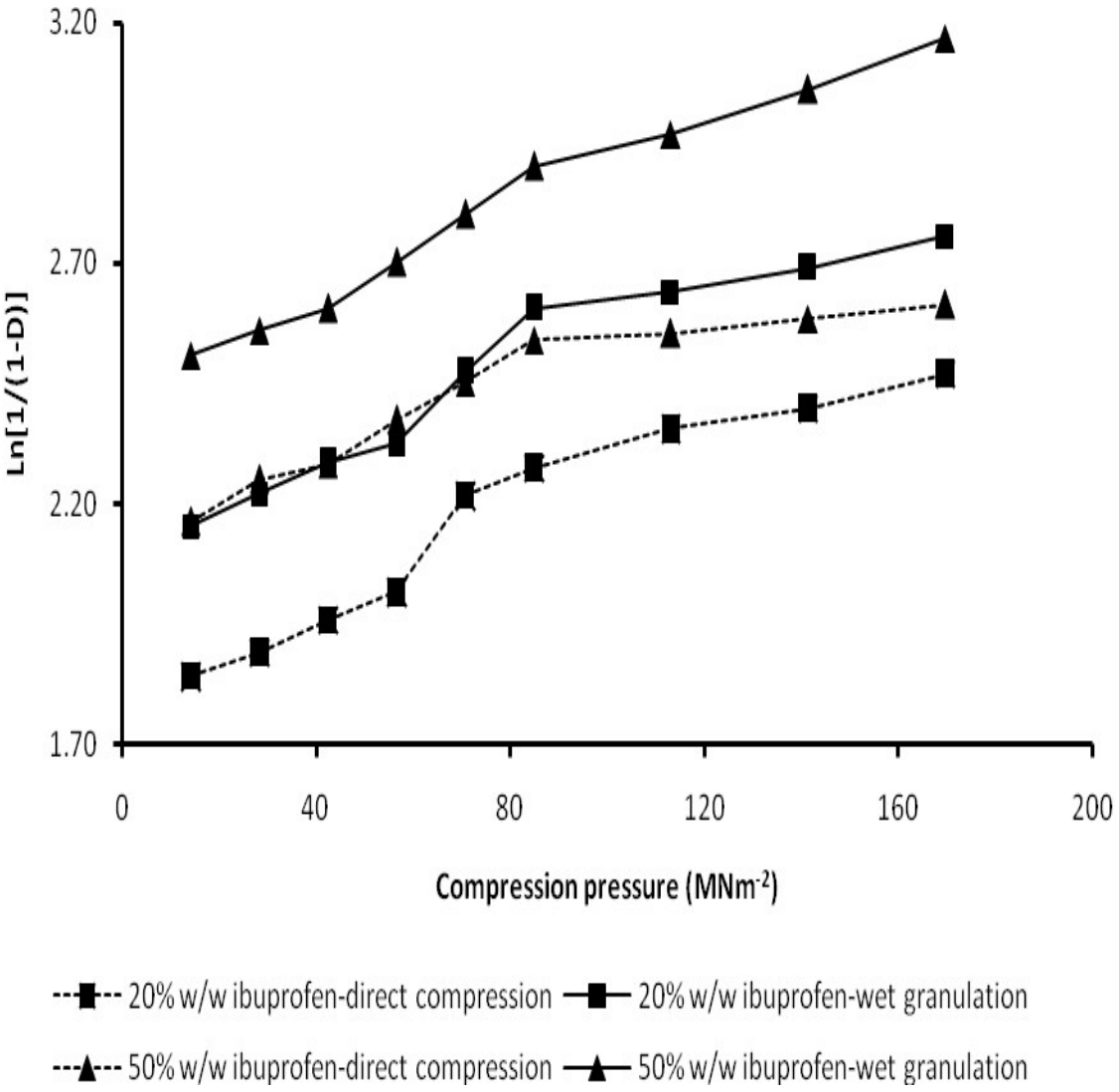


Figure 4.26. Heckel plots for oven dried *Irvingia* kernel mucilage matrices made using (—) wet granulation and (-----) direct compression.

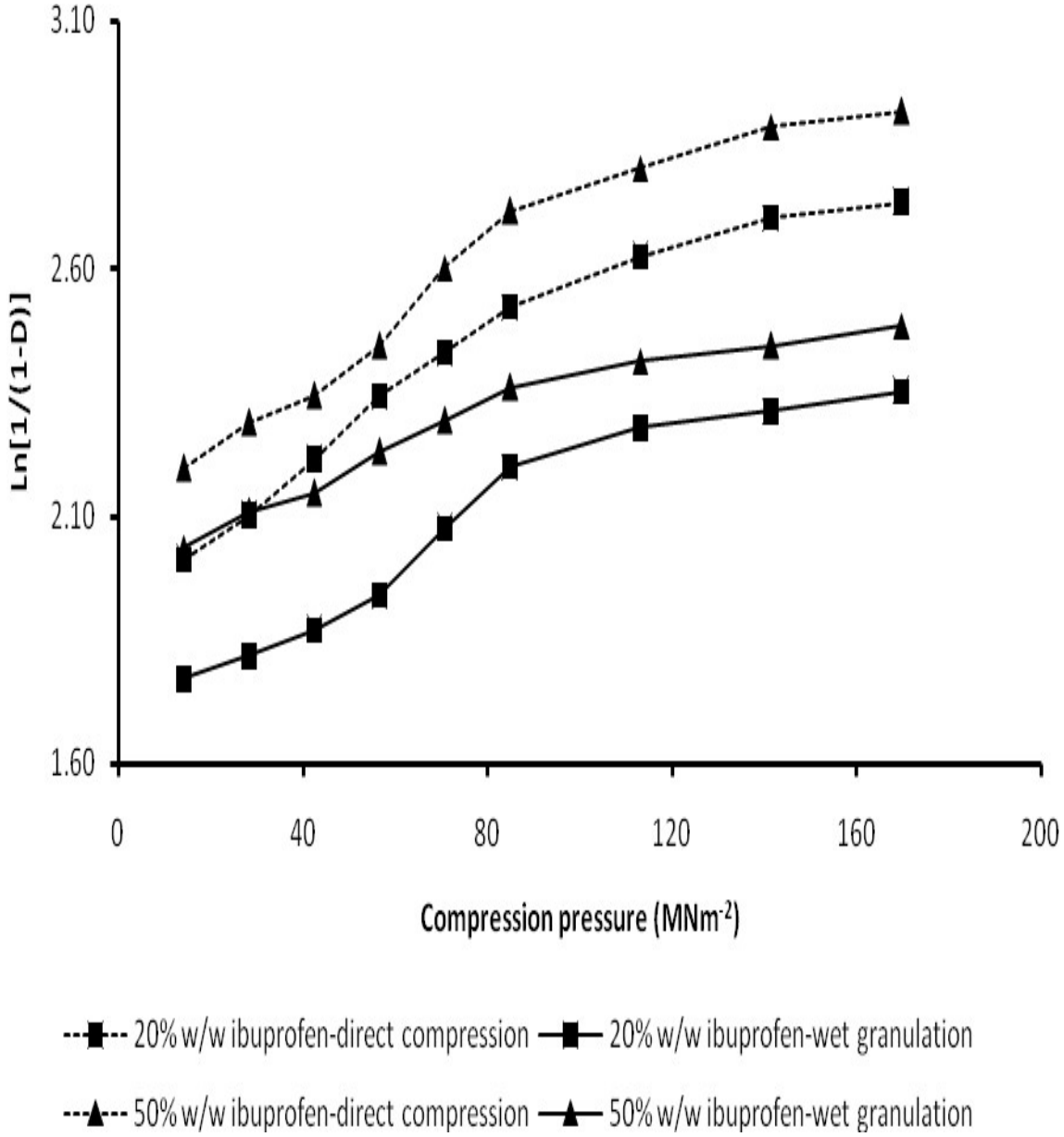


Figure 4.27. Heckel plots for freeze dried Irvingia kernel mucilage matrices made using (—) wet granulation and (-----) direct compression.

Table 4.35. Applied pressure (P), volume at no pressure (V_0), volume (V_P), volume decrease extent (C) and P/C for ibuprofen matrices formed using wet granulation process

Mucilage	Conc. of Ibuprofen (%w/w)	Applied pressure (MNm^{-2})	V_0	V_P	C	P/C
Oven dried *Irvingia*	10	14.14	1.330	0.480	0.639	22.13
		28.28		0.476	0.642	44.03
		42.42		0.469	0.647	65.53
		56.56		0.468	0.648	87.22
		70.70		0.465	0.651	108.68
		84.84		0.460	0.654	129.73
		113.13		0.451	0.661	171.10
		141.41		0.445	0.666	212.40
		169.69		0.434	0.674	251.76
	20	14.14	1.426	0.489	0.657	21.51
		28.28		0.482	0.662	42.73
		42.42		0.478	0.664	63.85
		56.56		0.474	0.667	84.75
		70.70		0.472	0.669	105.71
		84.84		0.469	0.671	126.43
		113.13		0.466	0.673	168.04
		141.41		0.463	0.675	209.48
		169.69		0.460	0.677	250.47
	30	14.14	1.521	0.481	0.684	20.67
		28.28		0.478	0.685	41.26
		42.42		0.477	0.686	61.81
		56.56		0.475	0.687	82.28
		70.70		0.474	0.688	102.74
		84.84		0.473	0.689	123.15
		113.13		0.470	0.691	163.76
		141.41		0.466	0.693	203.97
		169.69		0.462	0.696	243.76

Table 4.35. cont.

Mucilage	Conc. of ibuprofen (%w/w)	Applied pressure (MNm^{-2})	V_0	V_P	C	P/C
Oven dried *Irvingia*	50	14.14	1.568	0.473	0.698	20.25
		28.28		0.470	0.700	40.39
		42.42		0.468	0.701	60.49
		56.56		0.467	0.702	88.55
		70.70		0.465	0.703	100.53
		84.84		0.464	0.704	120.53
		113.13		0.463	0.705	160.56
		141.41		0.461	0.706	200.38
		169.69		0.459	0.707	240.02
Freeze dried *Irvingia*	10	14.14	1.473	0.496	0.663	21.33
		28.28		0.491	0.667	42.43
		42.42		0.484	0.671	63.20
		56.56		0.480	0.674	83.90
		70.70		0.474	0.678	104.23
		84.84		0.471	0.680	124.78
		113.13		0.466	0.684	165.50
		141.41		0.458	0.689	205.22
		169.69		0.454	0.692	245.28
	20	14.14	1.521	0.492	0.676	20.91
		28.28		0.489	0.678	41.68
		42.42		0.481	0.683	62.07
		56.56		0.479	0.685	82.57
		70.70		0.471	0.690	102.40
		84.84		0.463	0.696	121.97
		113.13		0.458	0.699	161.89
		141.41		0.456	0.700	201.93
		169.69		0.452	0.703	241.52

Table 4.35. cont.

