`

THE USE OF GELATIN-ACACIA CO-PRECIPITATE (GELAC) IN THE FORMULATION OF SUSTAINED RELEASE MATRIX TABLETS OF DICLOFENAC SODIUM

BY

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AUGUST, 2018

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BY

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DEPARTMENTOF PHARMACEUTICS AND PHARMACEUTICAL MICROBIOLOGY,
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ZARIA NIGERIA

AUGUST, 2018

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DECLARATION

I declare that the work in thisdissertation entitled "The use of gelatin-acacia co-precipitate(GELAC) in the formulation of sustained release matrix tablets of diclofenac sodium" has been performed by me in the Department of Pharmaceutics and Pharmaceutical Microbiology. The information derived from the literature has been duly acknowledged in the text and a list of references provided. No part of this dissertation was previously presented for another degree or diploma at this or any other Institution.

Mponan GUGA _____ _____

Signature Date

`

CERTIFICATION

This dissertation entitled THE USE OF GELATIN-ACACIA CO-PRECIPITATE(GELAC) IN THE FORMULATION OF SUSTAINED RELEASE MATRIX TABLETS OF DICLOFENAC SODIUMby Mponan GUGA meets the regulations governing the award of the degree of MASTER OF SCIENCE IN PHARMACEUTICS of the Ahmadu Bello University, and is approved for its' contribution to knowledge and literary presentation.

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Abbreviations

‘n’:	Diffusion exponent
API:	active pharmaceutical ingredients
BDDCS:	Biopharmaceutics Drug Disposition Classification System
FT-IR:	Fourier transform infra-red
HPMC:	Hydroxypropyl methylcellulose
MCC:	Microcrystalline cellulose
NSAID:	Non-steroidal anti-inflammatory drug
r^2:	Correlation co-efficient
S.D:	Standard deviation
SEM:	Scanning electron microscopy

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ABSTRACT

Gums find application in tablet formulation as binder because of their adhesive nature. Natural gums are promising biodegradable polymeric materials. The aim of this study was to prepare a gelatin and acacia co-precipitate (GelAc) to be used as a release retardant in the formulation of sustained release matrix Tablets of diclofenac sodium. Gelatin and acacia solution was precipitated in a ratio of 1:1 using acetone as the precipitating solvent. The dried product was size reduced and the physicochemical properties of the precipitate (GelAc) were evaluated with respect to micromeritics and Fourier Transform Infrared (FT-IR) spectroscopy. FT-IR of GelAc showed no interaction between GelAc and diclofenac. GelAc was used in varying percentages of (10 - 50 %) of the total weight of the Tablet formulation. The formulated tablets were analysed for uniformity of weight tablet thickness and diameter, crushing strength, disintegration time, friability and content uniformity. *In-vitro* drug release profile of diclofenac sodium from GelAc matrix tablets were also studied using Simulated Gastric Fluid (SGF) for the first two hours and Simulated Intestinal Fluid (SIF) for the next eight hours. Hydroxypropylmethylcellulose (HPMC) was used as a standard matrix to compare the sustaining action of GelAc as a drug retardant for diclofenac sodium. Result from this study showed a good yield of GelAc (92.39 %) from the Co-precipitation. GelAc also had good flow properties. The tablets produced passed the official test for Tablets and had a good content uniformity. Dissolution tests carried out showed that with an increase in GelAc concentration there was a reduction in release rate. GelAc sustained the release of diclofenac sodium for over ten hours. Tablet formulation G2 containing 20 % GelAc was considered the best as it gave the highest release co- efficient value (n) at 0.963.The result from this study shows that GelAc can be used to formulate sustained release tablets of diclofenac sodium.

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CHAPTER ONE

1.0 INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes (Rao *et al.*, 2013).

It is the most commonly usedroute of drug administration, with more than 70% of all medicines being delivered via this route (McConnel and Basit, 2013).Recently, there has been a decrease in the number of new drugs from research and development and the already existing drugs are presenting with adverse effects, non-compliance and the problem of resistance, specifically in case of antibiotics. Hence, the change in focus is a suitable and optimized way to make some of the current drugs in use more effective by slight alteration in their delivery (Rao *et al.*, 2013).

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and maintain the desired drug concentration i.e. the drug-delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of treatment. The two most important aspects of drug-delivery are spatial placement and temporal delivery of a drug. Spatial placement relates to the targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed controlled-release drug-delivery system can be a major advance towards solving these two problems (Robinson, 2002).In conventional therapy, the administration of drug either by intravenous injection or by extravascular route e.g. orally, intramuscularly or rectally does not maintain drug blood levels within the therapeutic range for an extended period of time due to the inability of conventional dosage forms to control

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temporal delivery (Bose *et al*., 2013). Conventional dosage forms are associated with various limitations, such as drug plasma level fluctuations (leading to adverse effects or toxicity due to overdoses), high dosage frequency, high dosage requirements, and poor patient compliance (Zheng *et al*., 2015) and formulating drugsas modified release dosage forms would help to tackle the problem of non-compliance by patients (Susanta and Durga, 2015).

1.1Sustainedand Controlled-Release Drug-Delivery Systems

In recent times, conventional dosage forms have been and are being rapidly replaced by the new and novel drug delivery systems. Amongst these, the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics (Bose *et al*., 2013).The goal in designing sustained- or controlled- delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug (Jantzen and Robinson, 2002).

1.1.1.Sustained release formulations

The term “sustained release” has been used to describe pharmaceutical dosage forms formulated such that the release of the active pharmaceutical is retarded over time, and a constant level of the drug is maintained within thesystemic circulation.Sustained release dosage form is defined as a well characterized and reproducible dosage form, which is designed to control drug release profile at a specified rate to achieve desired drug concentration either in blood plasma or at target site (Agarwal*et al*., 2017).

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1.1.2Controlled release formulation

Controlled release system means any drug delivery system that maintains adequate and desired release of drug over an extended period of time (Brahmankar *et al.*,2009).Controlled release dosage forms cover a wide range of prolonged action formulations which provide continuous release of drug at the specific site for a predetermined time at a predetermined rate (Goyal *et al.*, 2017).

1.1.3 Difference between sustained-release and controlled-release

Controlled drug delivery- delivers the drug at a pre-determined rate for a specified period of time. Controlled release is perfectly zero order release that is the drug release over time is constant irrespective of concentration (Bose *et al.*, 2013).

Sustained release dosage form is the type of dosage form in which a portion i.e. (initial dose) of the drug is released immediately, in order to achieve desired therapeutic response more promptly, and the remaining(maintenance dose) is then released slowly there by achieving a therapeutic level which is prolonged, but not maintained constant. Sustained releasealso implies slow release of the drug over a time period. It may or may not be controlled release.

1.1.4Rationale for sustained drug release

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems. Thus, optimal design of controlleddrug release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of drug.

The rational for the formulation of sustained drug release include

- To extend the duration of action of the drug
- To reduce the frequency of dosing

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- To minimize the fluctuations in plasma level
- Improved drug utilization
- Less adverse effects (Robinson and Lee, 1987)**.**

1.1.5Characteristics of drug for formulation as sustained release dosage form

Certain factors have to be put into consideration while selecting a drug candidate for sustained release system. Drugs with the following characteristics are not suitable for formulation as sustained release systems:

1. Those which are not effectively absorbed in the lower intestine

2. Those having short biological half-lives (<1hr) e.g. Furosemide

3. Those having long biological half-lives (>12hrs) e.g. diazepam

4. Drugs that require large doses e.g. sulphonamides

5. Drugs with low therapeutic indices e.g. Phenobarbital

6. Those with extensive first pass metabolism.

7.Drugs with low solubility (Satish *et al*., 2013).

1.1.6Factors influencing Sustained-Release Dosage Form Design

The factors that influence the design of sustained release have being broadly classified into two.

A) Biological and B)Physicochemical factors.

1.1.6.1Biological factors influencing sustained-release dosage form design

1. Biological Half-Life:The usual goal of an oral sustained-release product is to maintain therapeutic blood levels over an extended period. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristic elimination rate, which is the sum of all elimination process, including metabolism,

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urinary excretion, and all other processes that permanently remove drug from the bloodstream.

Therapeutic compound with short half-lives are excellent candidates for sustained release preparations, since this can reduce dosing frequency. However, this is limited, in that drug with very short half-lives may require excessively large amounts of drug in each dosage unit to maintain sustained effect, forcing the dosage form itself to become large in size. Compounds with long half-lives, more than 8 hours, are generally not used in sustaining drug release, since their effect is already sustained.

2. Absorption:The characteristics of absorption of a drug can greatly affect its suitability for sustained-release formulation. Since the purpose of forming a sustained-release product is to control the drug delivery, it is necessary that the rate of release is much slower than the rate of absorption.

If drug transport is limited to specific region of the intestine then absorption may not be of advantage to sustain release.

3. Metabolism**:**Drug metabolism can result in either inactivation of an active drug or conversion of an inactive drug to an active metabolite. Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during specific period, allowing more complete conversion of the drug to its metabolites. Formulation of these enzymatically susceptible compounds as pro-drugs is another viable solution.

4. Protein Binding:The characteristics of protein binding by a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form. Extensive binding to plasma proteins will be evidenced by a long half-life of

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elimination for the drug, and such drugs generally do not require a sustained release dosage form(Satish *et al* 2013).

The Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes sustained release drug delivery system is not required for this type of drug.

5. Margin of safety: The larger the value of therapeutic index the safer the drug. Drugs with low therapeutic index are usually poor candidate for formulation of oral sustained release drug delivery system due to technological limitation of control over release rates. If the system fails in the body, dose dumping may occur, resulting in toxicity (Ratnaparkhi *et.al,* 2013).

1.1.6.2 Physicochemical factors influencing sustained-release dosage form design

The following are the physicochemical factors that influence drug release from oral sustained release systems

1. Dose size:For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

2. Aqueous solubility:For a drug to be absorbed it must first of all be dissolved in the aqueous phase surrounding the site of administration and then partitioned into the absorbing membrane. Two of the most important physicochemical properties of a drug

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that influence its absorptive behaviour are its aqueous solubility and its pKa(if it is a weak acid or base). These properties play a big role in the performance of controlled release systems.

The aqueous solubility of a drug influences its dissolution rate, poorly soluble drugs (<0.01mg/ml) are often dissolution rate-limited, hence are inherently sustained since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug and as such do not require any additional control over their dissolution rate which establishes its concentration in solution and hence the driving force for diffusion across membrane (Jantzen and Robinson, 1996, Satish *et al.*,2013).In general drugs with extremes of solubility are generally not ideal for sustained release.

3. pKa:pKa is a measureof the strength of an acid or base. The pKa allows for determination of the charge on a drug molecule at any given pH. Drug molecules are active only in undissociated form, unionized molecules cross the lipid membrane much rapid than the ionized molecules. Drugs which exist in ionized form are poor candidates for sustained release dosage form.(Dusane *et al.*,2011)

4. Partition Coefficient:Between the time that a drug is administered and the time it is eliminated from the body,it must diffuse through a variety of biological membranes that act primarily as lipid like barriers. A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes isits apparent oil / water partition coefficient defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Drugs that have lower partition coefficient are not suitable for oral sustained release drug delivery system and drugs that have higher partition co-efficient are also not suitable for oral sustained release drug delivery system (Ho*et al.*,1987).This is to say extremes in partition coefficient, will demonstrate either low flux into the tissues or

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rapid flux followed by accumulation in tissues. Both cases are undesirable for sustained release system (Satish *et.al.* 2013, Kumar *et al.*,2011).

5. Stability:Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state as compared to those in solution or suspension; therefore, this is the preferred composition of delivery for problem cases. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form and as suchcan be formulated to deliver in the stomach. For the drugsthat are unstable in stomach, systems that target delivery to the intestine are beneficial. This is because more drugs are absorbed in the small intestine. Propentheline and probanthine are representative example of such drug (Tapaswi *et al.*,2013; Dusane*et al.*,2011).

1.1.7Method for preparing oral sustained release drug delivery system

Sustained release tablets can be manufactured by wet granulation, dry granulation or Sintering technique.

1.1.7.1Wet granulation technique

This method involves milling and gravitational mixing of drug, polymer and excipients followed by preparation of a binder solution whichis used in wet massing. The resulting mass is then screened, and dried and the dried granules will be screened again followed by blending with lubricant and disintegrant to produce “running powder” and then finally compression intotablet.

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1.1.7.2 Dry granulation technique

The process follows milling and gravitational mixing of drug, polymer and excipients and then compression into slugs or roll compaction. Slugs will then be screened and mixed with lubricant and disintegrant and finally compression of tablet.