Mucilage	Conc. of ibuprofen (%w/w)	Applied pressure (MNm^{-2})	V_0	V_P	C	P/C
Freeze dried *Irvingia*	30	14.14	1.568	0.486	0.690	20.50
		28.28		0.483	0.692	40.86
		42.42		0.480	0.694	61.13
		56.56		0.473	0.698	80.99
		70.70		0.466	0.703	100.60
		84.84		0.459	0.707	120.00
		113.13		0.456	0.709	159.48
		141.41		0.450	0.713	198.41
		169.69		0.449	0.714	237.72
	50	14.14	1.616	0.479	0.707	20.10
		28.28		0.473	0.707	39.99
		42.42		0.471	0.709	59.86
		56.56		0.467	0.711	79.55
		70.70		0.462	0.714	98.99
		84.84		0.457	0.717	118.38
		113.13		0.451	0.721	156.99
		141.41		0.449	0.722	195.80
		169.69		0.444	0.725	234.08

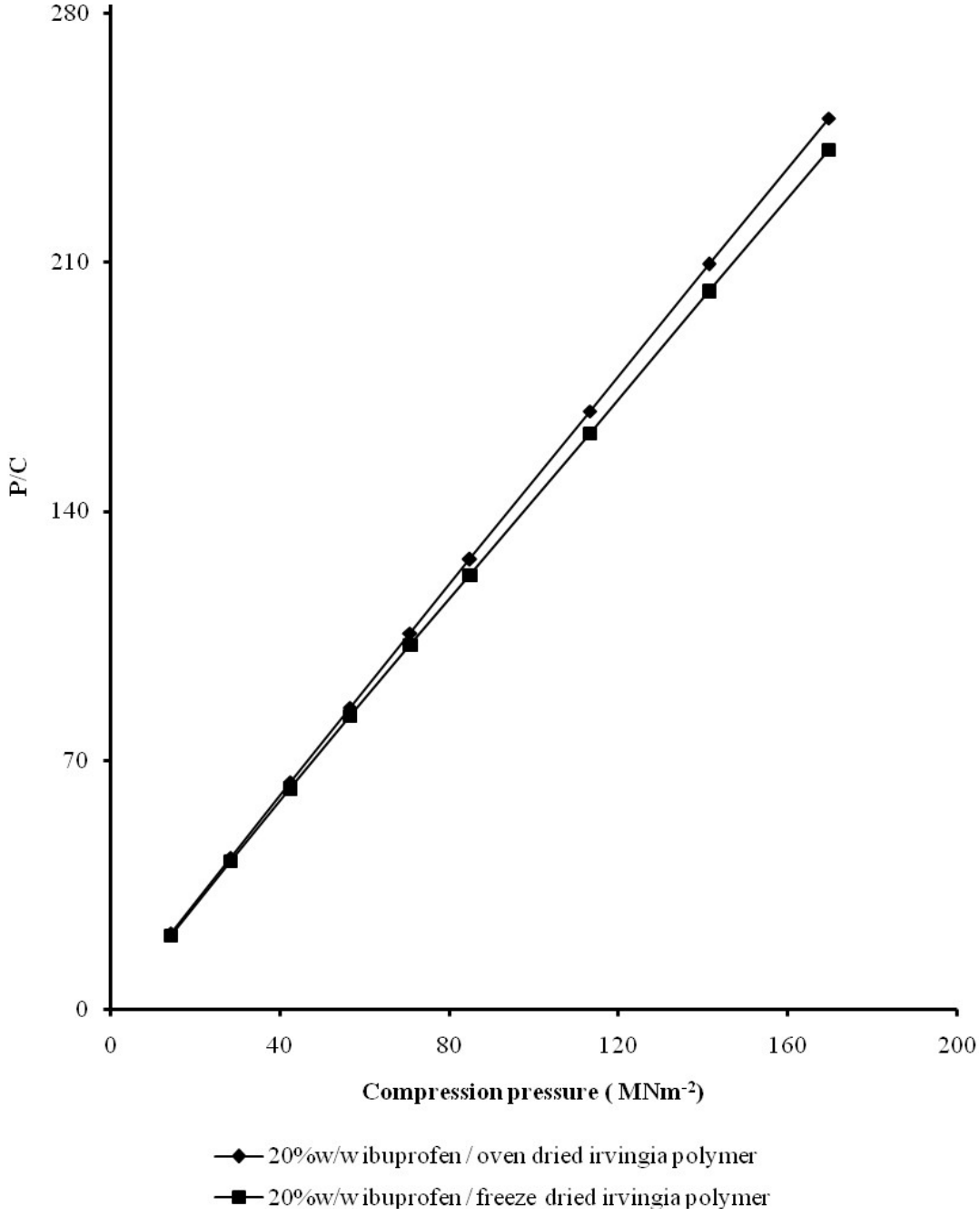


Figure 4.28. Kawakita plots for *Irvingia* kernel mucilage matrix tablets containing 20% w/w ibuprofen prepared by wet granulation

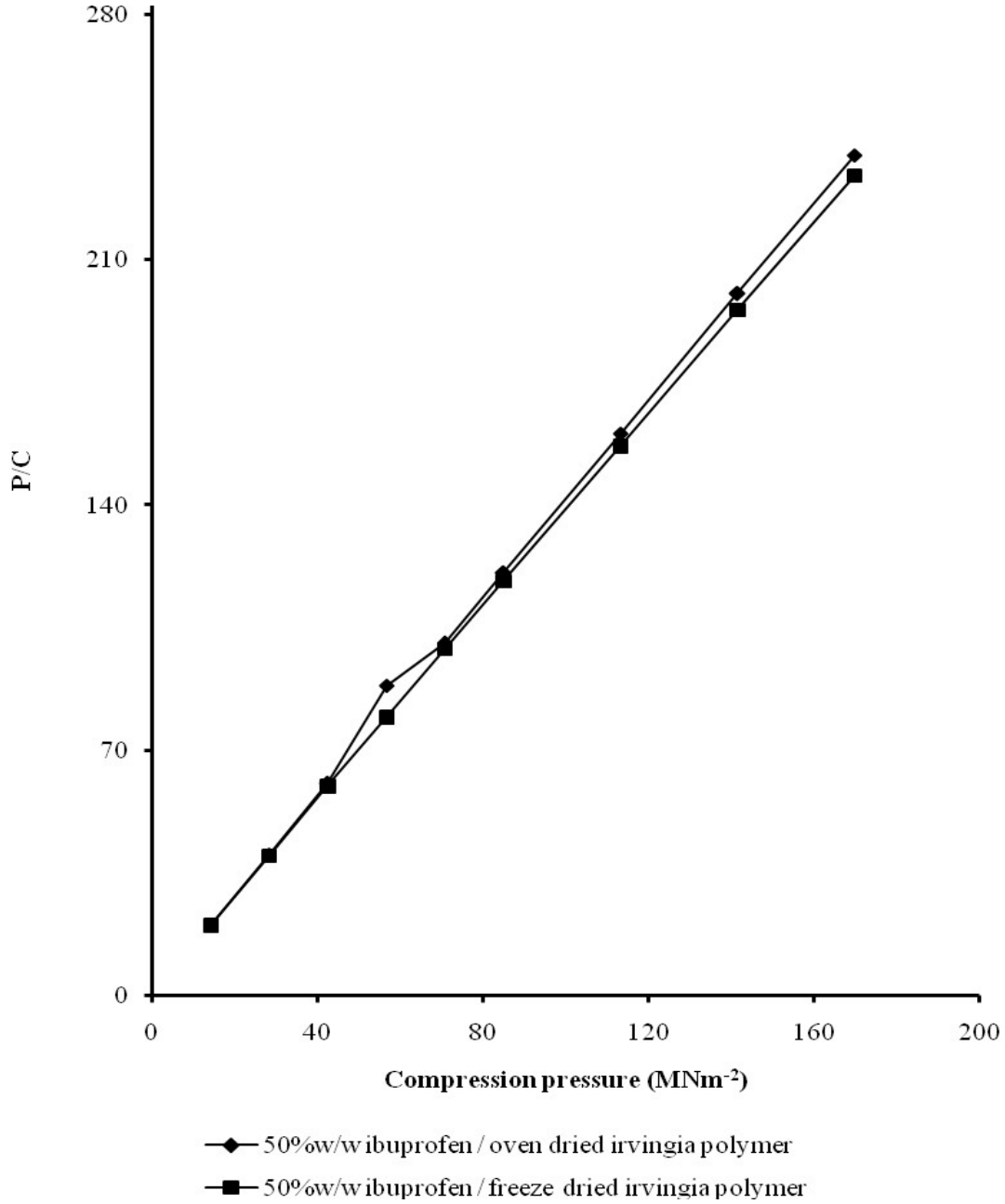


Figure 4.29. Kawakita plots for *Irvingia* kernel mucilage matrix tablets containing 50% w/w ibuprofen prepared by wet granulation

4.4.2 Mechanical properties of ibuprofen-*Irvingia* kernel mucilage matrices prepared by wet granulation

4.4.2.1 Friability

The friabilities at different packing fraction (relative density) of ibuprofen-*Irvingia* kernel mucilage matrices made employing wet granulation process are presented in Table 4.36. Representative graphs of friability versus packing fraction of ibuprofen-*Irvingia* kernel mucilage matrices containing 20 and 50% w/w ibuprofen are shown in Figure 4.30 and 4.31.

4.4.2.2 Crushing strength

Crushing strength of ibuprofen-*Irvingia* kernel mucilage matrices at different relative density prepared by wet granulation are shown in Table 4.37. Representative graphs of crushing strength against relative density (packing fraction) for 20 and 50% w/w ibuprofen-*Irvingia* kernel mucilage matrices are displayed in Figures 4.32 and 4.33. Crushing strength and CSFR at relative density of 0.90 of the ibuprofen-*Irvingia* kernel mucilage matrices are given in Table 4.38.

4.4.3 Drug release from ibuprofen-*irvinga* kernel mucilage matrices prepared by wet granulation

Representative drug release profile of the ibuprofen-*Irvingia* kernel mucilage matrices at 20 and 50% w/w ibuprofen concentration prepared by wet granulation are presented in Figures 4.34 and 4.35.

Table 4.36. Values of friability of ibuprofen matrix tablets at different relative densities made by wet granulation process

Mucilage	Conc. of ibuprofen (% w/w)	Relative density (D)	Friability (%)
Oven dried *Irvingia*	10	0.821	0.61 ± 0.01
		0.833	0.54 ± 0.02
		0.847	0.45 ± 0.01
		0.866	0.37 ± 0.03
		0.887	0.31 ±0.02
	20	0.854	0.65 ± 0.02
		0.868	0.57 ± 0.03
		0.900	0.49 ± 0.03
		0.905	0.42 ± 0.01
		0.919	0.34 ± 0.01
	30	0.873	0.68 ± 0.03
		0.889	0.59 ± 0.02
		0.904	0.50 ± 0.01
		0.914	0.42 ± 0.03
		0.923	0.35 ± 0.02
	50	0.897	0.69 ±0.07
		0.906	0.60 ± 0.02
		0.919	0.53 ± 0.02
		0.921	0.46 ± 0.01
		0.929	0.38 ± 0.02
Freeze dried *Irvingia*	10	0.811	0.53 ± 0.02
		0.827	0.43 ± 0.02
		0.846	0.37 ± 0.01
		0.860	0.30 ± 0.02
		0.873	0.23 ±0.06
	20	0.837	0.56 ± 0.02
		0.854	0.45 ± 0.04
		0.889	0.39 ± 0.02
		0.896	0.36 ± 0.02
		0.905	0.28 ± 0.02

Table 4.36. cont.

Mucilage	Conc. of ibuprofen (% w/w)	Relative density (D)	Friability (%)
Freeze dried *Irvingia*	30	0.859	0.56 ± 0.03
		0.878	0.45 ± 0.01
		0.895	0.39 ± 0.03
		0.896	0.36 ± 0.01
		0.911	0.28 ± 0.02
	50	0.878	0.64 ±0.02
		0.889	0.54 ± 0.03
		0.906	0.49 ± 0.04
		0.912	0.44 ± 0.03
		0.919	0.32 ± 0.01

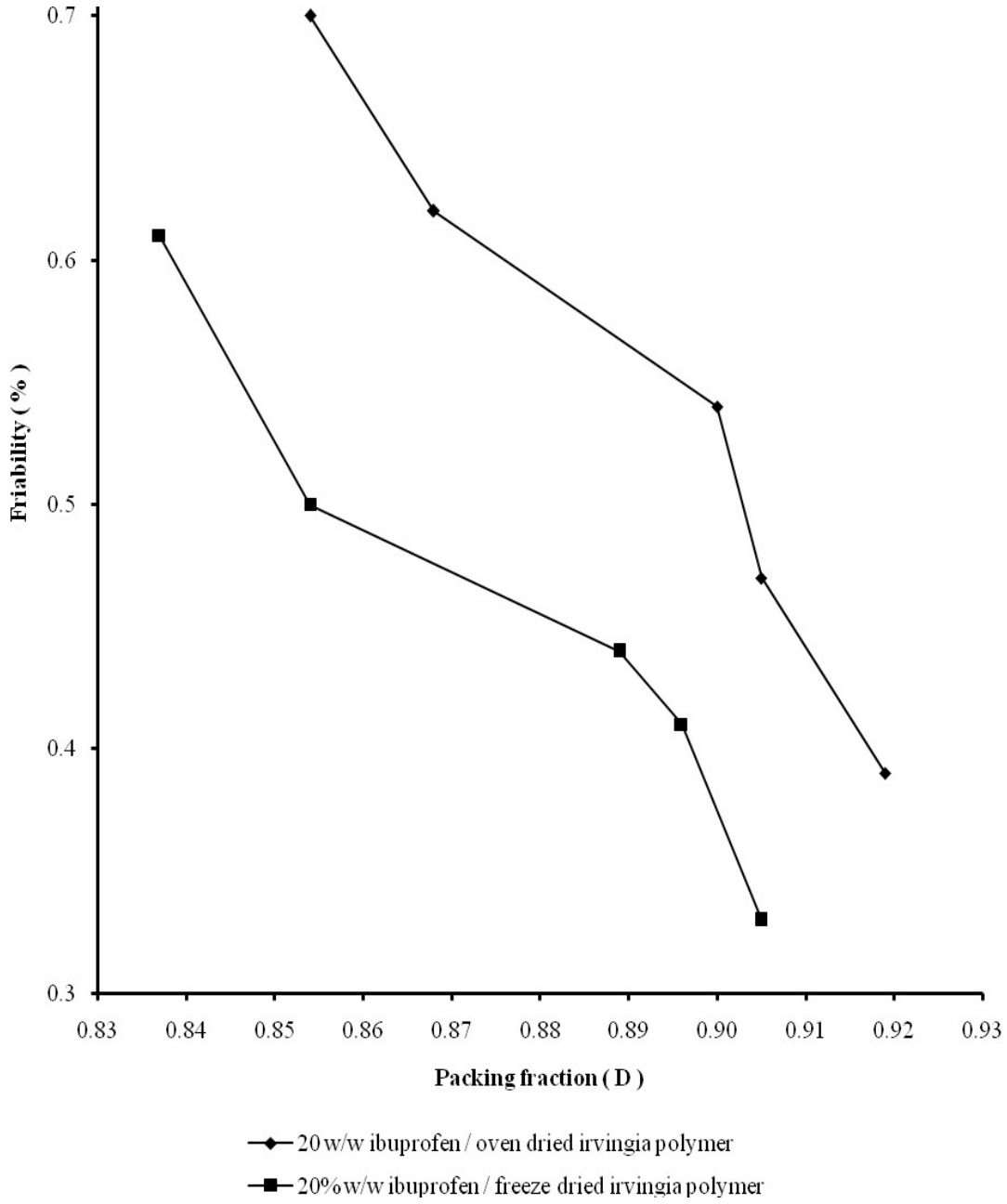


Figure 4.30. Friability versus packing fraction plot for *Irvingia* kernel mucilage matrix tablets containing 20% w/w ibuprofen prepared by wet granulation

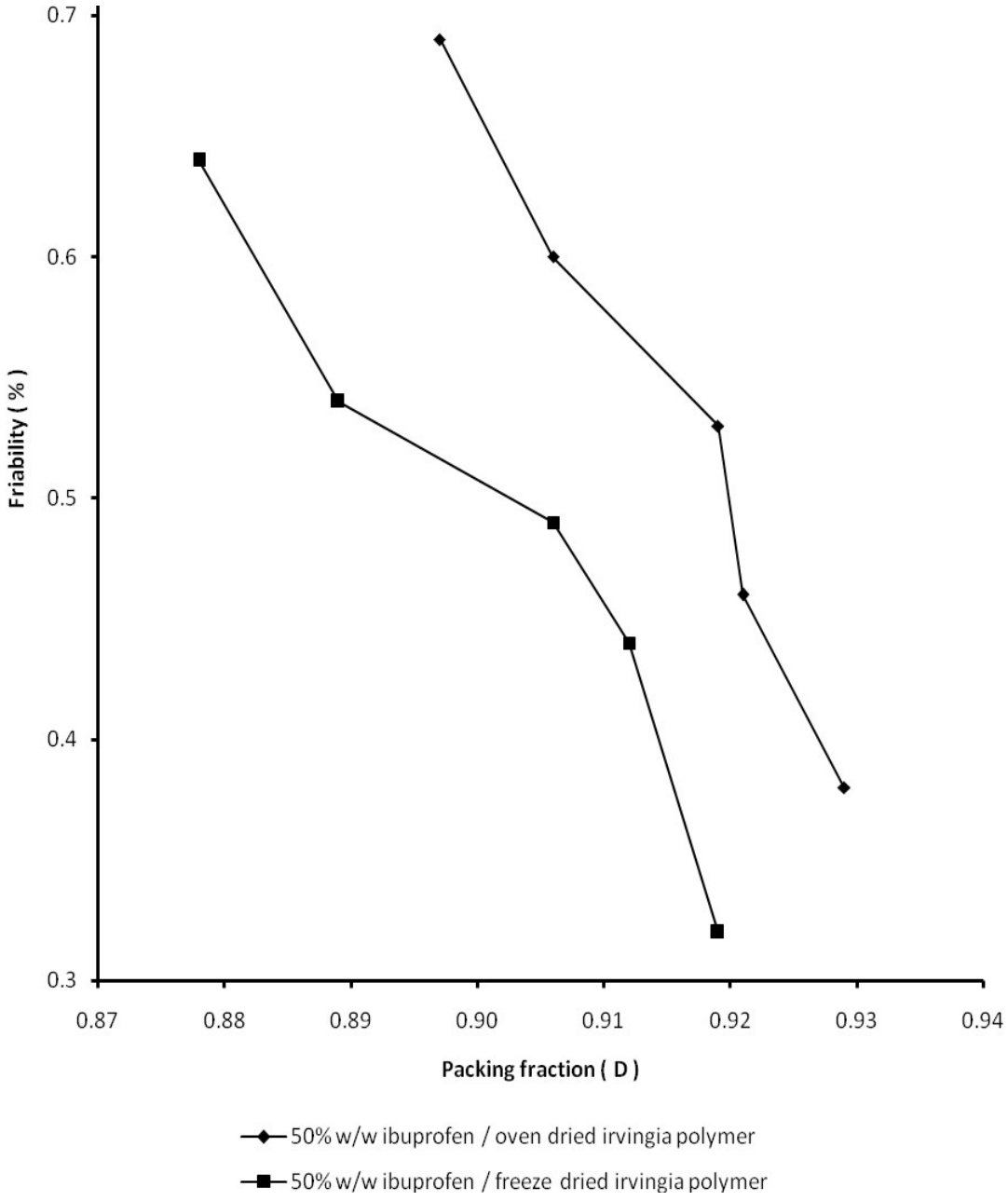


Figure 4.31. Friability versus packing fraction plot for *Irvingia* kernel mucilage matrix tablet containing 50% w/w ibuprofen prepared by wet granulation

Table 4.37. Values of crushing strength of ibuprofen matrix tablets at different relative densities prepared by wet granulation method

Mucilage	Conc. of ibuprofen (% w/w)	Relative density (D)	Crushing strength (N)
Oven dried *Irvingia*	10	0.824	78.33 ± 0.49
		0.836	83.05 ± 0.57
		0.849	87.72 ± 0.25
		0.867	93.23 ± 4.60
		0.885	99.22 ± 2.86
	20	0.852	76.41 ± 0.61
		0.865	80.19 ± 0.52
		0.899	85.16 ± 0.66
		0.906	90.05 ± 0.47
		0.918	96.05 ± 0.53
	30	0.875	69.88 ± 0.51
		0.890	73.04 ± 0.55
		0.905	80.91 ± 1.39
		0.911	82.95 ± 0.95
		0.922	90.22 ± 0.33
	50	0.896	63.03 ± 0.30
		0.909	65.42 ± 1.27
		0.918	70.26 ± 0.91
		0.921	75.86 ± 0.54
		0.928	78.55 ± 0.49
Freeze dried *Irvingia*	10	0.812	85.73 ± 0.13
		0.828	96.10 ± 0.42
		0.849	98.80 ± 0.28
		0.859	110.90 ± 0.71
		0.874	119.25 ± 1.20
	20	0.836	80.03 ± 0.75
		0.853	87.10 ± 1.56
		0.889	96.25 ± 0.64
		0.897	100.40 ± 0.28
		0.906	109.50± 1.84

Table 4.37. cont.

Mucilage	Conc. of ibuprofen (% w/w)	Relative density (D)	Crushing strength (N)
Freeze dried *Irvingia*	30	0.857	77.55 ± 0.64
		0.876	84.90 ± 0.71
		0.891	93.75 ± 0.92
		0.900	97.85 ± 0.35
		0.908	106.50 ± 0.28
	50	0.879	75.40 ± 0.28
		0.887	85.94 ± 0.76
		0.905	93.30 ± 0.28
		0.909	97.90 ± 0.71
		0.917	104.70 ± 0.14

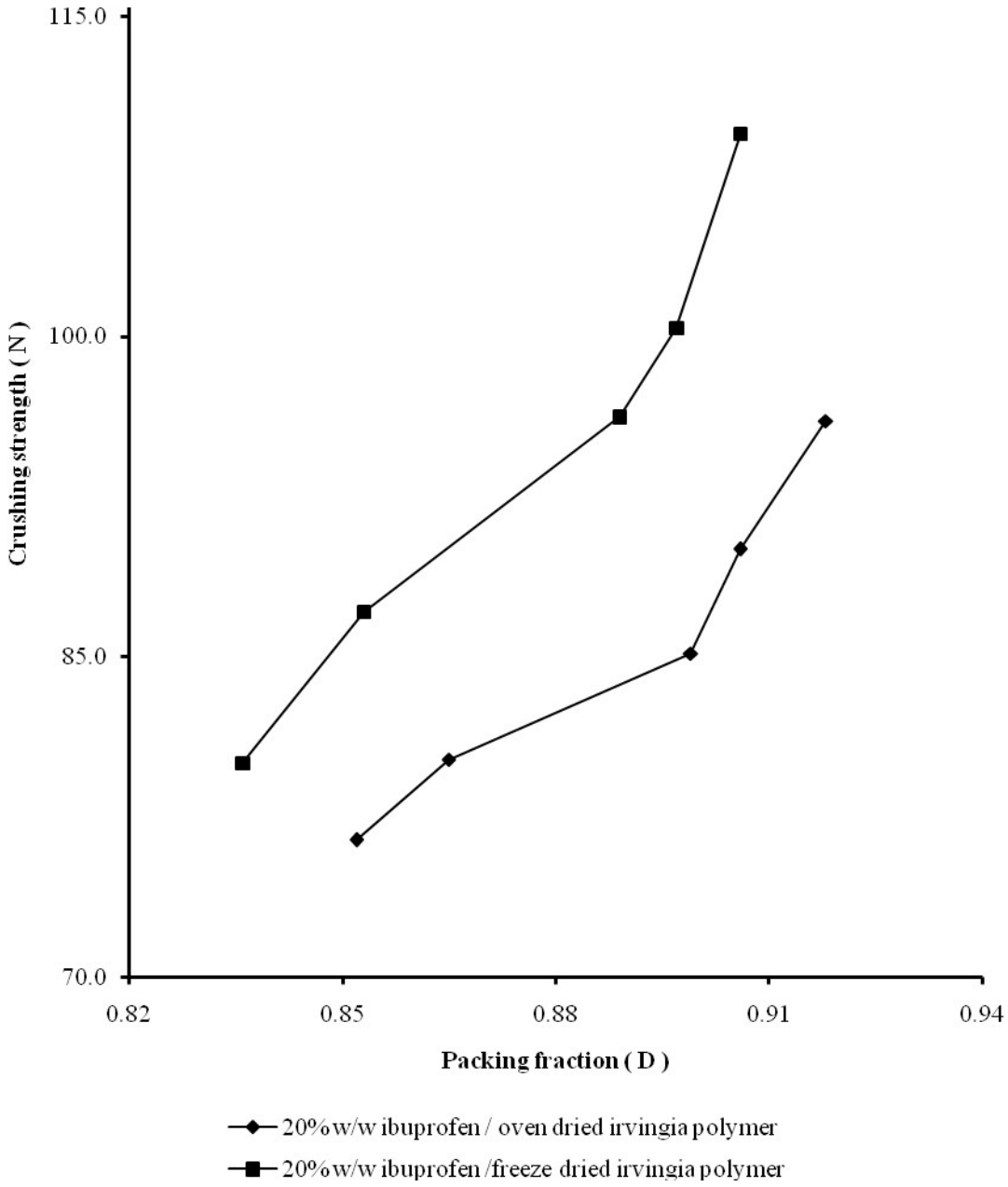


Figure 4.32. Crushing strength versus packing fraction plot for *Irvingia* kernel mucilage matrices containing 20% w/w ibuprofen prepared by wet granulation