1.1.7.3 Sintering technique.

Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat. The sintering process has been used for the fabrication ofsustained release matrix tablets for the stabilization of drug release (Lachman and Liebermann, 1991)

1.1.8Strategy for oral sustained release drug delivery system

The most common methods used to achieve sustained release of orally administered drugs are as follows;

1.1.8.1 Dissolution-controlled systems

Drugs with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. Therefore, the sustained-release preparations of highly soluble drugs could be made by decreasing their rate of dissolution. The approaches to achieving this include, preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material or incorporating it into a tablet with a slowly dissolving carrier (Jantzen and Robinson,2002).

Once the coating is dissolved, the drugbecomes available for dissolution. By varying the thicknesses of the coat and its composition, the rate of drug release can be controlled. Some preparations contain a fraction of the total dose as an immediatereleasecomponent to provide a pulse dose soon afteradministration. Dissolution-`controlled products can be sub-divided into two types (Satish*et al.*,2013):-

A. Encapsulation Dissolution controls (Satish*et al.*,2013)

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These systems involve coating of individual particles (or) granules of drug with a slowly dissolving material. The coated particles can be compressed directly into tablets or placed in capsules. The rate of dissolution of the drugis controlled by micro encapsulation. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thicknesses of the coat and its composition, the rate of drug release can be controlled. These products should not be chewed as the coating may be damaged.

B. Matrix Dissolution control: (Satish*et al.*,2013)

In this system an alternative approach is to compress the drug with a slow dissolving carrier. Here the rate of drug release is controlled by the rate of penetration of the dissolution fluid into the matrix, porosity, presence of hydrophobic additives and the wettability of system and surface of particle.

1.1.8.2 Diffusional systems

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually this barrier is an insoluble polymer. There are generally two recognized diffusional systems (Jantzen and Robinson, 2002)

A. Reservoir Devices

In this system a water insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particles (or) tablet. The active agent is released to the surrounding environment by diffusion process through the rate limiting membrane. In the reservoir systems the drug delivery rate remains fairly constant. (Satish*et al.*,2013)

B. Matrix Devices

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In the matrix devices the drug is dispersed in polymer matrix to form a homogeneous system known as a matrix system. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release. (Satish*et al.*,2013; Zalte and Saudagar, 2013).

1.1.8.3 Erosion products

In this system drug is mixed with a biodegradable polymer. These materials degradewithin the body as a result of natural biologicalprocesses and drug release occurs at a constant rate.Most biodegradable polymers are designed to degradeas a result of hydrolysis of the polymer chains into biologically acceptable and progressively smallercompounds. The release of drug from these products is controlled by the erosion rate of a carrier matrix. Therefore; the rate of release is determined by the rate of erosion.

1.1.8.4 Osmotic pump systems

The osmotic pump is the active agent in saltform) which acts to imbibe water from the surroundingmedium similar to a reservoir device butcontains an osmotic agent (e.g., via a semi-permeable membrane. Pressure isgenerated within the device which forces the activeagent out of the devicethrough an orifice (of a size designedto minimize solute diffusion, whilst preventing thebuild-up of a hydrostatic pressure head). The advantageof this type of product is that the constant release isunaltered by the environment of the gastrointestinaltract and relies simply on the passage of water into thedosage form. The rate of release can be modified byaltering the osmotic agent and the size of the hole.

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1.1.8.5. Ion exchange resins

Drug-resins have been successfully usedcommercially. The drug is bound to the resin andreleased by exchanging with appropriately chargedions in contact with the ion exchange groups. Thistechnique is applicable to certain drugs which have particular characteristics in terms of their relatively affinity for the polymers being used (Satish *et al.*, 2013).

1.2 Statement of the Research Problem

The dwindling revenue earnings of the country call for the need to look inwards into local production as source of raw materials for the growing Pharmaceutical industry in Nigeria to reduce the high cost of production from the importation of expensive raw materials.

Conventional drug release formulations have been associated with poor compliance as a result of multipledosing as well as side effects as a result of fluctuations in the plasma concentrations of the drugs.

Diclofenac sodium (a drug with a short half-life of 1-2 hours) is one of the most commonly used drugs for pain management in rheumatoid and osteoarthritis which are chronic diseases prevalent in the elderly, however, it requires multiple dosing and it has been associated with gastric irritation hence there is need for a formulation that is affordable and will maintain constant drug plasma levels to minimize adverse effects and improve patient compliance, a locally produced drug retardant for diclofenac will be desirable as a possible solutions to these challenges.

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1.3 Justification

A sustained release formulation eliminates multiple daily dosing, and fluctuations in drug blood level, this will enhance patient compliance and decrease overall cost of treatment for the patient and caregiver due to enhanced therapeutic benefit and fewer side effects.

Gelatin and acacia are both natural products, readily available locally, safe, bio-degradable and relatively cheaper as compared with other synthetic retardants, this will greatly reduce the cost of production and make the medications more affordable.

Gelatin-acacia co-precipitate had been used in a preliminary study as a binder and it had an excellent binding property (Olowosulu and Ojile, 2015)

The production and sale of the proposed drug retardant can improve the economic status of the country by saving valuable foreign exchange from importation of the expensive drug retardants and by providing employment opportunities from the production, sale and or export of these raw materials.

Improvement on marketed formulation by modifying release can extend a product's patent life.

Diclofenac sodium if formulated as a sustained release matrix tablet will be able to provide morning relief of pain associated with arthritis through bedtime dosing as well as prevent patient from experiencing pain intermittently through maintenance of therapeutic drug level.

1.4 Aim and Objectives

The aim of this study is to formulate the matrix tablet of diclofenac sodium using gelatin –acacia co-precipitate (GelAc) as drug release retardant and evaluate its release retarding properties.

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In this study, GelAc will be used as hydrophilic matrix for retarding release of sparingly water soluble diclofenac sodium.

1.4.1 Specific objectives

1. To prepare a drug release retardant containing gelatin and acacia by the method of co-precipitation.
2. To characterize the physicochemical properties of the drug release retardant.
3. To evaluate the retarding properties and kinetic profile of GelAc in matrix tablets of diclofenac.

1.5 Hypothesis

1.5.1Null hypothesis

GelAc a Gelatin-acacia Co-precipitate cannot be used as a hydrophilic matrix former to sustain the release of Diclofenac sodium

1.5.2 Alternate hypothesis

GelAc a Gelatin-acacia Co-precipitate can be used as a hydrophilic matrix former to sustain the release of Diclofenac sodium.

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CHAPTER TWO

2.0 LITERATURE REVIEW

2.1Matrix System

Matrix system is the most commonly used method for modulating drug release in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. A matrix device consists of a drug dispersed homogeneously throughout a polymer (hyrophillic or hydrophobic) matrix, which serves as a rate retardant. Drug in the outer layer exposed to the bathing solution is dissolved first and which then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving towards the interior (Sarika *et al.,* 2013). Matrix devices, due to their chemical inertness, drug embedding ability and drug release character, have gained steady popularity for sustaining the release of a drug (Yogesh *et al.*,2013)

2.1.1 Classification of matrix systems

Matrix tabletare generally classified into different types based on polymer type and porosity:

2.1.1.1Classification based on nature of polymer

1. Hydrophobic Matrices

In hydrophobic matrices, drug is mixed with an inert or hydrophobic polymer and then compressed into a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and

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acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion (Martini *et al.,* 2000; Sayed *et al.*,2009; Patel *et al.*,2013).

2. Hydrophilic Matrices:They are most widely used to control the release rate of drugs because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Hydrophilic matrix tablets may be defined as "Homogeneous dispersion of drug molecules within a skeleton of hydrophilic polymers, such as cellulose derivatives, sodium alginate, xanthan gum, polyethylene oxide, or carbopol, that swells upon contact with water"(Tapaswi *et al.*,2013).

These systems are also called swellable controlled release systems (Sayed *et al.,* 2009).

Apart from swelling and diffusion mechanisms polymer dissolution is another important mechanism that can modulate the drug delivery rate. Swelling or dissolution can be the predominant factors for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms (Patel *et al.*,2011). The release rate observed is possibly the zero-order release.

The basic operations involved in the preparation of the matrices are the same as those used to prepare conventional tablets, such as mixing and compressing the components. Granulation prior to mixing and the coating of matrix tablets are complementary operations widely used to manufacture matrix tablets. As well as the drug and the release-limiting polymer, other excipients are usually added as diluents, lubricants and anti-adherents.The polymers used in the preparation of hydrophilic matrices are divided in to two groups (Kumar *et al.*,2011)

- Cellulose derivatives*:*Methylcellulose 400 and 4000cPs, Hydroxyethylcellulose, Hydroxylpropylmethlcellulose (HPMC) 25, 100, 4000 and 1500 cPs and Sodium carboxymethylcellulose.

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- Non cellulose natural or semi synthetic polymers: Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, chitosan and modified starches.

3. Lipid Matrices: These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

4. Biodegradable Matrices: These consist of the polymers which are comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process into oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices:These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (*Phaephyceae*) by the use of dilute alkali (Gothi *et al.*, 2010).

2.1.1.2 Classification based on Porosity of Matrix:

There are three classes based on the porosity of material used(Basak *et al.*,2006; Khatri *et al.*,2013).

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1. Macro porous systems: In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusing molecule size. Adsorbent used here ethylene vinyl acetate (Khatri *et al.,* 2013)

2. Micro porous system:Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusing molecules size. Polypropylene foam powder is used here (Khatri*et al.,* 2013)

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

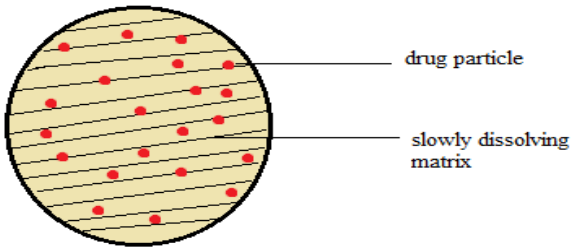
2.1.2 Mechanism of drug release from matrix tablet

a. Dissolution control matrix system

This consists of mixture of drug, polymer & excipients (filler/diluents as well as other excipients) prepared by hydrophilic polymer r in the matrix. A range of polymers areused here either singly or in combination with different polymers for release rate control (Ratnaparkhi, 2013).

This method involves compression of the drug with a slowly dissolving carrier in a tablet form. Here the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix.

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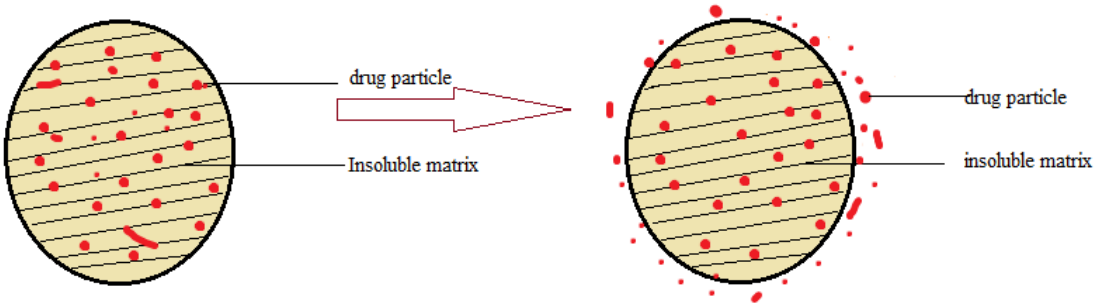


SCHEME 1: Schematic representation of a dissolution controlled matrix system

b. Diffusion control matrix system

Diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration.

A solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution (Ratnaparkhi *et.al.*, 2013) The diffusion type matrix system is shown in below



SCHEME 2: Schematic representation of a diffusion control matrix system

2.1.3 Polymers used in matrix tablet

1. Hydrogels: Polyhydroxyethylemethylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA)

2. Soluble polymers: Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC)

3. Biodegradable polymers: Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters

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4. Non-biodegradable polymers:Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)

5. Mucoadhesive polymers: Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin.

6. Natural gums Xanthan gum, Guar gum, Karaya gum, Locust bean gum.

(Vyas and Khar 2002).

2.1.4 Release limiting factor on drug release from a matrix system

Various factors affect drug release mechanism from hydrophilic matrices. These factors include; particle size of polymers, matrix swelling ratio (which depend on polymer type and controls water and drug diffusion coefficients),polymer and drug concentration.

The study of the drug release from the hydrophilic matrices requires knowledge of properties and interaction of the polymers used as the binder.