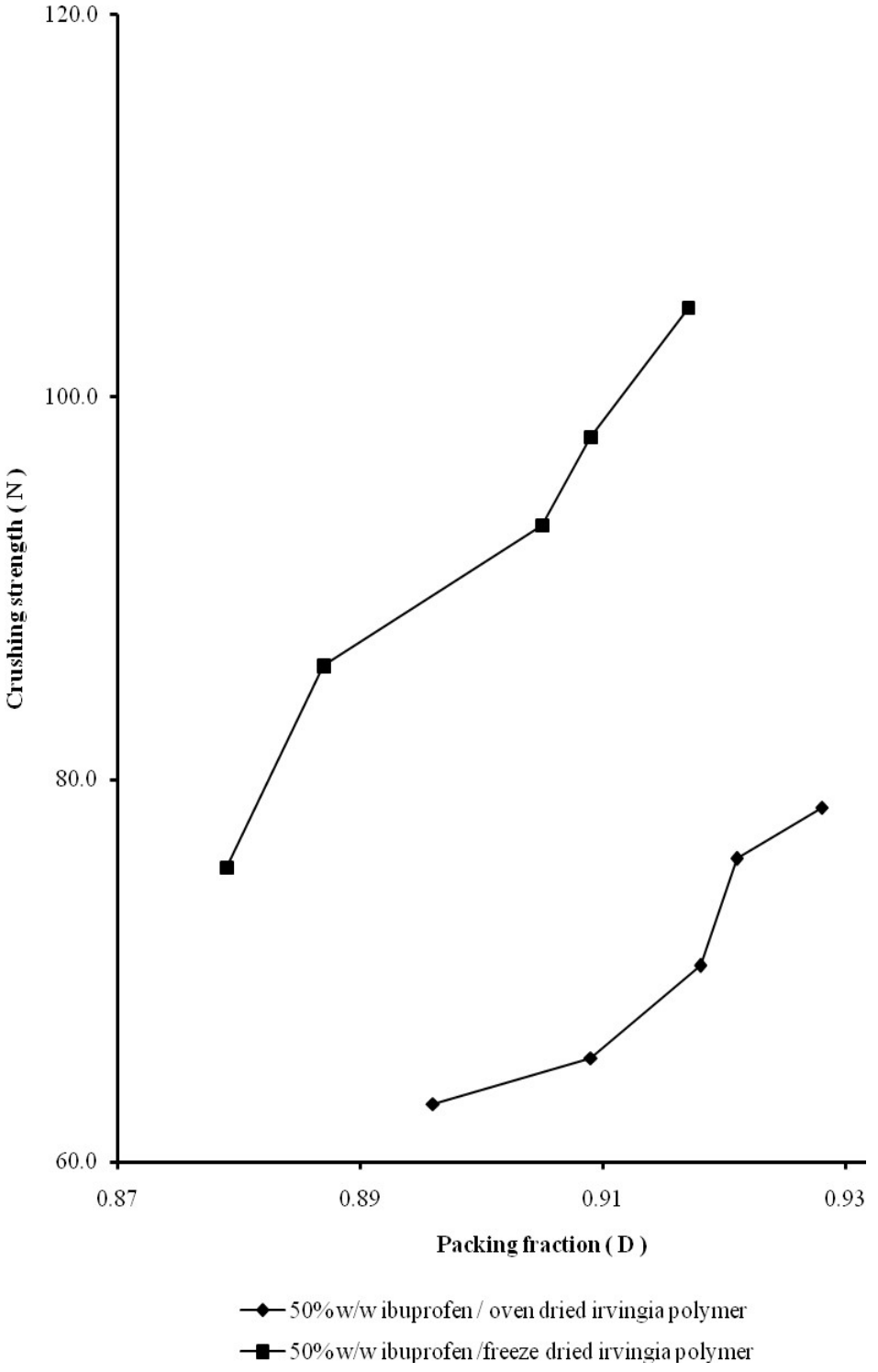


Figure 4.33. Crushing strength versus packing fraction plot for *Irvingia* kernel mucilage matrix tablets containing 50% w/w ibuprofen prepared by wet granulation

Table 4.38. Values of friability (FR), crushing strength (CS) and CSFR of ibuprofen matrix tablets at relative density of 0.90 prepared by wet granulation method

Mucilage	Ibuprofen Conc.(%w/w)	Crushing strength (N)	Friability (%)	CSFR
Oven dried	10	94.00	0.39	241.03
Irvingia	20	85.00	0.52	163.46
	30	78.00	0.60	130.00
	50	63.50	0.78	81.41
Freeze dried	10	126.00	0.20	630.00
Irvingia	20	102.00	0.46	221.74
	30	97.85	0.53	184.62
	50	90.50	0.68	133.09

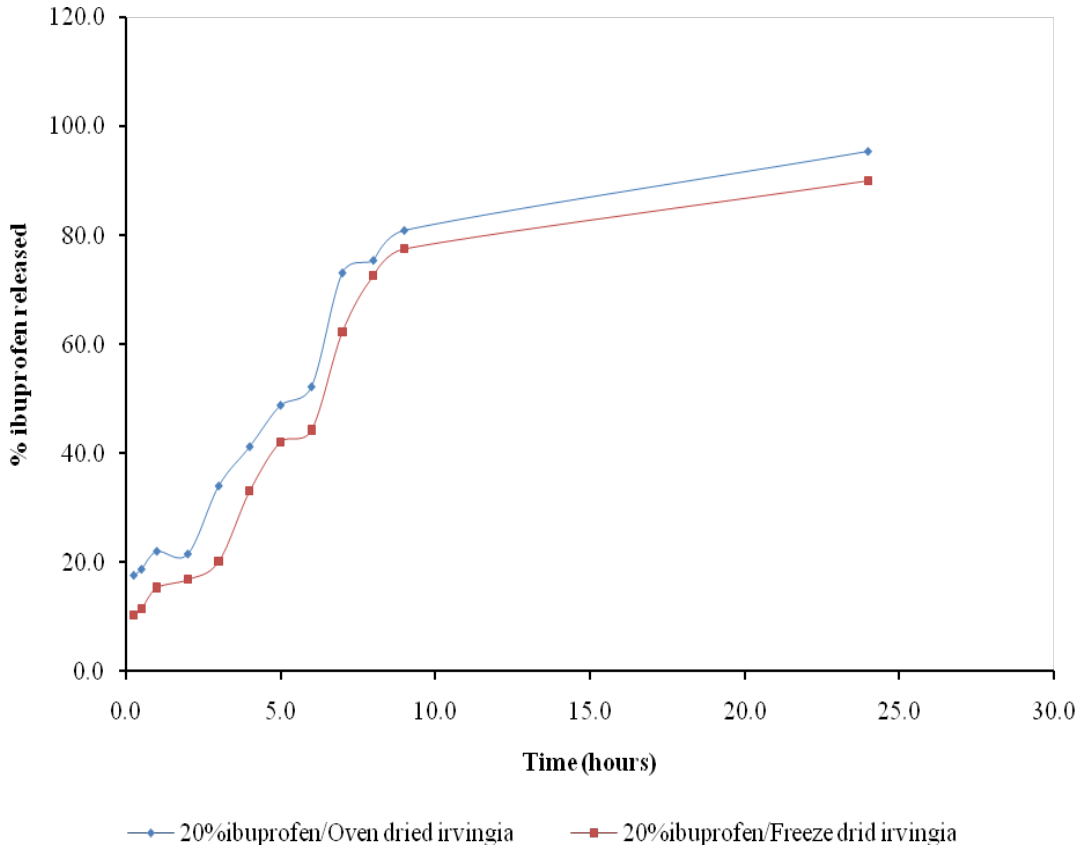


Figure 4.34. Release profile of ibuprofen from *Irvingia* kernel mucilage matrix tablets having 20% w/w ibuprofen formed using wet granulation

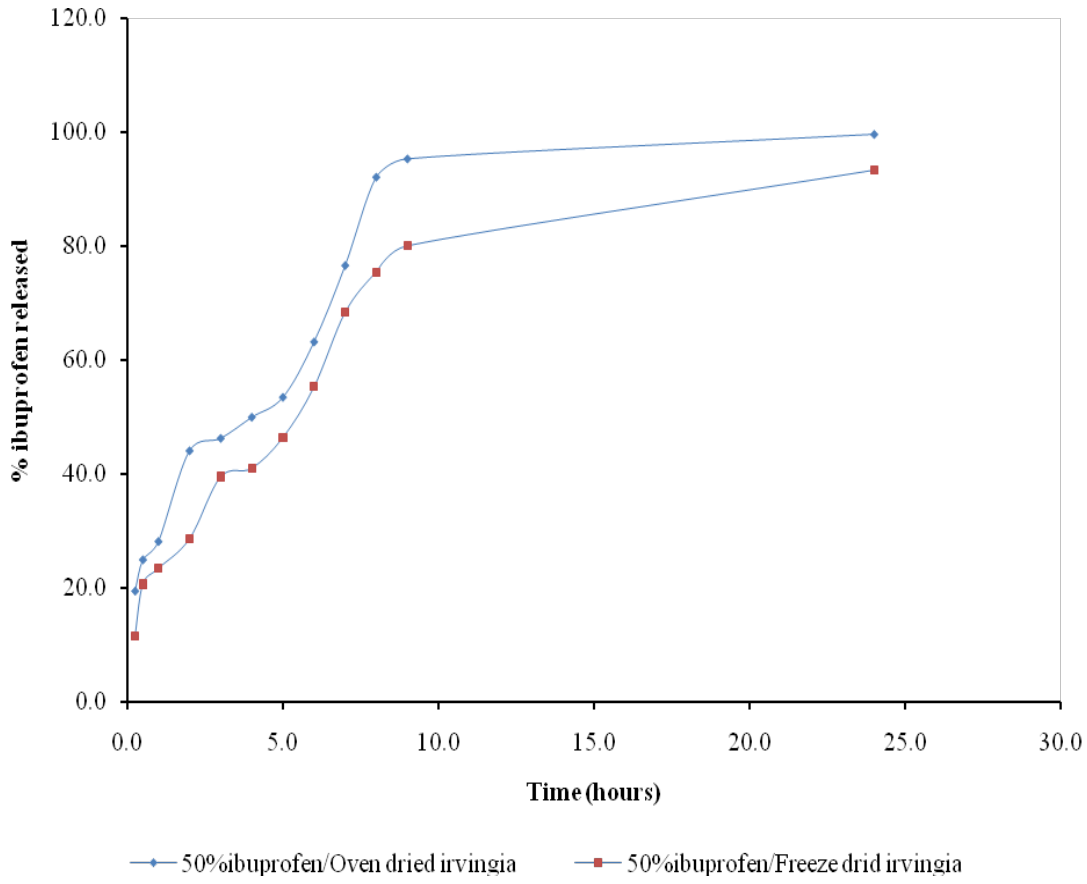


Figure 4.35. Release profile of ibuprofen from *Irvingia* kernel mucilage matrix tablets having 50% w/w ibuprofen made via wet granulation

4.5 *Irvingia* kernel mucilage as a coating device for drug targeting to the colon

The values of friability and crushing strength of *Irvingia* kernel mucilage coated 100 mg 1:1 ibuprofen-avicel tablets for colon targeted delivery of ibuprofen are contained in Table 4.39. The drug release profile of the core tablet and coated tablets are given in Figure 4.36.