A. Polymer hydration:It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important step in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

For example; The Methocel K polymer, which has a low content of methoxy groups, hydrate quickly, which justifies its application in the controlled release matrices. The first minutes of hydration are the most important because they correspond to the time when the protective gel coat is formed around matrices containing HPMC.

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B. Drug solubility:Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

C. Polymer viscosity:With cellulose ether polymers, viscosity is used as an indication of matrix weight. Viscosity of the gelling agent retards or hastens the initial process of hydration. Increasing the viscosity of the polymer in a matrix formulation increases the gel layer viscosity and this slows drug dissolution. Also, the greater the viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

D. Polymer concentration:An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.

E. Thickness of polymer diffusional path:The controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:

$JD = D\, dc/dx$ ----------9

Where, JD is flux of diffusion across a plane surface of unit area D is diffusibility of drug molecule; dc/dx is concentration gradient of drug molecule across a diffusion path with thickness dx.

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F. Thickness of hydrodynamic diffusion layer:It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer.

G. Drug loading dose:The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, with increasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically increases. In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs another phenomenon also has to be taken in to account. When the amount of drug present at certain positions within the matrix, exceeds the amount of drug soluble under given conditions, the excess of drug has to be considered as non-dissolved and thus not available for diffusion. The solid drug remains within tablet, on increasing the initial drug loading of poorly water soluble drugs, the excess of drug remaining within matrix increases.

H. Surface area and volume:The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and experimentally. Both the *in vitro* and *in vivo* rate of the drug release, are observed to be dependent upon surface area of dosage form.Siepman*et al.*,(2002)found that release from small tablet is faster than large cylindrical tablets.

I. Diluent's effect: The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents

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like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix. The reason behind this is that water soluble filler in matrices stimulate the water penetration in to inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.

J. Additives:The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydrosoluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipients are insoluble like tricalcium phosphate (Brahmankar and Jaiswal 2000; Patel *et al.,* 2011; Satish*et al.,* 2013).

2.1.5Advantages of sustained release matrix drug delivery

1. With proper control of the manufacturing process, reproducible release profiles arepossible

2. System allows an immediate release of small amount of active principle.

3. Their capacity to incorporate active principle is large, which suits them to delivery oflarge doses.

4. The manufacturing processes are notably simple. Tablet formulation can be done viadirect compression or by wet granulation techniques.

5. The safety margin of high-potency drugs can be increased.

6. The drug release from hydrophilic matrices show a typical time dependence

7.Possible to formulate high molecular weight compounds especially using the diffusion controlled matrix system.

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8. The insoluble matrix system increases the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.(Brahmankar and Jaiswal, 1995; Ratnaparkhi, 2013).

2.1.6 Disadvantages of sustained release matrix drug delivery

1) The remaining matrix must be removed after the drug has been released from insoluble systems.

2) Greater dependence on GI residence time of dosage form. The release rates are affected by various factors such as, food and the rate transit through the gut.

3) Increased potential for first-pass metabolism.

4) Delay in onset of drug action.

5) Release rates are affected by food and the rate transit through the gut.

6) The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

7. Probability of dose dumping with the soluble matrix system.

8. Reduced potential for dose adjustment.

9. Requirement for additional patient education for proper medication.

(lachman and Lieberman 1990).

2.2 Drug Release Mechanisms

There are a number of kinetic models, which described the overall release of drug from the dosage forms. The release patterns can be divided into those that release drug at a

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slow zero or first order rate and those that provide an initial rapid dose, followed by slow zero or first order release of sustained component (Anonymous, 1977)

2.2.1 Zero order kinetics

Ideal delivery of drugs would follow "zero order kinetics", wherein blood levels of drugs would remain constant throughout the delivery period. This ideal delivery is particularly important in certain classes of medicines intended, for example, for antibiotic delivery, heart and blood pressure maintenance, pain control and antidepressants.

Zero order release kinetics refers to the process of constant drug release from a drug delivery device such as oral matrix tablets with low-soluble drugs and other delivery systems. In its simplest form, zero order release can be represented as

$Q = Q_0 + K_0t$----------1

Where,

Q=the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves),

Q_0=the initial amount of drug in solution (it is usually zero), and

K_0=the zero order release constant

The plot made: Cumulative % drug release vs. time (Suvakanta *et al.,* 2010, Satish *et al.,* 2013).

2.2.2 First order kinetic (log cumulative percentage of drug remaining versus time)

This model has also been used to describe absorption and/or elimination of some drugs. The release of the drug which followed first order kinetics can be expressed by the equation:

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$\log C = \log C_0 - Kt / 2.303$----------2

where :-

C_0 is the initial concentration of drug,

K is the first order rate constant, and

t is the time.

2.2.3 Hixson-Crowell model: (cube root law)

Hixson and Crowell (1931) derived the following equation to describe drug released from the matrix device by diffusion.The equation describes the release from systems where there is a change in surface area and diameter of tablet.

$W_0^{1/3} - W_t^{1/3} = ƙt$----------3

Where

W_0 is the initial amount of drug in the pharmaceutical dosage form,

W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and

ƙ (kappa) is a constant incorporating the surface-volume relation.

To study the release kinetics, data obtained from in vitro drug release studies are plotted as cube root of drug percentage remaining in matrix versus time.

Application: This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time (Chen *et al.*, 2007).

2.2.4 Higuchi model(cumulative % drug release versus square root of time)

The first example of a mathematical model aimed to describe drug release from a matrix system was proposed by (Higuchi, 1963). Initially conceived for planar systems,

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it was then extended to different geometrics and porous systems (Grassi *et al.,* 2002). This model is based on the hypotheses that

I. Initial drug concentration in the matrix is much higher than drug solubility;

II. Drug diffusion takes place only in one dimension (edge effect must be negligible);

III. Drug particles are much smaller than system thickness;

IV. Matrix swelling and dissolution are negligible;

V. Drug diffusivity is constant; and

VI. Perfect sink conditions are always attained in the release environment. Accordingly, model expression is given by the equation:

$f_t = Q = K_{H\times} t^{1/2}$----------4

Where, K_H is the Higuchi dissolution constant.

Q is the amount of drug released in time t per unit area A,

The data obtained are plotted as cumulative percentage drug release versus square root of time (Silvina *et al.*, 2002). And if such a plot gives a straight line it indicates that the drug was released by diffusion (sarika *et al.,* 2013)

Application: This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some matrix tablets with water soluble drugs (Suvakanta *et al.,* 2010).

2.2.5Korsmeyer- Peppas model (log cumulative % drug release versus log time)

Korsmeyer–Peppas model is described by the equation

$Q_t/Q_\alpha = K t^n$----------5

Where,

Q_t/Q_α is fraction of drug released at time t, and

k is the rate constant and

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n is the release or diffusional exponent.

The n value is used to characterize delivery release mechanisms as given

Where: n=0.5----------fickian release or huguchi kinetics

0.5<n<1---------- non-fickian release

n=1----------zero order

2.3 Acacia

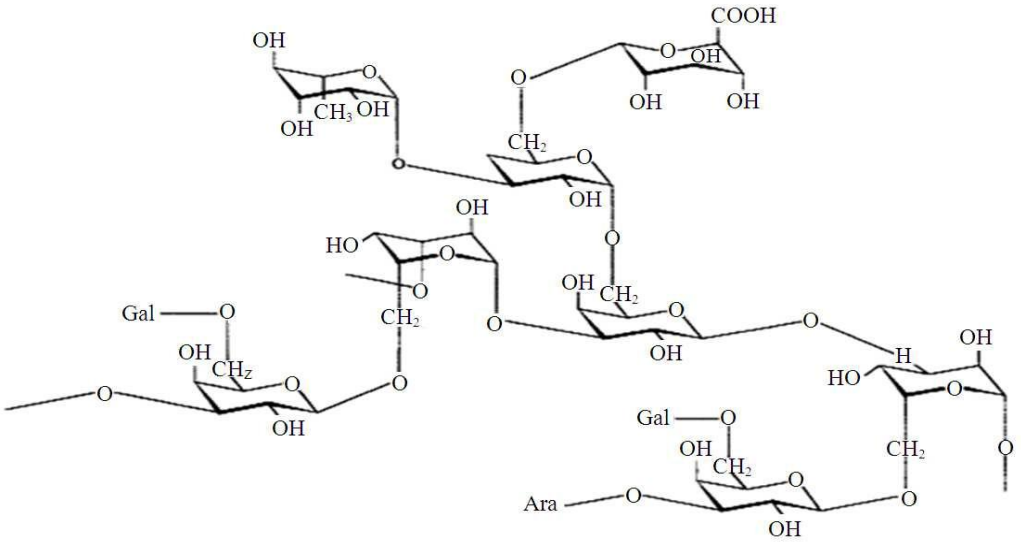


Figure 2.1:Structure of Gum Arabic

Acacia gum also called Gum Arabic (GA) is the dried gummy exudate from the stems and branches of Acacia Senegal (Fam. *Leguminosae*) and other related African species of acacia. Gum arabic is a branched molecule of 1, 3-linked β-D galactopyranosyl units. It consists of monosaccharide sugars such as arabinose, glucuronic acid and rhamnose (Ogaji *et al.*,2012).

It is classified as a tree/shrub exudate according to source and natural anionic polysaccharide according to charge and a Tetra-heteroglycan according to monomeric unit in chemical structure (Goswami & Naik, 2014).

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Gum Arabic is a solid of a pale to orange brown colour which, when ruptured, secretes a vitreous substance. Gum Arabic of excellent quality is tear shaped, round, with an orange-brown colour. After it is crushed, the pieces are paler in colour and have a vitreous appearance. Contrary to other vegetable gums, gum arabic dissolves very well in water (up to 50%). The viscosity of *A. Senegal* is weak (16ml/g on average). The resulting solution is colourless, tasteless and does not interact easily with other chemical compounds (ITC, 2008).

In the pharmaceutical industry, Gum Arabic is being used in pharmaceutical preparations and as a carrier of drugs since it is considered a physiologically harmless substance. The GA is a heterogeneous material having both hydrophilic and hydrophobic affinities. Itsphysicochemical responses can be handled depending on the balance of hydrophilic andhydrophobic interactions. The functional properties are closely related to its structure, whichdetermines, for example, solubility, viscosity, degree of interaction with water and oil in an emulsion, microencapsulation ability, among others.

GA has high water solubility and a relatively low viscosity compared with other gums. Most gums cannot dissolve in water in concentrations above 5% due to their high viscosity. Instead, GA can get dissolved in water in a concentration of 50% w/v, forming a fluid Solution with acidic properties (pH 4.5)(Montenegro*et al.*,2009)

2.4 Gelatin

Gelatin is defined as a product obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue and bones of animals (GMIA, 2012).

Gelatin is a heterogeneous mixture of water-soluble proteins of high average molecular weights, present in collagen. The proteins are extracted by boiling skin, tendons,

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ligaments, bones, etc. in water. Type-A gelatin is derived from acid-cured tissue and Type-B gelatin is derived from lime-cured tissue (George, 2008).

Gelatin is nearly tasteless and odourless. It is a vitreous, brittle solid faintly yellow in colour. Gelatin contains 8 - 13% moisture and has a relative density of 1.3 -1.4. When gelatin granules are soaked in cold water they hydrate into discrete, swollen particles. On being warmed, these swollen particles dissolve to form a solution. Behaviour of gelatin solutions is influenced by temperature, pH, Ash content, method of manufacture, thermal history and concentration (GMIA, 2012).

2.5 Co-Precipitation

Co-precipitation is the simultaneous precipitation of a soluble component with a macro-component from the same solution by the formation of mixed crystals, by adsorption, occlusion or mechanical entrapment (Battista, 1971). The aim of co-precipitation, e.g., polymer-polymer interaction, is to produce a stable polymer with better properties than theindividual polymers (Wu,1978). Co-precipitation which is an example of solid dispersion is a recognized technique for increasing the dissolution of poorly water-soluble drugs so as to improve their bioavailability(Adikwu*et al.*,2003*)*

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2.6 Diclofenac Sodium

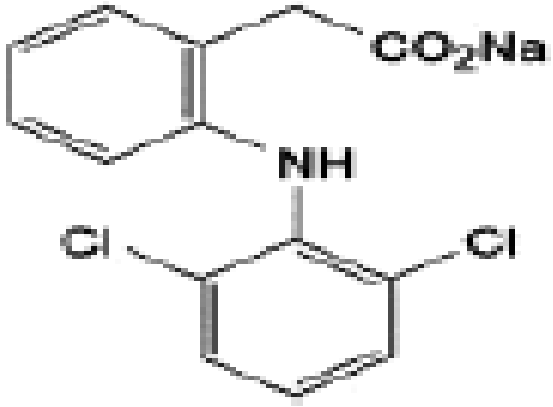


Figure 2.2: Chemical structure of diclofenac sodium(Adapted from www.chemspider.com/chemical-structure253.html)

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAIDs)Diclofenac Sodium [2-[(2, 6-dichlorophenyl) amino] benzene acetic acid monosodium salt] is a drug which is sparingly soluble in water and freely soluble in organic solvent like methanol (Ganesh *et al.,* 2010).