4.6 Factorial experimental analysis of individual and interaction effect for ibuprofen matrices

The values of crushing strength and crushing strength-friability ratio of ibuprofen-*Irvingia* kernel mucilage matrix tablets at 0.9 relative density for the variables and combination codes for the factorial experiment are displayed in Table 4.40. Table 4.41 shows results of the individual effect of processing factor, method of preparation and ibuprofen concentration on the crushing strength and crushing strength-friability ratio (CSFR) of the ibuprofen-*Irvingia* kernel mucilage matrices. Concentration of ibuprofen had the greatest effect on both crushing strength and CSFR. Thus changing the concentration from its low (10%) to high (50%) will cause greater effect on the crushing strength and CSFR than doing same for processing factor and method of preparation. The interaction effect of processing factor, method of preparation and concentration of ibuprofen on the crushing strength and CSFR of the ibuprofen-*Irvingia* kernel mucilage matrices at packing fraction 0.9 are shown in Table 4.42. The greatest interaction effect was between processing factor and concentration of ibuprofen.

Table 4.39. Values of friability (FR) and crushing strength (CS) of *Irvingia* mucilage coated ibuprofen/avicel tablets for colon targeted delivery

Coat type	Coating weight (mg)	Crushing strength (N)	Friability (%)	% released after 5 h	% released after 9h
Core tablet (ibuprofen/avicel, 1:1 -100 mg)	-	-	4.3 ±0.20	-	-
Oven dried *Irvingia* (OIV)	300	101.36±0.14	0.37±0.11	65.66	87.43
	400	189.76±0.22	0.29±0.06	53.49	72.60
Freeze dried *Irvingia* (FIV)	300	212.18±0.18	0.25±0.10	60.90	76.82
	400	278.14±0.15	0.22±0.04	46.68	70.30

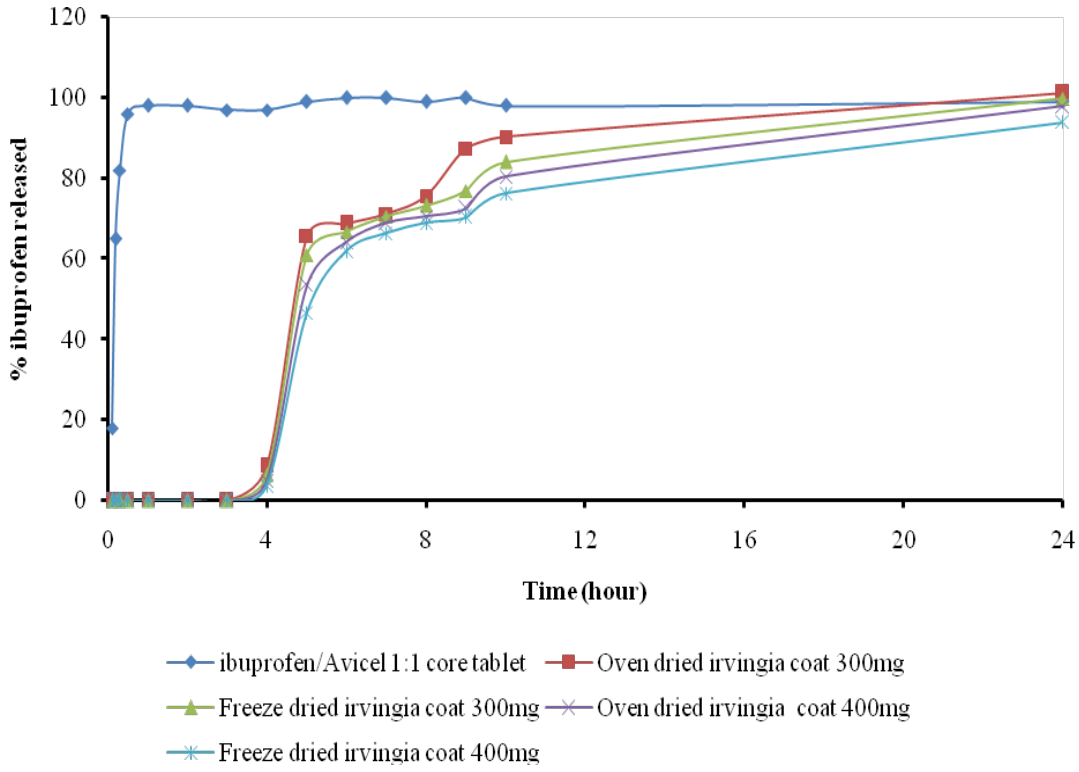


Figure 4.36. Release profile of ibuprofen from 300 mg and 400 mg, *Irvingia* kernel mucilage coated tablets for colon targeted drug delivery in 0.1m HCl for 2 hs, Sorensen's buffer (pH 7.4) for 3 hs and then simulated colonic fluid.

Table 4.40. Values of crushing strength and CSFR of ibuprofen-*Irvingia* kernel mucilage matrix tablets at 0.9 relative density for factorial experimental design.

Variable and Combination codes	Crushing strength	CSFR
$F_LM_LC_L$	60.00	103.45
$F_LM_LC_H$	34.90	26.24
$F_LM_HC_H$	63.50	81.41
$F_LM_HC_L$	94.00	241.03
$F_HM_HC_H$	90.50	133.09
$F_HM_HC_L$	126.00	630.00
$F_HM_LC_L$	108.00	300.00
$F_HM_LC_H$	47.00	49.47

Table 4.41. Individual effect of processing factor (F), method of preparation (M) and concentration of ibuprofen (C) on the crushing strength and CSFR of ibuprofen-*Irvingia* kernel mucilage matrix tablets at 0.9 relative density

Variables	Crushing strength	CSFR
F	29.78	155.11
M	31.03	151.58
C	-38.03	-246.07

Table 4.42. Interaction of processing factor (F), method of preparation (M) and concentration of ibuprofen (C) on the crushing strength and CSFR of ibuprofen-*Irvingia* kernel mucilage matrix tablet at relative density of 0.9

Variables combination	Crushing strength	CSFR
F-M	-0.28	55.22
F-C	-20.23	-127.65
M-C	5.03	-82.20

CHAPTER FIVE
DISCUSSION

5.1 Discussion

5.1.1 *Irvingia* extraction and phytochemical characteristics

Irvingia gabonensis kernel mucilage yield of 43.8% w/w is a very appreciable for natural product. It shows *Irvingia gabonensis* kernel mucilage has good prospect for use on industrial scale (or in the pharmaceutical industry). The presence of carbohydrate and reducing sugars in *Irvingia gabonensis* kernel mucilage is an indication that *Irvingia gabonensis* kernel mucilage is a polysaccharide.

The elemental constituents' analysis of *Irvingia gabonensis* kernel mucilage indicates the absence of heavy metals such as lead, arsenic and nickel in *Irvingia gabonensis* kernel mucilage. If present, this would have limited the use of *Irvingia gabonensis* kernel mucilage as food condiment and other industrial use because they are hazardous to health. Mineral composition is influenced by soil type on which plant is grown, thus there could be variation from samples of the same species planted on different soil type (Bamiro, 2011; Wang *et al*., 2015).

The proximate composition of *Irvingia gabonensis* kernel mucilage shows the presence of protein, fat, fibres and carbohydrate in *Irvingia gabonensis* kernel mucilage. This indicates its usefulness as a food additive. The pH of *Irvingia gabonensis* kernel mucilage at a temperature of 30.5^0C was 5.23 for oven dried sample and 5.80 for freeze dried sample. *Irvingia gabonensis* kernel mucilage is thus acidic. The stability and physiological activity of most preparation is determined by their pH, therefore, it is important to have knowledge of the pH of an excipient (Bamiro, 2011; Liang et al, 2017).

5.1.2 Physicochemical properties of *Irvingia gabonensis* kernel mucilage

Scanning electron microscopy of the *Irvingia gabonensis* kernel mucilage indicates the morphology and surface characteristics of the particles (Odeku *et al.*, 2013). *Irvingia gabonensis* kernel mucilage particles were mostly irregular in shape and appear flaky. Particle shape has been shown to affect the compaction characteristic of powders (Wray, 1992). The more irregular the particles of a material, the greater the likelihood of them fragmenting during compaction thus better compactibility. In addition particle irregularity allows for closer packing during compression, hence higher compact strength.

X-ray diffraction pattern of mucilage gives the crystallinity of the mucilage. The comparative quantity of each kind of dispersing of the x-ray diffraction pattern shows the level of crystallinity of the mucilage (Odeku *et al*., 2013). The results indicate that *Irvingia gabonensis* mucilage exhibit some level of crystallinity as shown by the intensity of the peaks, with the freeze-dried mucilage appear slightly more crystalline than the oven dried.

The Fourier transform infrared (FTIR) spectrum of *Irvingia gabonensis* mucilage display several function groups. Infrared spectroscopy is a process based on the vibrations of atoms of a molecule. It shows the functional groups that are available in molecules of a sample. Usually the spectrum is obtained by passing infrared radiation through a material and determining the portion of incident radiation absorbed at a particular energy. The frequency of vibration of a part of molecule in the sample is the energy at which any peak in absorption spectrum appears (Stuart, 2004; Michael, 2017).

The IR spectrum's X-axis is labeled as a wave number and ranges from 400 to 4000 in number. The absorbance numbers are given by the X axis. The Y-axis is called "percent transmittance" and extends from the bottom of zero (0) to the top of 100. It is possible to divide the spectrum into four regions, the first, second, third and fourth regions, which ranges from 4000 to 2500, 2500 to 2000, 2000 to 1500 and 1500 to 400 respectively. The first, second and third regions are the functional group region while the fourth region is the

finger print region and contains a large number of absorption peaks that accounts for a large variety of single bonds (Michael, 2017). If the peaks of an IR spectrum of a sample (both the finger print region and the other regions) are identical or superimpossable to the IR spectrum of another sample, then, the two samples or molecules are identical (Michael, 2017).

The functional group region of *Irvingia gabonensis* kernel mucilage showed five distinct absorption peaks. A broad band at 3351.68 and 3358.48 for oven dried and freeze dried *Irvingia* kernel mucilages, respectively. This is as a result of hydrogen bondings that contribute to the complex vibrational stretches arising from free inter and intra-molecular bound hydroxyl groups (O-H) that makes up the entire structure of carbohydrates. Hydrogen bonding has a strong influence on peak shape and intensity. It generally cause peak broadening ranging between 3600 to 3200 cm^{-1}(Hsu, 1997; Eddy *et al*., 2013). The sharp absorption peak at 2916.81 for both samples is due to C-H aliphatic stretch. The sharp absorption peak at 2850.27 for oven and freeze dried *Irvingia gabonensis* mucilage is because of a strong C-H stretch of alkane. Sharp absorption peaks 1741.41 and 1742.37 for oven and freeze dried *Irvingia* mucilages respectively shows strong carbonyl C = O stretch. The absorption peak 1654.62 for oven dried *Irvingia* mucilage and 1651.73 for freeze dried *Irvingia* mucilage indicates C = O stretch of ketone group and/or C = C stretch of alkene (John, 2000; Abdulsamad *et al*., 2012; Eddy *et al*., 2013 and Udoh *et al*., 2017).

The finger print region of the *Irvingia gabonensis* kernel mucilage FTIR spectrum comprises of several absorption peaks. The peaks at 1175.4, 1105.01 and 720.28 for both oven and freeze dried *Irvingia* mucilage are note worthy. Peaks 1175.4 and 1105.01 are due to C-O stretching of carboxylic acid, ether, ester or alcohol, suggesting the presence of these moeties. The absorption at 720.28 is as a result of C-H bending of phenyl ring substitution indicating the presence of aramatic group (Eddy *et al*, 2013; Udoh *et al*., 2017).

5.1.3 *Irvingia gabonensis* mucilage powder characteristics

The particle density influences powder compaction behavior (Odeku and Itiola, 2007). Dense, hard materials usually require higher compression pressure to produce less friable cohesive tablet (Alderborn, 1988). Materials of lower particle density will give more cohesive compacts than ones of higher particle density at a given compression pressure. *Irvingia* kernel mucilages were observed to have slightly lower particle density than HPMC, but xanthan gum has clearly higher values. Both bulk and tapped densities give understanding on the particle packing and rearrangement and the compact profiles of a material. Like the particle densities, *Irvingia* kernel mucilages bulk and tapped densities, were slightly lower than HPMC and xanthan gum values were slightly higher.