The biological half-life of Diclofenac sodium is about 1-2 h; therefore it requires multiple dosing to maintain therapeutic drug blood level. The most frequent side effects of Diclofenac sodium on long-term administration are gastrointestinal disturbances, peptic ulceration and gastrointestinal bleeding. Diclofenac sodium is poorly soluble in water and has acidic pH (1-3) but is rapidly soluble in alkaline pH (5-8) (Hindustan *et al.,* 2010).

It is well absorbed orally, 99% protein bound, metabolized and excreted both in urine and bile (Charu *et al.,*2014).

Diclofenac undergoes first-pass metabolism, with 60% of unchanged drug reaching systemic circulation. About 40% to 60% is excreted in the urine; the balance is excreted in the bile.

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2.6.1 Mechanism of action of diclofenac sodium

The primary mechanism responsible for itsanti-inflammatory, antipyretic, and analgesic action is thought to be inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX). It also appears to exhibit bacteriostatic activity by inhibiting bacterial DNA synthesis(Dastidar *et al.,* 2000)

2.6.2 Dosage

1. For the relief of osteoarthritis, the recommended dosage is 100 mg q.d.
2. For the relief of rheumatoid arthritis, the recommended dosage is 100 mg q.d.

(Norvatis,2011).

2.6.3 Side Effects

Diclofenac sodium have many side effects like anxiety, depression, dizziness, insomnia, hypertension, oedema, taste disorder, transient stinging, abdominal pain or cramps, bleeding, colitis, acute renal failure, nephritic syndrome, heart failure (Ganesh, 2010).

In patients taking diclofenac sodium extended-release tablets or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1 to 10% of patients are: Gastrointestinal experiences including: abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal) and vomiting(Norvatis 2011).

2.6.4 Uses of diclofenac

For the relief of pain in Rheumatoid arthritis, osteoarthritis

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2.6.5 Choice of diclofenac sodium

Diclofenac sodium is a most widely used NSAID, useful in the treatment of rheumatic disorders, and is characterized by rapid systemic clearance, and thus warrants the use of a Sustained release formulation for prolonged action, and to improve patient compliance. Various experimental reports such as solubility, pH, half-life, indicated diclofenac sodium as a good candidate for sustained release formulation (Hingmire, 2013).

2.6.6 BCS Classification of diclofenac sodium

Wu and Benet 2005 assigned diclofenac to Class II in a Biopharmaceutics Drug Disposition Classification System (BDDCS), meaning it has a high absorption number but a low dissolution number.

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CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Materials and Equipment

Diclofenac sodium powder received as a gift from Marleyshree pharmaceutical company (Kano), hydroxylpropylmethylcellulose (HPMC) (JRS, Germany), microcrystalline cellulose (MCC) (JRS, Germany), Magnesium Stearate (Sigma Aldrich), Acacia gum (TIC Gums, USA), Gelatin gum (Sigma Aldrich), Distilled water, HCL, Acetone.

3.2 Equipment

1. Blender (model M5 176 NR, Mutsushita Electric industrial co. Ltd Osaka, Japan)
2. Brook field viscometer (VHA 605-0100)
3. Digital callipers (Z540-1)
4. Digital Weighing Balance (Metler, p163, USA)
5. Endecott sieve shaker (ENDECOTTS LTD,LONDON S. W. 19 ENGLAND)
6. Erweka flowability tester (Type: GDT, Germany)
7. Erweka Friabilator (TA3R, Western Germany)
8. Erweka tableting machine (EKO 1000p)
9. Fourier transform infra- red spectroscopy(Shimadzu cooperation model)
10. Hot air oven (Gallenkamp, BS, England)
11. pH meter (pH 1100 series, Eutech Instrument Singapore)
12. Ultraviolet – Visible spectrophotometer (Shimadzu cooperation model)
13. USP type II dissolution apparatus (RC-1 Lily corporation, hongkong)

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3.3 METHODS

3.3.1 Preparation of matrix former GelAc

This was done using gelatin and acacia in a ratio of 1:1. A 50g weight of acacia was dissolved in 150 ml of distilled water (i.e. one part acacia to three parts water); then 50g gelatin was also weighed and dissolved in three parts (150 ml) hot distilled water(80 ^{o} C). The solution of both acacia and gelatin was mixed together and stirred vigorously for 10 minutes, 2 L Acetone was used to precipitate the mixture. The mixture was then blended till it formed coarse particles. The supernatant was decanted and the precipitated mixture (GelAc)was dried in the oven at 40 ˚ c for 10 minutes. GelAc was then sized reduced in a mortar and passed through a mesh screen of 0.8 mm to obtain a uniform particle size.

3.3.2Physicochemical evaluation of GelAc

1.Organoleptic properties: The Colour, texture, and odour of GelAc where identified.

2. Evaluation of micromeritic properties

i) Particle size distribution

Particle size distribution was performed on samples of gelatin-acacia co-precipitate (GelAc) using a nest of standard sieves (1mm and 710,300, 180, 125 μm opening). The sieves were agitated on Endecott sieve shaker (Endecotts ltd,London s. w. 19 England) for 10 min. From the percentage weight of powders retained on each sieve, the mean weight of powder was calculated.

ii) Bulk Density and Tapped density determination

A 10 g quantity of the powder samples was placed in a clean 50 ml measuring cylinder and the volume, V_0(bulk volume), occupied by the sample without tapping was noted. The cylinder was tapped 500 times on a hard table top and the tapped volume,

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V_{500}recorded. The experiment was repeated in triplicates. The bulk and tapped densities were calculated as the ratio of mass to volume ($V_0$and V_{500}respectively) (Ohwoavworhua and Adelakun, 2005).

$$\text{LBD} = \frac{\textbf{weightofthepowder}}{\textbf{volumeofthepacking}} \quad \text{---------- 6}$$

Where LBD: is Loose Bulk Density

$$\text{TBD} = \frac{\text{weight of the powder}}{\text{tapped volume ofthe packing}} \quad \text{---------- 7}$$

TBD: is Tapped Bulk Density

iii) Determination of Hausner's ratio and Carr's index

Hausner's ratio was calculated as the ratio of the tapped density to bulk density of the samples.

$$\text{Hausner's ratio} = \frac{tappeddensity}{poureddensity} \text{----------8}$$

$$\text{Carr's compressibility index (CI)} = \frac{[TBD-LBD]}{TBD} \times 100 \quad \text{----------9}$$

vi) Determination of Angle of Repose

A clean glass funnel was clamped on a retort stand such that the perpendicular height of the tip of the funnel was 10 cm from the flat table surface with a clean sheet of paper.20 g of GelAc was poured into the funnel, while the opening of funnel was blocked with a cotton wool. The cotton wool was removed and the height (h) of powdered heap formed was measured (cm).

The diameter of the circumference of the heap was taken and divided to give the radius, (r).

$$\text{Tan } \theta = \frac{\boldsymbol{h}}{\boldsymbol{r}} \quad \text{----------10}$$

Where θ =angle of repose, h=height of the of powder and r=radius of heap base

vii) Flow rate

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A 10 g sample of powder was passed through the Erweka flowability tester (Type: GDT, Germany). The time taken for the sample to pass through the tester was recorded. This experiment will repeated three times and the average reading recorded in g/sec.

Flow Rate = $\frac{w}{t}$ ----------11

Where w: Weight of powder in grams

t: Time taken in seconds for powder to flow through

3. Determination of Swelling Capacity:The method described by Bowen and Vadino (1984) was adopted. 5 g of GelAc was poured into a 100 ml measuring cylinder and the bulk volume measured (V_1). Distilled water (90 ml) was added and the dispersion well shaken for 5 min. Water was added to make 100 ml and the dispersion allowed to stand for 24 h before the sedimentation volume is read (V_2). The swelling capacity was calculated as$\frac{V2}{V1}$. ----------12

Determination was done in triplicate.

4. Hydration capacity:one gram (1g) of GelAc was placed in a centrifuge tube and covered with10 ml distilled water. The tube was shaken intermittently for about two hours and left to stand for 30 minutes before centrifuging at 3,000 rpm for ten minutes. The supernatant was decanted and weight of GelAc after water uptake and centrifuging was determined.

Hydration capacity was calculated as $\frac{\boldsymbol{x}}{\boldsymbol{y}}$----------13

Where;X is weight of GelAc after centrifugation and

Y is weight of dry GelAc.

5. Determination of Moisture Content:The moisture content of 1 g of GelAc was determined by the loss on drying method on a weight basis using a hot air oven (Gallenkamp, BS, England). One (1) g of powder sample was weighed and placed in an

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evaporating dish of known weight which was transferred into a Gallenkamp oven and dried at 105 ^{0}C until a constant weight was obtained. The % moisture content was determined as the ratio of weight after moisture loss (W_2) to the weight of original powder (W_1) expressed as a percentage (% w/w).

Moisture Content = $\frac{W2}{W1} \times 100$----------14

6. Ash Content: 2g of GelAc will be placed in a pre-weighed crucible and ignited in a furnace at 550^o c until a constant weight is achieved. It will be allowed to cool at room temperature and the ash content calculated using the formula below.

Ash Content % = $\frac{Aw}{Iw} \times 100$ ----------15

Where $\mathbf{A_w}$ –: Ash weight

$\mathbf{I_w}$ **-:**Initial weight of GelAc

3.3.3 Compatibility studies

Fourier Transform Infra-Red (FTIR) Studies

Fourier transform infrared (FTIR) spectral data was taken on Shimadzu instrument (model FTIR-8300S, Tokyo, Japan) to find out the chemical stability of excipients. FTIR spectra of Acacia gum, Gelatin, the co-precipitate of Acacia-Gelatin (GelAc) and GelAc and drug mixture was taken. All the samples were crushed with potassium bromide to get pellets at 1 ton/cm2. Spectral scanning was done in the range between 4000-400 cm-1.

3.3.4. Scanning electron microscopy

The samples were subjected to scanning electron microscopy to compare the gelatin and acacia as well as the co-precipitate.

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3.3.5 Preparation of matrix embedded tablet.

Sustained release matrix tablet of diclofenac sodium was prepared by wet granulation method, using varying proportions of GelAc at 10 – 50% (Table3.1).

The Formulations were made by taking different proportions of GelAc and HPMC, in all the formulations, 100 mg of Diclofenac sodium was incorporated and final weight was made up to 250 mg. Microcrystalline cellulose (MCC) was employed in the formulation of matrix tablets of the as a bulking agent because of its versatility. MCC works as diluent creating the desiredbulk as well as giving the right compression characteristics it also improves the compactibility or tabletability of the compression mix of tablet formulations (Silvina, 2002; Thoorens *et al*., 2014). Magnesium stearate was employed as a glidant to enhance the flow of the blended powders (Ofori-Kwakye, *et al* 2015).Water was used as the granulating fluid. Granules were by formed by trituration method.

Granules formed where evaluated for micromeritic properties as described above and then compressed using an Erweka tableting machine (EKO 1000p) in an 8mm punch and die cavity.

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TABLE 3.1: Formula for matrixtablet of diclofenac sodium 100 mg

		Formulation batches									
Ingredients		**G1**	**G2**	**G3**	**G4**	**G5**	**H1**	**H2**	**H3**	**H4**	**H5**
Diclofenac	(mg)	100	100	100	100	100	100	100	100	100	100
GelAc	(%)	10	20	30	40	50	-	-	-	-	-
HPMC	(%)	-	-	-	-	-	10	20	30	40	50
MCC	(%)	49	39	29	19	9	49	39	29	19	9
Mg stearate	(%)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Tablet weight	(mg)	250	250	250	250	250	250	250	250	250	250

KEY: G1- G5: formulation with 10-50 % GelAc, respectively H1- H5: formulation with 10-50 %HPMC respectively.

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Each batch of the formulation contained hundred tablets. For each ingredient used total eight for hundred tablets was calculated and weighed on an electronic weighing balance.

Diclofenac sodium(100 mg) was weighed into a mortar, MCC was weighed and triturated into the diclofenac as a diluent, followed by matrix former(GelAc and HPMC done separately) and water was added into the powder mixture to form a wet mass which was then passed through a 0.8 mm mesh screen and dried in a Gallenkamp oven at 40 o C for 10 minutes. 1 % 0f total weight magnesium stearate was added as glidant. And the granules were evaluated as described in section 3.3.2.

3.3.6Evaluation of the designed matrix tablet of diclofenac sodium.

A. Pre-Compressional Studies of granular blend of GelAc with diclofenac sodium

1. Bulk Density and Tapped density determination
2. Determination of Hausner's ratio
3. Determination of Carr's compressibility index
4. Determination of Angle of repose
5. Flow rate

B. Post-Compressional Studies of granular mix for tablets.

Granules formed were compressed using an Erweka tableting machine (EKO 1000p) in an 8mm punch and die cavity at 10 metric tonnes pressure, powered by hand and the die cavity was filled manually using a spatula. Tablets were allowed to rest for 24 hours to allow for elastic recovery before evaluations were carried out.

The following tests were carried out on the designed tablets.

1. Weight variation test: To study weight variation twenty tablets of the formulation from each batch were selected randomly and weighed individually using a

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digital balance to check for weight variation and mean weight was taken and standard deviation in weight was calculated for each batch.

2. Tablet thickness: This was determined using Vernier callipers (TOH-700K, USA), by placing the tablets vertically in between the two jaws and the thickness expressed in mm. Ten tablets were used and the mean thickness was calculated and recorded.

3. Tablet diameter test: The diameter of ten tablets was determined using Vernier callipers and the mean calculated and recorded.

4. Tabletcrushing strength: This was carried out on six tablets using the Monsanto tablet hardness tester (Phillips, England). The tablet was fitted lengthwise between the plunger and the force applied. The pressure at which tablet was crushed was measured in Kgf.

5. Friability test: The friability of the tablets was measured in a friability apparatus (Erweka Friabilator, TA3R, Western Germany). Ten tablets will initially be weighed ($W_{initial}$) and placed into the friabilator. The friabilator was operated at 25 rpm for four minutes and then the tablets were dusted and weighed (W_{final}). Percentage friability was calculated from the loss in weight as given in the equation below. The weight loss should not be more than 1%. Determination was done in triplicate.

$$\text{Friability} = \frac{W_{initial} - W_{final}}{W_{initial}} X\ 100 \qquad \text{----------15}$$

6. Disintegration test: Six (6) tablets were placed each in a compartment of the Erweka Disintegration Test Apparatus (Type ZT3, Western Germany) with distilled water thermostated at 37 ± 0.5 ^{o} C as the medium. Time taken for the tablet to disintegrate and pass through the mesh was noted and the average calculated.

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7. Content uniformity test: Five tablets were selected randomly and powdered. A quantity of this powder corresponding to 100 mg of Diclofenac sodium was dissolved in 100 ml of pH 6.8 phosphate buffer stirred for sixty minute and filtered. 1mL of the filtrate was diluted to 100 mL with pH 6.8 phosphate buffer. Absorbance of this solution was measured at 276 nm using pH 6.8 phosphate buffer as blank and content of Diclofenac sodium was estimated.

8. Swelling behaviour oftablets: The swelling behaviour of formulation was studied. One tablet from each formulation was kept in a Petri dish containing phosphate buffer pH 6.8. At the end of 2 h, the tablet was withdrawn, and kept on a tissue paper and weighed. The weighing was continued for every 2 h, till the end of 12 h. The percentage weight gain by the tablet was calculated by the formula given below (Andrepoulos, 2001).

$$S.I = \frac{Mt - Mo}{Mo} \times 100 \quad \text{----------16}$$

Where, S.I = swelling index,

M_t = weight of tablet at the time (t) and

M_o = weight of tablet at time 0.

3.3.7*In-vitro* dissolution studies drug release

3.3.7.1 Preparation of Simulated gastric Fluid (Sgf) Without Pepsin pH 1.2

Two (2) grams quantity of sodium chloride was dissolved in 7 ml of concentrated Hydrochloric acid and the volume was made up to 1000 ml with distilled water. The pH was adjusted to 1.2 using Oaklon pH meter (pH 1100 series, Eutech Instrument Singapore) by adding four drops of concentrated hydrochloric acid (Ofokansi *et al.*,2012).

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3.3.7.2Preparation of simulated intestinal fluid (Sif) without Pancreatin pH6.8.

Monobasic potassium phosphate (6.8g) was dissolved in 77 ml of0.2 N sodium hydroxide and the volume was made up to 1000 ml. The pH was adjusted to 6.8 using oaklon pH meter (pH 1100 series, Eutech Instrument Singapore) by adding three drops of 0.2 N sodium hydroxide (Ofokansi *et al.*,2012).

3.3.7.3 Determination of the wavelength of maximum absorption and construction of beer lambert plot for diclofenac sodium.

A stock solution of Diclofenac sodium was prepared by dissolving 100mg of drug in 100ml of phosphate buffer of pH 6.8 (1 mg/ml) . From this stock solution, 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 µg/ml dilutions was prepared. The λ_{max} of the drug was determined by scanning one of the dilutions between 400 to 200 nm using a UV- visible spectrophotometer.

3.3.7.4 Dissolution test

Dissolution test was carried out according to USP30 method for dissolution test on Diclofenac sodium.

The formulated tablet samples were subjected to in-vitro dissolution studies using USP Type II dissolution apparatus (RC-1 Lily Corporation, Hongkong) at 37±2°C and 50 rpm speed. As per the official recommendation of USP, 900 ml of 0.1 N HCl (2hr) and pH 6.8 Phosphate buffer (next 8hrs) was used as dissolution medium. 5 ml aliquots were withdrawn at specific time intervals of 2 hours and the dissolution media volume was complimented with fresh and equal volume of blank media (0.1 N HCl). The aliquots were filtered and scanned with appropriate dilution and amount of diclofenac sodium released from the tablet samples was determined spectrophotometrically at a wavelength of 276 nm by comparing with the standard calibration curve(USP30, 2007).

`

3.3.8Kinetic modelling of drug release

The dissolution data obtained were fitted to into the various kinetic models namely;

- Zero order.
- First order kinetics (log cumulative percentage of drug remaining versus time).
- Higuchi's model (cumulative percentage drug release versus square root of time.)
- Korsmeyer peppas equation (log cumulative percentage drug release versus log time).
- Hixson-crowell equation (cube root law).

batchl with the highest linearity was selected as the optimised batch and compared against a similar formulation containing HPMC,

Data obtained were subjected to student t-test

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CHAPTER FOUR

4.0 RESULTS

4.1 Percentage Yield Of Gelac After Co-Precipitation

The percentage yield of GelAc from the co-precipitation of acacia and gelatin was 92.39 %.

4.2 Physicochemical Characterisation Of Gelac

The result of the physicochemical studies and flow properties of GelAc are presented in Tables 4.1and 4.2 respectively.

The Hausner's ratio and the Carr's index have been widely used to estimate the flow properties of powders. The Hausner's ratio and the Carr index values obtained for GelAc are 1.11 and 9.921% respectively. The angle of repose for GelAc was found to be 25.44^{o}with bulk and tapped0.5774 and 0.6410g/cm^{3} respectively.

The product was acceptable withcoarse texture and a creamy colour and odourless. The product was soluble inphosphate buffer (pH 6.8) and water. Moisture content was 10%, pH of 1 % w/v solution of GelAc in distilled water was found to be 7.73, ash content 2.5% and hydration capacity 11.05.

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TABLE 4:1Organolepticand PhysicochemicalProperties ofGelAc

S/N	Parameters	Description
	Organoleptic Properties	
	A) Odour	Odourless
1.	B) Colour	Beige Coloured
	Solubility	
	A)Phosphate buffer pH 6.8	Soluble
2.	B) Water	Soluble
3.	Loss on drying (%)	10
4.	pH	7.73
5.	Ash content (%)	2.5
6.	Hydration capacity	11.05

n=3

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Table 4:2 Flowproperties of GelAc

S/N	PARAMETERS		RESULT
1.	Flow Rate	(g/sec)	5.56
2.	Angle of Repose	(º)	25.44
3.	Bulk Density	(g/cm^3)	0.5774
4.	Tapped Density	(g/cm^3)	0.6410
5.	Hauser's Ratio		1.1101
6.	Carr's Index	(%)	9.921

n=3

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4.3 Particle Size Analysis

The histogram of the particle size distribution of GelAc is shown in Figure 4.1. The particles of GelAc are skewed to the median position of 300 μm.

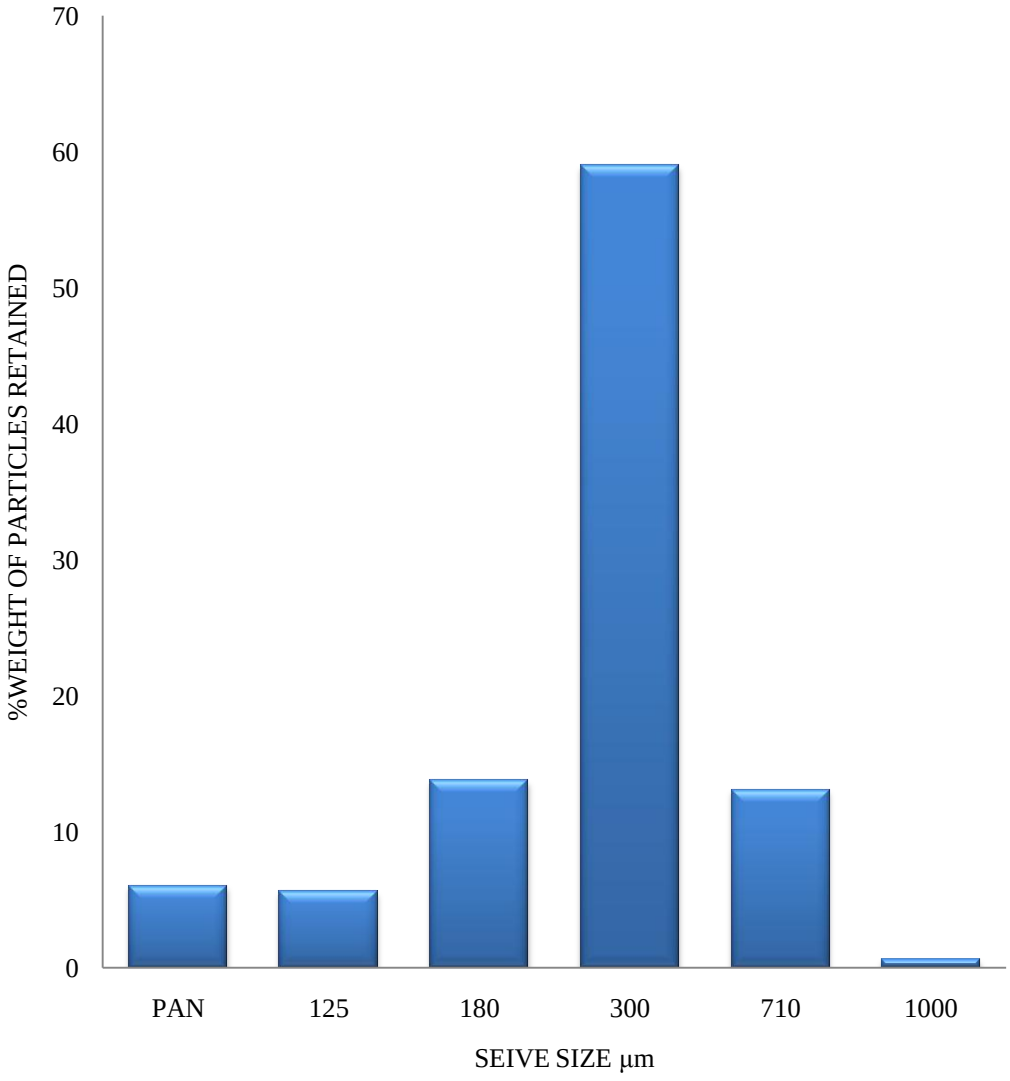


Figure 4: 1 Histogram Showing Percent Frequency of Particles Retained on each Sieve.

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4.3.1 SEM analysis

Plates I to IIIshows photomicrograph of acacia, gelatin and GelAc. Acacia was observed to have a spherical shape 10 -50 μm with the smaller particles larger in number, gelatin particles were large (200 μm) with an irregular shape. GelAc was observed to have a sponge-like nature with the presence of pores (particle size was about 100 μm).