Hausner's ratio is a measure of inter-particle friction while Carr's index is indicative of the powder ability to decrease in volume i.e a measure of powder compressibility. Both are useful in predicting powder flowability (Staniforth and Aulton, 2007). Oven and freeze dried *Irvingia* kernel mucilage had closely comparable Hausner ratio and Carr's index to HPMC which were lower than those of xanthan gum (Table 4.6).

Angle of repose is an indication of powder degree of cohesiveness, thus important in knowing powder flowability. It is a quantitative evaluation of cohesive and frictional impact within the powder under lower level external loading like the case during powder blending or tablet die or capsule shell filling (Marshall, 1986). Freeze dried *Irvingia* kernel mucilage angle of repose was lowest, following by HPMC. The angle of repose of oven dried *Irvingia* kernel mucilage and xanthan gum were about the same (Table 4.6).

5.1.4 Compressional behaviour of *Irvingia gabonensis* kernel mucilage and the ibuprofen-mucilage matrices

Irvingia kernel mucilage was compressible on its own as it formed intact tablets at both low (14.14 MNm^{-2}) and high (169.69 MNm^{-2}) compression pressure used in this study like the standard polymers, xanthan gum and HPMC. All the tablets at various relative densities

had friability values < 1%. The ranking of the crushing strength at relative densities of 0.85 which is an approximate representation of commercial tablets was freeze dried *Irvingia* kernel mucilage > oven dried *Irvingia* kernel mucilage. Crushing strength of HPMC and xanthan could not be determined because the tablets remained intact at the maximum crushing strength (500N) of the testing device. While the ranking for the friability at relative density of 0.85 was oven dried *Irvingia* kernel mucilage > freeze dried *Irvingia* kernel mucilage > xanthan gum > HPMC (Table 4.16).

The values of particles densities, granules densities (wet granulations), loose bulk densities and relative densities at zero pressure (D_o) for all the ibuprofen-polymer formulations decreased with increase in ibuprofen concentration. The mean granule size (G) for the ibuprofen-*Irvingia* kernel polymer formulations during wet granulation generally increased with increase in ibuprofen concentration. The ranking of the mean granule size (G) was freeze dried *Irvingia* kernel mucilage formulations > oven dried *Irvingia* kernel mucilage formulations.

Heckel plots for the mucilages and ibuprofen - mucilage formulation exhibited two regions or two phases of compression. The second phase of compression generally started at 70 MNm^{-2} up to 169.69 MNm^{-2} and displayed higher correlation coefficient for linearity of > 0.989 for all formulations. This region was used to obtain values of K (slope) and A, the intercept of the extrapolation of the region used in calculating K. Py is the mean yield pressure and reciprocal of K. The intercept, 'A 'is the exact point of formation of a suitable tablet within the compression process. D_A and D_B are both relative densities (Table 4.13). D_A represents the total degree of densification obtained at zero and low pressure, while D_B is relative density resulting from the particles rearrangement at the beginning of compression and defines the particle rearrangement phase at the onset of compression due to the initial packing of particles within the die during the filling. However fragmentation can take place simultaneously as elastic and plastic deformation is occurring (Odeku, 2007).

The values of D_o for all the ibuprofen - mucilage formulations decreased with increase in ibuprofen concentration. D_o values of direct compression formulations were slightly higher than those of wet granulation formulations. Odeku and Fell (2006) reported similar observation in their study of khaya gum matrices using paracetamol and attributed it to the fact that granules are more loosely packed than powders. D_A and D_B, on the other hand increased as the ibuprofen proportion in the formulations increases. However, wet granulation formulations D_B values were higher but D_A values lower than direct compression formulations. This also is similar with Odeku and Fell (2006) findings and suggests granules fragments more and exhibited lower degree of packing than powders. D_A values of *Irvingia* kernel mucilage were a little higher than HPMC and xanthan gum. This indicates a higher degree of packing at zero and low pressure.

The Kawakita plots for the mucilages and all ibuprofen - mucilage formulations displayed a linear relationship at all compression pressures with correlation coefficient of 0.999. The slope and intercept of the plots gives the constants **a** and **b** respectively. **a** refers to the minimum porosity of the powder bed before compression and **b** which is also known as the coefficient of compression, is associated with the plasticity of the material. D_i, the initial relative density of the formulation is obtain from **a** by subtract **a** from **1** i.e **1-a**. P_k is a pressure term obtained from **b** as the reciprocal of **b** and is the pressure needed to reduce the powder bed by 50% (Alderborn, 2002; Odeku, 2007).

P_k and P_y are both pressure parameters and are inverse measure of plasticity (Odeku *et al.*, 2005; Odeku and Fell, 2006; Ogunjimi and Alebiowu, 2014). P_k relates to the amount of plastic deformation taking place during compression process while P_y mainly relates to the onset of plastic deformation (Heckel 1961; Odeku and Itiola, 2003; Adedokun *et al*., 2014). P_y values of the formulations increased with increase in ibuprofen concentration for both direct compression and wet granulation formulations with wet granulation formulations having lower values. Therefore, wet granulation formulations displayed quicker start of plastic deformation than direct compression formulations. Wet granulation

formulations containing freeze dried *Irvingia* kernel mucilage exhibited lower P_y thus display faster onset of plastic deformation when compared to those containing oven dried *Irvingia* kernel mucilage. Materials that are brittle or easily fragmenting are known to have high P_y (yield pressure) values while those that deform plastically or elastically exhibit typically low yield pressure (Doelker.E, 1993; Odeku and Fell, 2006; Ogunjimi and Alebiowu, 2014). The increase in P_y values with increase in ibuprofen concentration is due to the reduction in plasticity of the mucilages with the inclusion of the nonmucilageic ibuprofen which decreases the plastic behaviour of the mucilages (Odeku and Fell, 2006; Ogunjimi and Alebiowu, 2014). Sanghvi *et al*., (1993); Talukdar *et al*., (1996) and Odeku and Fell (2006) made similar observations in their different studies.

5.1.5 Mechanical properties of *Irvingia gabonensis* kernel mucilage and ibuprofen-mucilage matrix tablets

The mechanical properties of the mucilage matrix tablets and the ibuprofen - mucilage matrices were tested using the crushing strength, friability and crushing strength-friability (CSFR) ratio. Crushing strength assesses the strength of the tablet while friability tests the weakness of the tablet, the greater the CSFR the stroger the tablet (Odeku and Itiola, 2003; Odeku and Fell, 2006; Bamiro *et al*., 2014; Adedokun *et al*, 2014). The crushing strength of the all the mucilage tablets and ibuprofen - mucilage matrix tablets increased with increase in relative density (packing fraction) as the compression pressure increased. This is likely due to the decrease in porosity. The decreased porosity enhances greater poximity of particles leading to increase in the number of contact points that give rise to the formation of more solid interparticulate bonds (Biu *et al*., 1999; Bamiro, 2011). Friability, on the other hand decreased for all mucilage tablets with increase in packing fraction.

Crushing strength and CSFR values of all the ibuprofen - mucilage matrix tablet formulations at a relative density of 0.90 (or estimated 0.85) representative of commercial tablets, decreased with a rise in drug concentration. Polymers are known to undergo plastic deformation, resulting in increased solid bond formation, which increases the strength of

the tablet (Odeku and Fell, 2006; Adedokun *et al*., 2014). But, the addition of drug in the polymer reduces the number of solid bond within the polymer, causing a decrease in the tablets strength and an increase in the friability (a measure of tablet weakness - Ogunjimi and Alebiowu, 2016).

Generally, there was statistically significant difference ($P < 0.001$) in the crushing strength, CSFR and friability values for each mucilage and among all the mucilages at relative density of 0.85 and 0.90 (Tables 4.19, 4.20 and 4.38) for all the drug concentrations used in both direct compression and wet granulation formulations. Freeze dried *Irvingia* kernel mucilage formulations had statistically significantly ($P < 0.01$) higher crushing strength, CSFR values and lower friability values than oven dried *Irvingia* kernel mucilage formulations. Also, the crushing strength and CSFR values of wet granulation formulations of *Irvingia* kernel mucilage were significantly ($P < 0.001$) higher than the direct compression formulations while the friability values were statistically significantly ($P < 0.01$) lower for wet granulation than direct compression. However, there was no significant difference ($P > 0.05$) in the release profile of ibuprofen from oven and freeze dried *Irvingia* kernel mucilage formulations prepared by both direct compression and wet granulation, but freeze drying slightly slowed the release. Therefore freeze drying and wet granulation enhanced the mechanical properties of the ibuprofen-*Irvingia* kernel matrix tablets. Odeku and Fell (2006) reported similar observation of wet granulation method improving the mechanical properties of matrix tablets, among others, compared to direct compression, without significantly affecting the dissolution times, in a study on *khaya* gum matrices containing paracetamol.

5.1.6 Drug concentration, excipient and polymer effect on the mechanical, drug release and mechanism of release from *Irvingia gabonensis* kernel-ibuprofen matrices

The assessment of the effect of drug concentration and addition of excipient on HPMC, xanthan gum, oven and freeze dried *Irvingia* kernel mucilage matrices containing ibuprofen showed that both the mechanical properties and the release of ibuprofen from the

matrices were altered. In general, there was a significant difference ($P < 0.03$) in crushing strength, friability, CSFR and t_{25} as ibuprofen concentration was increased for each mucilage from 10 percent w/w to 50 percent w/w. However, freeze-dried *Irvingia* kernel mucilage containing 10 and 20 percent w/w ibuprofen t_{25} values and friability of xanthan gum matrices show no statistically significant difference ($p > 0.05$). With increasing drug concentration, the crushing strength, CSFR and t_{25} values for the formulations decreased. Friability values increased with increase in drug concentration. The ibuprofen release rate increased as the quantity of ibuprofen added in the matrix tablet increases. This may be as a result of decrease in the cohesive forces within the matrix lattice because of the increasing concentration of the non-polymric ibuprofen in the matrices. Mucilages are plastoelastic. Increasing the concentration of drug which is non-polymeric (i.e decreasing the mucilage content of the binary mixture) during compression results decrease in plastic deformation. This in turn leads to decrease in formation of solid bonds in the matrix tablets, thus decrease in crushing strength. The increase in friability with increase in drug concentration is also likely due to the formation of less solid bonds which produces tablets with less resistance to abrasion and fracture (Odeku and Itiola, 2003). The results are similar to Bamiro's (2011) observation in a study on *terminala* gum as a controlled release agent using carvedilol as test drug.

Considering the effect of drug concentration across all polymers on crushing strength, friability and CSFR, there was significant difference ($P < 0.03$) between oven and freeze dried *Irvingia* kernel mucilage in both direct compression and wet granulation formulations and among all the polymers. The ranking of the crushing strength and CSFR values of the formulation was HPMC > xanthan gum > freeze dried *Irvingia* mucilage > oven dried *Irvingia* mucilage, but the reverse was the case for friability. However, xanthan gum matrices had significantly ($P < 0.02$) higher t_{25} values than HPMC and *Irvingia* kernel mucilage formulations at the various ibuprofen concentrations used. Thus, xanthan gum retarded the release of ibuprofen from the matrices more than HPMC, oven and freeze dried *Irvingia* kernel mucilage (Table 4.22). Talukdar *et al*., (1996) made similar

observation that xanthan gum, not withstanding its relatively lower crushing strength, slowed drug release more than HPMC in their comparative study using indomethacin, indomethacin sodium and caffine. Also, Tiwari *et al*., (2009) reported the same finding that xanthan gum displayed higher ability to slow drug release than HPMC.

Irvingia kernel matrix tablets containing up to 50% w/w ibuprofen were able to release the drug in a controlled manner over 9 hours like xanthan gum and HPMC standard polymers. However, *Irvingia* kernel mucilage matrix tablets were statistically significantly ($P < 0.02$) more friable. At higher drug concentration, 50% w/w for freeze dried *Irvingia* kernel and 30 and 50% w/w for oven dried *Irvingia* kernel mucilage, the tablets failed the friability test i.e had friability values more than 1% (Table 4.22). Thus, these matrix tablets showed inability to cope with the rigors of transportation and handling.