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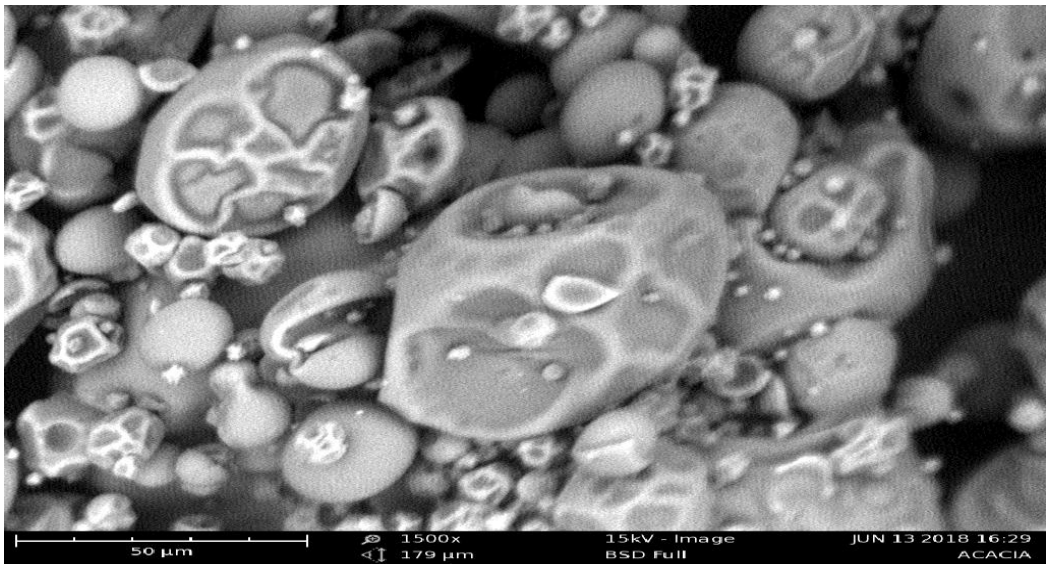


Plate I. SEM photomicrograph of Acacia

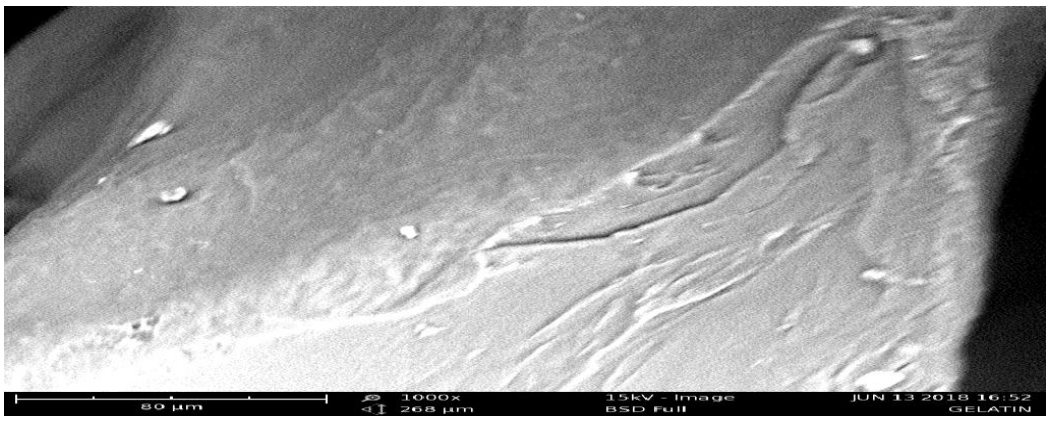
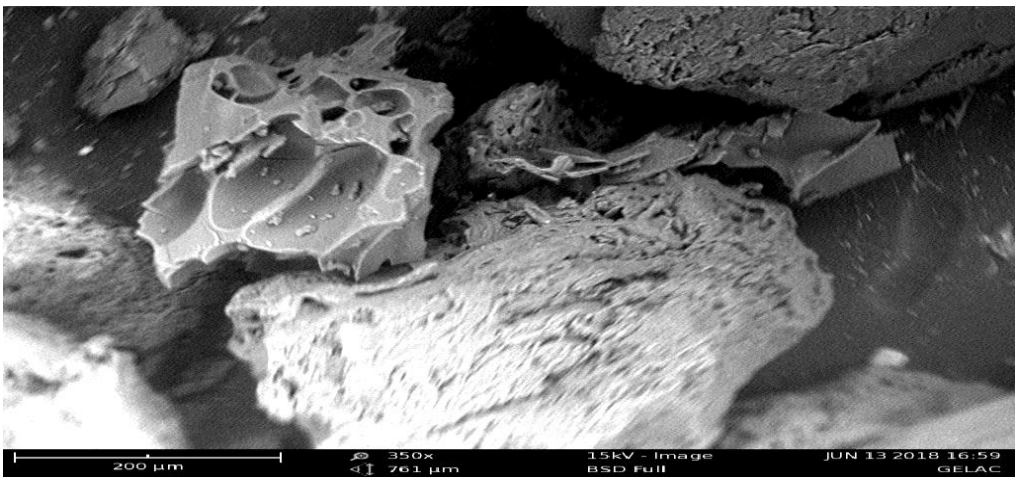


Plate II. SEM photomicrographof gelatin



PlateIII. SEM photomicrograph of GelAc

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4.4 FT-IR Studies

FT-IR spectrum analysis of gelatin, acacia, gelatin-acacia Co-precipitate (GelAc), diclofenac (pure drug), and drug with GelAc are illustrated in figures 4.2 to 4.6 below. This was carried out to determine any incompatibility between the pure drug diclofenac and the matrix former GelAc. The interaction between drug and the excipients often leads to identifiable changes in the FT- IR spectra of the drug excipient mixture (Mahapatra *et al.,* 2014). Major functional groups present showed characteristic peaks in the IR spectrum. No new functional groups were observed upon co-precipitation of acacia and gelatin and upon combination of the co-precipitate with diclofenac sodium.

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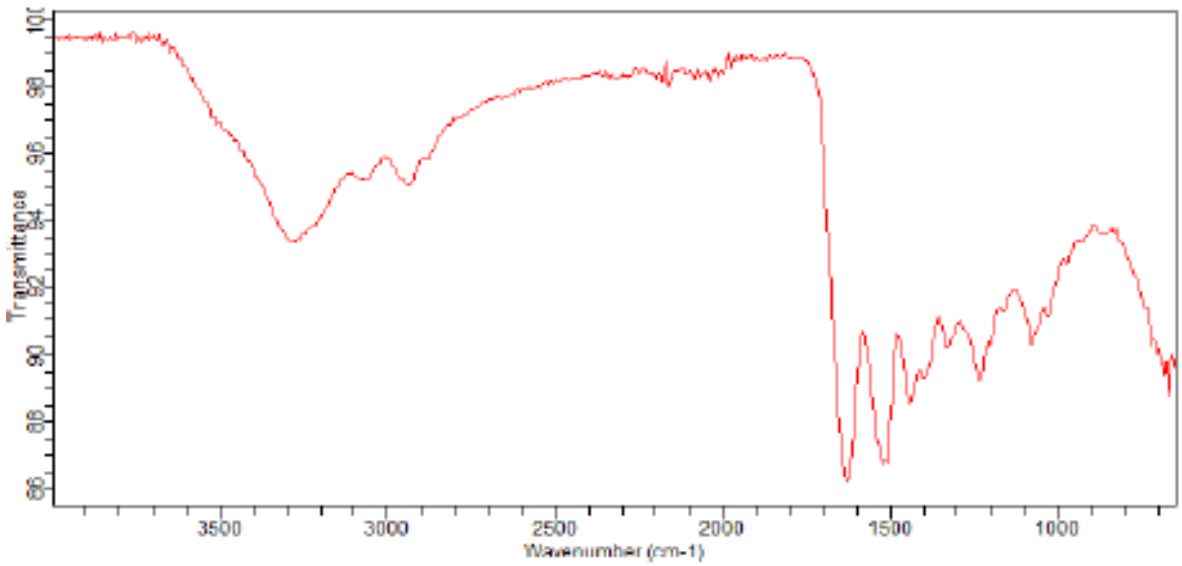


Figure 4: 2 FT-IR Spectra for gelatin

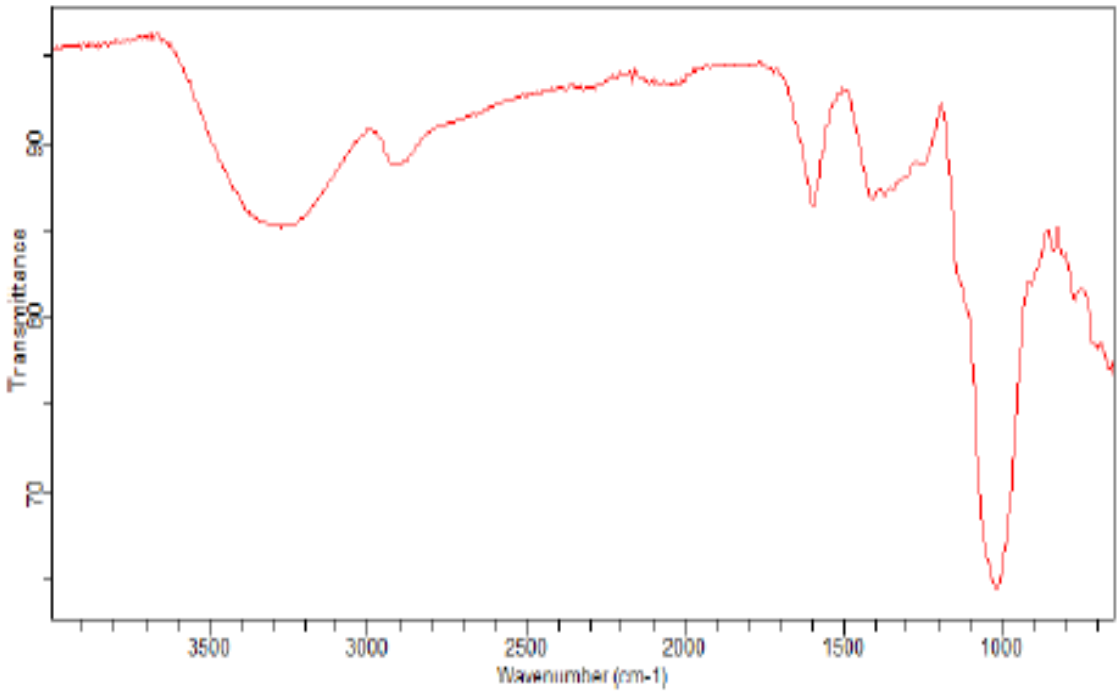


Figure 4: 3 FT-IR Spectra for acacia

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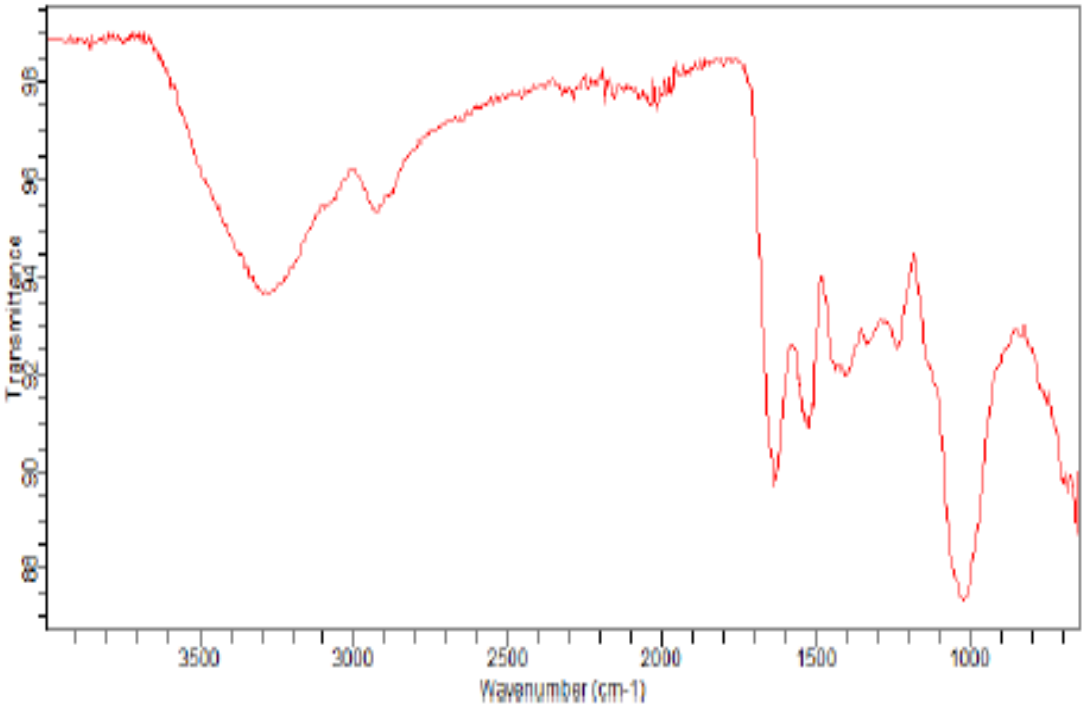


Figure 4: 4 FT-IR Spectra for GelAc

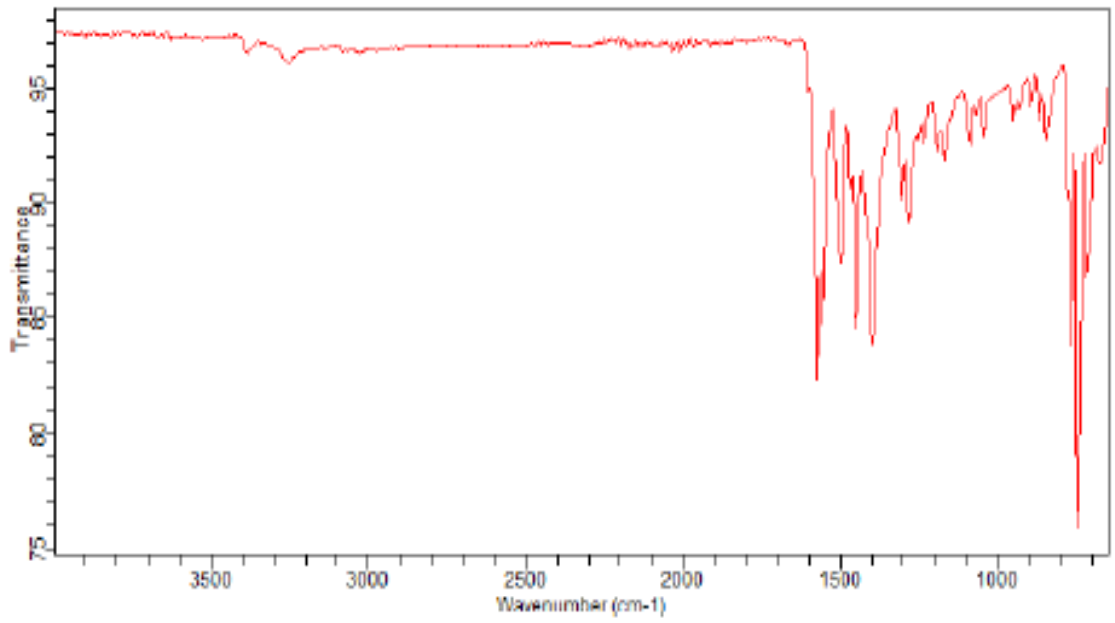


Figure 4:5 FT-IR spectraof diclofenac

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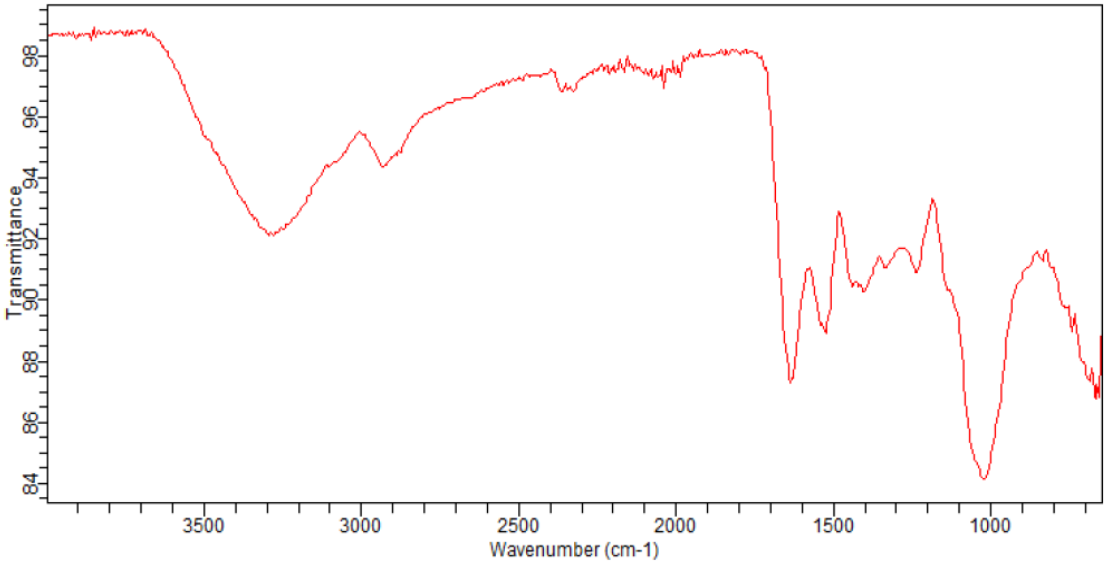


Figure 4:6 FT-IR spectra of GelAc + diclofenac

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TABLE 4:3 Interpretation of FT-IR spectra

S/N	Functional group	Wavenumber (cm^3)	Diclofenac standard powder	Diclofenac + GelAc
1	Aromatic overtone	2000-1667	+	+
2	OH	3200-3500	+	+
3	NH	1650-1580	+	+
4	C-Cl	1300-1250	+	+
5	C=O	1720-1706	+	+
6	C-O	1320-1210	+	+

`

4.5 Pre-Compression Evaluation of HPMC and GelAc Containing Granules

Table 4:4 Present the result of the evaluation carried out on granulation of diclofenac sodium powder before compression using GelAc and HPMC.

The granules of different formulations were evaluated for angle of repose, bulk density, tapped density, Carr's compressibility index and Hausner's ratio. The results as shown in (Table 4:4) all fell within pharmacopoeial limit with the results complimenting each other by inferring good flow of granules.

Granules containing GelAc had bulk density between 0.45-0.57g/$cm^3$and tapped density between 0.51-0.68 g/cm^3both increasing with increase concentration of GelAc while those containing HPMC had a bulk density between 0.48-0.51 g/$cm^3$and tapped density between 050 -0.59g/cm^3. Hausner's ratio fell below 1.25 ranging between 1.06-1.19 for GelAc granules and 1.03-1.23 for HPMC granules. Angle of repose for all batches fell below 40^o within 31.91 - 38.29^o. Flow rate for all fell below 5.01 g/sec.

`

TABLE 4:4 flow properties of the granular blend containing GelAc and HPMC for compression

Batches	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)	Angle of repose (^{0})	Flow rate (g/sec)
G1	0.45	0.51	1.13	11.76	34.67	4.12
G2	0.48	0.51	1.06	5.88	35.13	3.97
G3	0.53	0.58	1.09	8.62	32.97	4.40
G4	0.57	0.67	1.18	14.92	35.24	4.84
G5	0.57	0.68	1.19	16.17	35.32	5.01
H1	0.51	0.52	1.03	1.92	32.55	4.56
H2	0.40	0.50	1.23	20.00	31.91	3.51
H3	0.44	0.50	1.14	12.00	32.50	4.04
H4	0.47	0.51	1.08	7.80	32.19	4.23
H5	0.48	0.59	1.23	18.64	38.29	3.44

KEY: G1- G5: formulation with 10-50 % GelAc, H1- H5: formulation with 10-50% HPMC respectively.

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4.6 Post Compression Studies ofPrepared Matrix Tablets of Diclofenac Sodium

Table 4.5 shows for the various properties evaluated for GelAc and HPMC Tablets.

The tablets showed low weight variations. The average weight of the tablets was found to be within 250 to 254 mg for GelAc tablets and 249 – 253mg for the HPMC tablets the standard deviation within limits specified for tablets weighing 130 - 324 mg (B.P, 2002).

Tablet diameter ranged between8.00 – 8.02 mm for GelAc tablets and 7.89 – 8.006 mm for HPMC tablets (Table4:5) and this was determine by the punch and die cavity of 8 mm while Tablet thickness ranged between 4.207 - 4.53 mmand 4.229 – 4.653 mm for GelAc and HPMC respectivelyas shown in Table 4.5.

4.6.1 Crushing strength

Tablet had a crushing strength ranging from 6.21 to 12 kgF,but matrix tablet G2 with 50% GelAc had the highest crushing strength at12 kgF.The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness (Syed Namath Ulla *et al.*,2011)Tensile strength was calculated and it range from 1.093 - 2.54MN/m^2.

4.6.2 Friability test

The percentage weight loss in friability of all formulations was found to be less than 1 % (0 to 0.51 %) as shown in Table 4:5.

4.6.3 Drug content uniformity

Good drug content uniformity was found among the different batches of tablets(Table 4:5) and the Percentage drug content ranged between 94.2 to 101.44 %. This is within the official drug content uniformity for diclofenac which is 90 to 110 % (U.S.P

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convention, 2007).The maximum percentage drug content for all the formulation was found to be 101.44 % in formulation G3. The minimum percentage drug content for all the formulation n was found to be 94.2% H5.

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TABLE 4:5 Physical characteristics of diclofenac sodium matrix tablets formulated with GelAc and HPMC respectively

Batch	Weight Variation (mg±SD)	Tablet Thickness (mm±SD)	Tablet diameter (mm±SD)	Crushing strength (KgF±SD)	Tensile strength (MN/m^2)	Friability (%).	Disintegration Time (min)	Content Uniformity (%).
G1	250 (0.01)	4.21 (0.08)	8.02 (0.02)	11.4 (0.89)	2.152	0	99.5 (0.707)	97
G2	251 (0.004)	4.36 (0.13)	8.01 (0.01)	12	2.186	0	46.33 (6.658)	100
G3	252 (0.01)	4.35 (0.13)	8.01 (0.01)	12	2.191	0	36.5 (4.949)	101.4
G4	251 (0.01)	4.53 (0.24)	8.01 (0.01)	12	2.106	0.51	39 (8.544)	97
G5	254 (0.01)	4.46 (0.08)	8 (0.004)	11.6 (0.55)	2.071	0.02	43 (2.828)	98.55
H1	251 (0.004)	4.23 (0.08)	8.01 (0.01)	9.5 (0.45)	1.79	0	54.67 (2.31)	101
H2	253 (0.01)	5.13 (0.22)	8.05 (0.01)	10.33 (0.52)	1.60	0.38	85.33 (15.3)	98.55
H3	251 (0.004)	4.46 (0.04)	8.004 (0.01)	10.75 (0.61)	1.92	0.39	106 (1.41)	100
H4	250 (0.01)	4.52 (0.07)	7.89 (0.02)	11.5 (0.55)	2.03	0.4	159.67 (3.51)	98.55
H5	250 (0.01)	4.65 (0.11)	7.98 (0.02)	12 (0)	2.06	0	222.67 (6.35)	94.2

*Values are in mean ±s .d (*n*=3) (() = standard deviation) KEY: G1- G5: formulation with 10 - 50 % GelAc, respectively H1- H5: formulation with 10 -50 % HPMC respectively.