Direct compressible excipients have been added to tablet formulations to alter their size, enhance the compaction and mechanical features of the tablets and to aid optimum release of drug from the matrices (Cox *et al*., 1999; Odeku and Fell, 2004; Mutalik *et al*., 2007; Bamiro *et al*., 2011).Therefore, three direct compressible excipients, lactose (freely water soluble), avicel (microscrytalline cellulose- MCC) and dicalcium phosphate (DCP) which are water insoluble, were added into the matrix tablet formulation in the drug-polymer-excipient ratio of 1:3:1. The addition of the excipients improved the mechanical properties and altered the drug release profile of the ibuprofen - polymer matrix tablets. The crushing strength and CSFR of the formulations increased while the friability decreased on adding the excipients (20% w/w ibuprofen-polymer values on Table 4.22 compared to Table 4.23). There was significant difference ($P < 0.000$ – oven dried *Irvingia*; $P < 0.007$ – freeze dried *Irvingia*; $P < 0.001$ – xanthan gum and $P < 0.000$ - HPMC) in the crushing strength and CSFR of the matrix tablets containing the excipients. Changing the excipient from lactose to avicel or dicalcium phosphate resulted in significant difference in the crushing strength and CSFR in xanthan gum, HPMC, oven and freeze dried *Irvingia* mucilage matrices. The ranking of the excipient effect on the crushing strength and CSFR for each

polymer was DCP > Lactose > MCC. For friability, this was reversed. Comparing all the polymers, the ranking of excipient effect on crushing strength and CSFR was HPMC > Xanthan gum > Freeze dried *Irvingia* kernel mucilage > Oven dried *Irvingia* kernel mucilage, while the reverse was the case for friability. Generally all the matrix tablets containing the three different excipient had friability values < 1% thus have enhanced ability to cope with the distreses they are exposeed to during formulations transport and handling.

The addition of the excipients in the test polymer matrix tablet formulations facilitated the release of ibuprofen from the tablets (t_{25} values of 20% w/w ibuprofen-polymer formulations on Table 3.22 compared to Table 4.23). Lactose and avicel had lower t_{25} values than dicalcium phosphate excipient (Table 4.23). There was no significant difference ($P > 0.05$) in t_{25} for lactose and avicel but dicalcium phosphate t_{25} values were significantly ($P < 0.01$) higher than them in both oven and freeze dried *Irvingia* kernel matrices. Lactose is soluble and when the tablet is placed in the dissolution medium dissolves creating a diffusion pathway for release of the dug. Avicel on the other hand, though water insoluble may have largely acted through its disintegrant property and caused the break up of the matrix tablets which increased the dissolution rate thus faster release of the drug.

Unlike *Irvingia* kernel mucilage, there was a slower release of ibuprofen from xanthan gum and HPMC standard polymers containing the excipients, more notably in HPMC formulations (See Tables 4.22 and 4.23) as shown by the longer t_{25} values. The t_{25} values of xanthan gum and HPMC matrices containing lactose, avicel and dicalcium phosphate excipients were significantly ($P < 0.000$) higher than the values for oven and freeze dried *Irvingia* kernel matrices with the three excipients. The water insolubility property of both avicel and dicalcium phosphate may have outplayed other properties here. Insoluble diluents such as tricalcium phosphate and dicalcium phosphate have been reported to increase the tortuosity of matrix tablets (Cox *et al*., 1999, Odeku and Fell, 2004; Bamiro *et*

al., 2011). Therefore, avicel and dicalcium phosphate may have likely increased the tortuosity of the matrices and elongated the diffusion path of the drug leading to slower release. How water soluble lactose slowed drug release in xanthan gum and HPMC is not clear. But it is not unlikely that it may have interacted with these mucilages in some ways to increase both their gel forming property and re-enforce the matrix lattice to reduce water penetration thus retarding drug release.

Polymer effect on the ibuprofen-*Irvingia* kernel matrices study showed that as the concentration of xanthan gum or HPMC polymer increased, t_{25} and t_{50} also increased while the percent released after 9 hours decreased. Xanthan gum t_{25} and t_{50} values were higher and the percentage released after 9 hours lower showing that it retarded the release of ibuprofen more. A careful selection of polymers, mixed together in appropriate proportion can be used to achieve time-independent controlled release of drug from matrix systems (Odeku and Fell, 2004). HPMC and xanthan gum are known to form strong viscous gel. The decrease in ibuprofen release rate with increase proportion of HPMC or xanthan gum manifested by the increasing t_{25} and t_{50} values is likely because of the raised difficulty of the gel layer to get eroded and great consistency of the gel serving to slow down the diffusion of ibuprofen from the ibuprofen-*Irvingia* kernel matrices. Odeku and Fell (2004) reported a similar decrease in drug (paracetamol) release from khaya gum matrices with increase in concentration of HPMC.

The dissolution data obtained from the various studies on ibuprofen-*Irvingia* kernel mucilage and the two standard polymer matrix tablets were fitted into the different dissolution mathematical models or kinetic equations to determine the drug release kinetics and from the n value of Korsemeyer-Peppas model, the release mechanism. The correlation coefficient 'r^2' (and the drug release exponent 'n' from Korsemeyer-Peppas equation) were obtained from the different models. The model that has the highest correlation coefficient 'r^2' is taken as the best fit drug release kinetics. Drug release following zero order kinetics means, the drug release is not dependent on the drug concentration. First order kinetic

indicates drug release is reliant on the concentration of drug remaining in delivery device while Higuchi model means drug release is mainly by diffusion (Higuchi, 1968). Release model that follows the Hixson-Crowel kinetics implies drug release is dependent on change in surface area and diameter of matrix tablets (Hixson-Crowell, 1931). Lastly the Korsemeyer-Peppas kinetics takes into account the structured and geometric features of the tablet (Korsemeyer *et al*., 1983). The drug release model most suitable for controlled release are the Higuchi model and Zero order kinetics while First order kinetics is more appropriate for conventional tablets (Chowdary *et al*., 2006; Bamiro, 2011).

Generally, drug concentration greatly affected the released model in all the polymers except freeze dried *Irvingia* kernel mucilage where the drug release kinetic followed the Korsemeyer-Peppas model irrespective of drug concentration. Also, it was observed that at low ibuprofen concentration of 10% w/w, the preferred drug release kinetics was Korsemeyer-Peppas for all four polymers. For oven dried *Irvingia* kernel mucilage, drug release for 20 and 30% w/w ibuprofen matrices was by first order while 50% ibuprofen formulation was through Korsemeyer-Peppas model. Xanthan gum containing 20 to 50% w/w ibuprofen matrix tablets released the drug via the Hixson-crowell model. The release kinetics for HPMC polymer containing 20 and 30% ibuprofen was both by Korsemeyer - Peppas and Hixson-Crowell while 50% w/w ibuprofen - HPMC matrices drug release was through Hixson-Crowell model.

The drug release from freeze dried *Irvingia* kernel mucilage matrix tablets containing added excipients was via first order kinetics not minding the excipient type. The release model in ibuprofen-oven dried *Irvingia* kernel matrices containing the three diluents (Avicel, lactose and DCP) was Hixson-Crowell kinetics, except for avicel containing matrices which also followed the Korsemeyer-Peppas model. Xanthan gum matrices containing avicel and lactose released ibuprofen following the first order kinetics while DCP excipient containing formulation was by Korsemeyer model. Ibuprofen release from

HPMC with all three directly compressible excipients was by Korsemeyer-Peppas model notwithstanding the excipient type.

Polymer effect on the release of ibuprofen from *Irvingia* kernel mucilage was quite varied for oven dried *Irvingia* kernel mucilage. Addition of HPMC at 10, 20, 30 and 40% w/w to oven dried *Irvingia* kernel mucilage caused the release of drug through first order, Hixson-Crowell, Korsemeyer and Higuchi kinetics respectively. The release of ibuprofen from freeze dried *Irvingia* kernel mucilage matrices containing 10 to 30% w/w HPMC followed the Hixson-Crowell model while 40% w/w HPMC containing formulation was by first order kinetic. Xanthan gum inclusion at lower proportions of 10 and 20% w/w in oven dried *Irvingia* kernel mucilage released ibuprofen following Hixson-Crowell kinetics, but by first-order kinetics when incorporated at higher concentrations of 30 and 40% w/w. The release kinetics of ibuprofen on inclusion of xanthan gum in freeze dried *Irvingia* kernel mucilage was the same as when HPMC was added to freeze dried *Irvingia* mucilage. Thus the release kinetics of ibuprofen from freeze dried *Irvingia* kernel mucilage matrices was independent of the type of polymer added in this study.

The mechanism of drug release (which was determined from the 'n' value of Korsemeyer - Peppas model) for drug concentration effect study was super case II transport ($n > 1$) but close to case II transport (zero-order release) for all drug concentrations in all mucilages except for 10% w/w ibuprofen-xanthan matrices which release mechanism was anomalous (non- Fickian) diffusion ($0.5 < n < 1.0$), but also approached zero-order (Case II transport). Drug release mechanism for excipient effect evaluation was super case II transport for both oven dried and freeze dried *Irvingia* kernel mucilage with avicel, lactose and DCP diluents. It was anomalous (non-Fickian) diffusion for xanthan gum and HPMC containing avicel, lactose and DCP excipient. At all proportions of both HPMC and xanthan gum added into both oven dried and freeze dried *Irvingia* kernel for the assessment of polymer effect on the ibuprofen - *Irvingia* kernel matrices, the release mechanism was super case II transport.

5.1.7 *Irvingia gabonensis* kernel assessment as coating substance for colon specific drug delivery

Colon specific drug delivery is constrained by the absorption and degradation pathway at the stomach and small intestine (El-kamel *et al.*, 2008). Thus any colon targeted delivery form should be capable of protecting drug through the upper gastrointestinal (GIT) during the GIT transit period and deliver it at the colon. Colonic microflora-activated delivery system i.e strategies that explore carrier or polymers which are metabolized only by colonic bacteria are the approaches with the greatest prospect so far for being site explicit (Krishnaiah *et al*., 2002; Odeku and Fell, 2004; Jain *et al*., 2007).

The study on evaluation of *Irvingia* kernel mucilage as coating device for colon targeted delivery showed that as the coating weight is increased, crushing strength increases, but friability decreased. The ibuprofen core tablet dissolution test was done in Sorensen's phosphate buffer (pH 7.4) because of ibuprofens weekly acidic nature (Pka of 4.9) and insolubility in acidic medium (Odeku, 2005). The t_{20} and t_{60} values were 6 minutes and 12 minutes respectively and thus conforming to the official requirement of 70% of active agent being released within 45 minutes. Ibuprofen release studies from the compression coated tablets were done using 0.1M HCL for the first two hours, then, for three hours in Sorensen's buffer (pH 7.4), accompanied for the remainder of the test by phosphate-buffered saline-PBS (pH 6.8) to replicate the physiological condition from mouth to colon (Odeku, 2005). The capacity of *Irvingia* kernel mucilage to remain unimpaired in the stomach and small intestine was thus tested. The percent of ibuprofen released after 5 hours from 300 mg oven dried *Irvingia* kernel mucilage was 16%, while 11% was released from the 400 mg coat. Freeze dried *Irvingia* kernel coating of 300 mg released 13.5% of ibuprofen after 5 hours and 400 mg coat released 10%. The amount of ibuprofen released is thus dependent on the weight of the coating material and also on the drying method of the kernel mucilage. The more the quantity of coating material the smaller the drugs release. Also, freeze dried *Irvingia* released slightly lower amount of drug. No statistically significant difference ($P>0.05$) was found between the quantity of ibuprofen released from

the two coating materials of the *Irvingia* kernel mucilage and the 300 mg and 400 mg coated tablets. The percent release after 5 and 9 hours of the 300 mg and 400 mg *Irvingia* kernel coated tablets (Table 4.39) also confirm the dependence of the amount of ibuprofen released on the coat weight. But, the values equally showed the lack of statistically significant difference between the oven dried and freeze dried *Irvingia* kernel mucilage. The results are similar to the observation of Odeku and Fell (2004) on Khaya and albizia compression coating tools to ensure delivering drugs at the colon as target site, although there was statistical significant difference ($P<0.05$) in indomethacin release from khaya and albizia gums in their evaluation.

5.1.8 Factorial experimental studies

The quantitative study or factorial experimental assessment of processing factor (F), method of preparation (M) and concentration of ibuprofen (C) on the crushing strength and CSFR individual effect showed that ibuprofen concentrate had the greatest effect on the crushing strength and CSFR of the ibuprofen-*Irvingia* kernel mucilage matrix tablets at relative density of 0.9. The ranking was C > M > F for crushing strength and C > F > M for CSFR (Table 4.41). For the combined effect study, the interaction between processing factor and concentration of drug (F-C) had the greatest effect on both crushing strength and CSFR with a ranking of F-C > M-C > F-M for both crushing strength and CSFR (Table 4.42).

CHAPTER SIX

SUMMARY, CONCLUSION AND RECOMMENDATIONS

6.1 Summary

Irvingia gabonensis kernel mucilage has been evaluated as a matrix system and compression covering tool for controlled drug delivery.

The mucilage was extracted (appreciable yield) from the dried kernel of *Irvingia* by known procedure, oven and freeze dried to have two samples and phytochemical and physicochemical characterisation done. Both direct compression (xanthan gum and HPMC as standards) and wet granulation methods were used to prepare *Irvingia* matrix tablets of different ibuprofen concentrations, exipients (lactose, avicel & DCP) and polymer (xanthan and HPMC). *Irvingia* kernel mucilage was also utilised as a compression covering material for colon targeted drug delivery. The compressional behaviour, mechanical properties of the mucilage and the drug (ibuprofen)-mucilage matrices were evaluated. The drug release from the matrices and the coated tablets were assessed in conditions mimicking the G.I.T. The drug release kinetics and mechanism were determined. The effect of drug concentration, excipient and polymer kind on the compression and tablet strength, release kinetics and mechanism was investigated. The quantitative individual and interaction effect of processing factor, preparation process and concentration of drug on crushing strength and CSFR of the drug- *Irvingia* mucilage matrices was assessed.

Irvingia gabonensis kernel mucilage was straightforwardly compressible, deformed plastically quickly and extensively relative to the standard polymers. Wet granulations improved strength of the matrices like Avicel and DCP excipients. Increasing ibuprofen concentration reduced the tablet strengtrh and speed up drug release. *Irvingia* mucilage having 50% ibuprofen achieved controlled release for beyond 9 hours with dissolution

times ranking of xanthan gum > freeze dried *Irvingia* mucilage > HPMC > oven-dried *Irvingia* mucilage. Ibuprofen release from *Irvingia* mucilage was facilitated by added excipients. The drug release kinetics for the kernel mucilage was mainly by Kersemeyer-Peppas model, but Hixon-crowell for xanthan gum and HPMC. Increasing the proportion of standard polymers in the *Irvingia* matrices reduce ibuprofen release rate and percentage over 9 h, xanthan gum slowing it more. Drug release mechanism from all polymers at all drug concentrations was generally super case II. *Irvingia* kernel mucilage successfully protected ibuprofen for upper GIT and delivered the drug at the colon in conditions similar to colonic environment in the colon specific delivery study.

6.2 Conclusion

The assessment of *Irvingia* mucilage obtained from the dried kernel or nuts of the seed of *Irvingia gabonensis* (O'Rorke) Bail (family *Irvingiaceae*) also known as African bush mango or wild mango, using matrix approach and compression coating substance for controlled drug release has shown that:

The kernel mucilage was directly compressible, served as a wet granulation matrix system and compression covering device to convey drug precisely to the colon for action. It deforms plastically, doing so quickly and extensively when compressed. The matrices properties (mechanical and drug release), drug release kinetics and mechanism were influenced by the drug concentration included in them, excipient and polymer, except the release mechanism that was not affect by the concentration of xanthan and HPMC polymers added. Drug concentration had the greatest individual effect on crushing strength and CSFR while interaction between processing factor and drug concentration showed greater interactive effect on crushing strength and crushing strength-friability ratio in the factorial experimental design.

Irvingia gabonensis kernel mucilage compared favourably with xanthan gum and HPMC standard polymers as matrix system for controlled drug delivery and can serve as a suitable

substitute. It protected the drug in the coated tablet from the stomach and small intestine and released it at the colon, thus manifesting good potentials for targeting drug to the colon for colon specific delivery.

6.3 Recommendations

i. Useful plants of potential raw material source need to be domesticated, propagated, and cultivated on a large scale.

ii. Government needs to urgently fix the challenge of epileptic electricity as steady power is indispensable for fruitful research.

iii. The Departmental authority may liaise with alumni of the Faculty to collaborate in supply of equipment to address the problem of non-availability because Government alone cannot do everything.

iv. The School authority and the government are encouraged to do more by increasing grants for research.

v. The Faculty authority may consider organizing more seminars on how to access research grants for postgraduate students early at the beginning of their programme.

6.4 Contribution to knowledge

i. *Irvingia* kernel mucilage is slightly acidic (pH 5.23-oven dried and 5.80-freeze dried), has particles that are irregularly shaped and flaky in appearance, exhibit some degree of crystallinity, possess several functional groups, devoid of heavy metals and appreciable yield of 43.8%.

ii. Freeze drying of *Irvingia* kernel mucilage compared to oven drying not only slightly improved the flow properties as reflected by the slightly lower Hausner's ratio, Carr's index and angle of repose values, but also the mechanical properties.

iii. Wet granulation formulations of ibuprofen-*Irvingia* kernel mucilage matrices were of higher mechanical properties compared to the direct compression formulations and displayed faster onset of plastic deformation. Freeze dried *Irvingia* kernel

mucilage wet granulation formulations exhibited faster start of plastic deformation relative to the oven dried *Irvingia* kernel mucilage wet granulation formulations.

iv. Freeze drying of *Irvingia* kernel and wet granulation improved the mechanical properties of the ibuprofen-*Irvingia* kernel matrix tablet without significantly altering the ibuprofen release profile.

v. Increasing the concentration of ibuprofen in the ibuprofen-polymer matrices generally decreased the mechanical properties and increased the release of ibuprofen from the matrix tablets. Xanthan gum retarded the release of ibuprofen most and *Irvingia* kernel compared closely to HPMC polymer in drug release.

vi. *Irvingia* kernel mucilage containing up to 50% w/w ibuprofen was able to release the drug in a controlled way over 9 hours like xanthan gum and HPMC but at higher percentage release than the two standard polymers.

vii. *Irvingia* kernel mucilage released ibuprofen from the matrices mainly through Korsemeyer-Peppas drug release model unlike xanthan and HPMC standard polymers where ibuprofen release followed mainly the Hixson-Crowell Kinetics except 20% and 30% w/w ibuprofen-oven dried *Irvingia* matrix tablets where ibuprofen release followed first order kinetics and 20% and 30%w/w ibuprofen-HPMC matrices which also followed the Korsemeyer-Peppas model in addition to Hixson-Crowell kinetics. At 10%w/w ibuprofen concentration, the drug release kinetics from all polymers was by Korsemeyer-Peppas Kinetics.

viii. Increase in proportion of HPMC or xanthan gum included in the ibuprofen-*Irvingia* kernel matrix tablets resulted in decrease in ibuprofen release and percentage ibuprofen released after 9 hours with xanthan gum having a higher effect.

ix. The mechanism of ibuprofen release at all drug concentrations for all polymers was supercase II, except 10%w/w ibuprofen-xanthan matrices which was anomalous (non-Fickian diffusion).

x. For all three directly compressible excipients incorporated, the mechanism of ibuprofen release from *Irvingia* kernel mucilage was supercase II, but anomalous (non-Fickian) for xanthan and HPMC.

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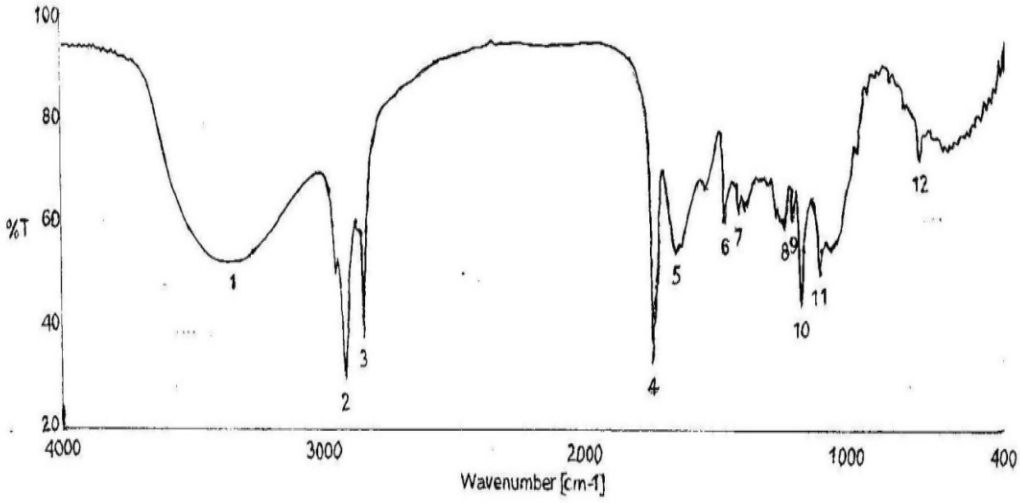
Appendix I



[Comments]

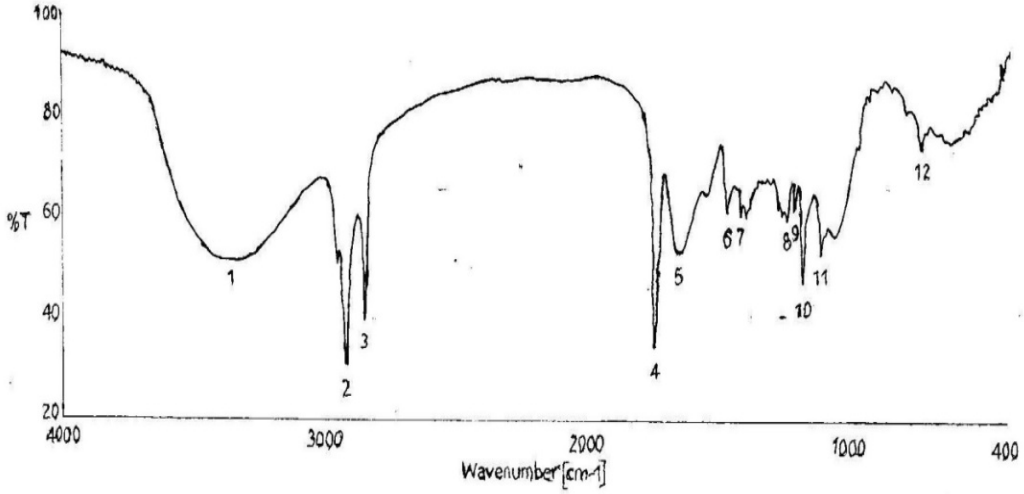
Sample name	V
Comment	KMCH COP
User	
Division	Pharm analysis
Company	KMCH

[Result of Peak Picking]

No	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	335.68	51.6831	2	2916.81	28.3049	3	2850.27	37.0787
4	174.41	32.566	5	1654.62	54.0682	6	1465.63	59.713
7	1413.57	61.4868	8	1238.08	58.7891	9	1205.29	60.3314
10	1175.4	43.6655	11	1105.01	50.0636	12	720.282	72.4893

FTIR spectrum of oven dried *Irvingia gabonensis* kernel mucilage

Appendix II



[Comments]

Sample name	FIV
Comment	KMCH COP
User	
Division	Pharm analysis
Company	KMCH

[Result of Peak Picking]

No	Position	Intensity	No.	Position	Intensity	No.	Position	Intensity
1	3358.43	50.8463	2	2915.81	29.4179	3	2850.27	38.6116
4	1742.37	33.9183	5	1651.73	52.7379	6	1465.63	60.5217
7	1413.57	60.7287	8	1238.08	59.9679	9	1205.29	61.8956
10	1175.4	46.5437	11	1105.01	53.0016	12	720.282	74.5911

FTIR spectrum of freeze dried *Irvingia gabonensis* kernel mucilage