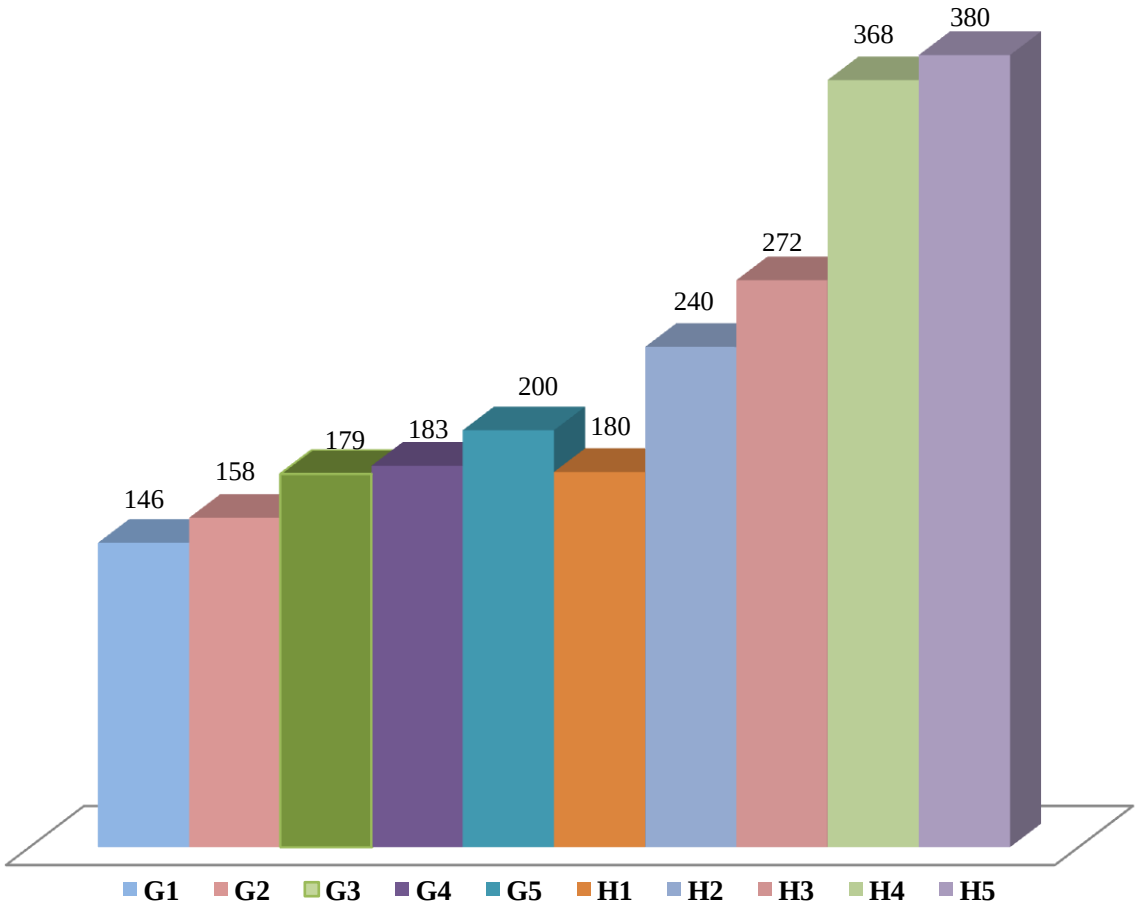
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4.6.4 Evaluation of swelling index of matrix tablets

Figure 4:8 shows the swelling index of matrix tablets. Swelling of the matrix tablets increased with increase in concentration of GelAc and HPMC. The tablets showed a rapid increase in weight. Tablets containing HPMC showed a more pronounced increase in weight.

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KEY:



G1- G5: formulation with 10 -50 % GelAc, respectively H1- H5: formulation with 10 -50 % HPMC respectively.

Figure 4: 7 Swelling index of diclofenac sodium matrix tablets in phosphate buffer pH 6.8at8 hr**.**

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4.7Dissolution Studies for Tablets

The resultof *in-vitro* dissolution profile of diclofenac sodium matrix tabletsis depicted in Figure 4.7.Less than 10% of the drug was released at 2 hours from the all batches of the formulations. At 8 hours less than 70% of the drug was released. It was observed from the dissolution study that the cumulative drug released in 10 h from formulation G1, G2, G3, G4 and G5 was 84, 80, 76,75 and 64 % respectively and for H1, H2, H3, H4, and H5 was 79.71, 74.30, 71.34, 65.87 and 50.59 % respectively. This shows that as concentration of GelAc increases in the matrix tabletthe rate of drug release from tablet decreased, so also for HPMC.

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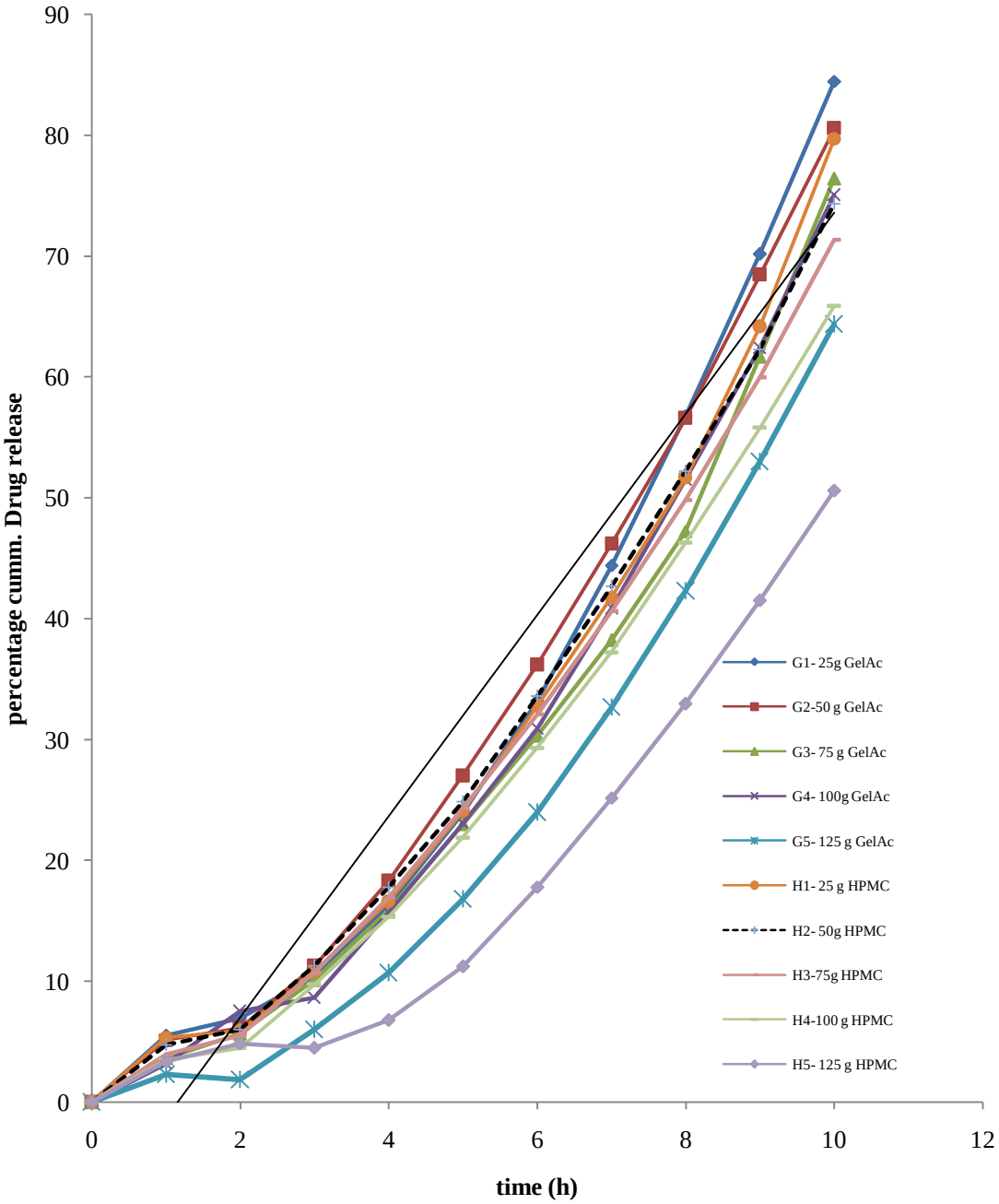


Figure 4: 8 Plot of percentage drug release over time

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TABLE 4:6Summary of dissolution studies of diclofenac sodium matrix tablets

		G1	**G2**	**G3**	**G4**	**G5**	**H1**	**H2**	**H3**	**H4**	**H5**
DR2h	(%)	6.92	6.13	5.67	7.51	1.85	5.86	5.99	5.53	4.48	4.81
DR8h	(%)	56.72	56.59	47.23	51.52	42.29	51.65	52.17	49.8	46.31	32.9
t25	h	4.16	4.10	4.55	4.47	5.45	5.20	5.03	5.14	5.72	6.70
t50	h	7.17	7.12	7.94	7.81	9.40	7.75	7.67	8.03	8.07	9.88

Key: t25, t50: time taken for 25% and 50% of drug to go into dissolution media, DR2h, DR8h: amount of drug to go into dissolution media after two hours and eight hours respectively.

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4.8Kinetic Modelling of Drug Release from Matrix Tablets

Release kinetics is an essential aspect of drug formulation, development and kinetic data are also employed in setting *in vivo* - *in vitro* correlation (IVIVC) of dosage forms (Thakkar *et al.*, 2009). The data obtained from in vitro dissolution studies were fitted in different kinetic models. zero order, first order, Higuchi, Hixson-Crowell and Korsemeyer- Peppas equation, and the kinetic model with the highest correlation coefficient value (R^2) was selected as the model that best described the dissolution data All data obtained from the dissolution studies were fitted into various kinetic models and the results are depicted in Figures 4:10 to 4:14.

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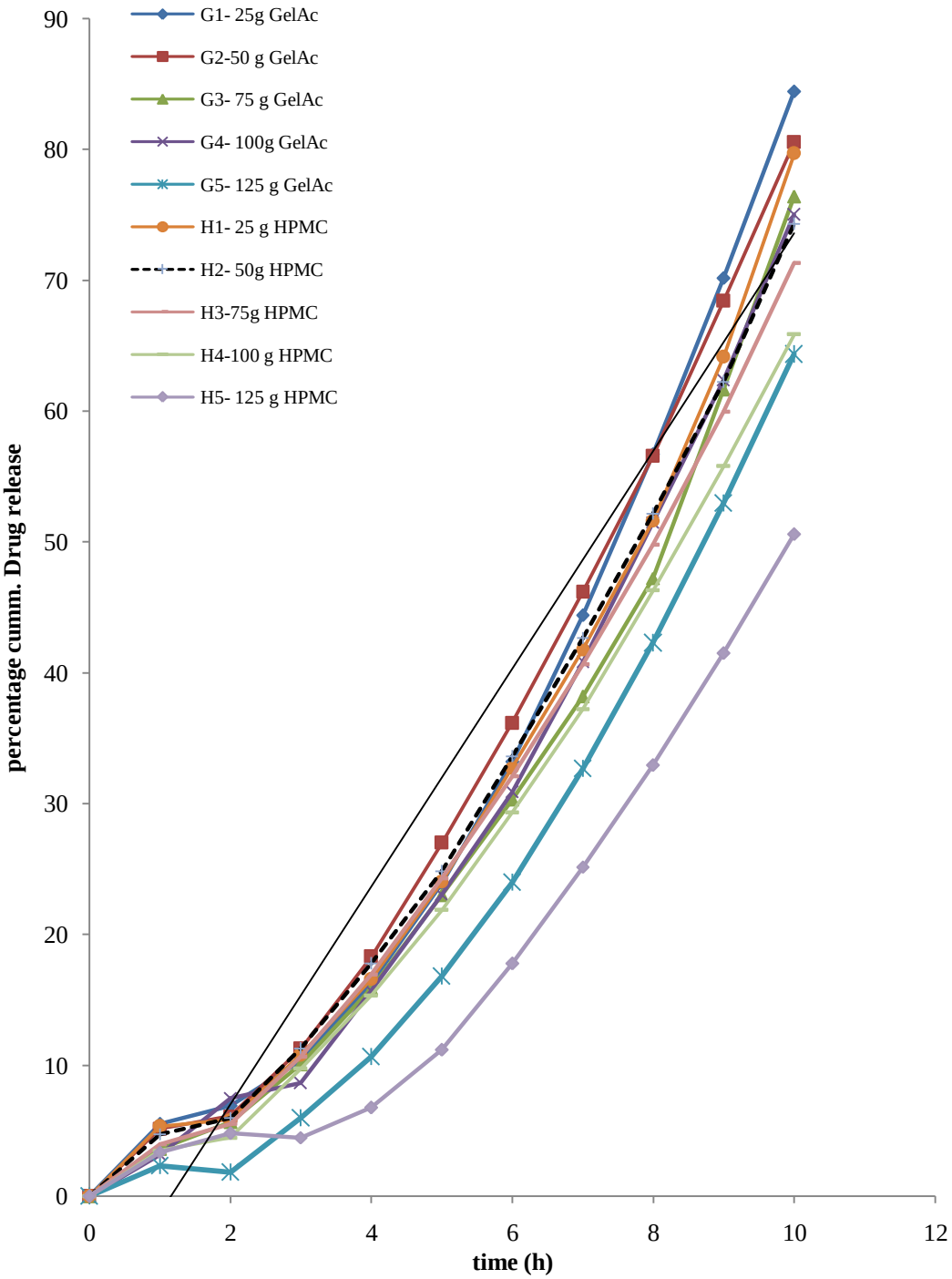


Figure 4:9 Zero order plot for formulations G1- H5

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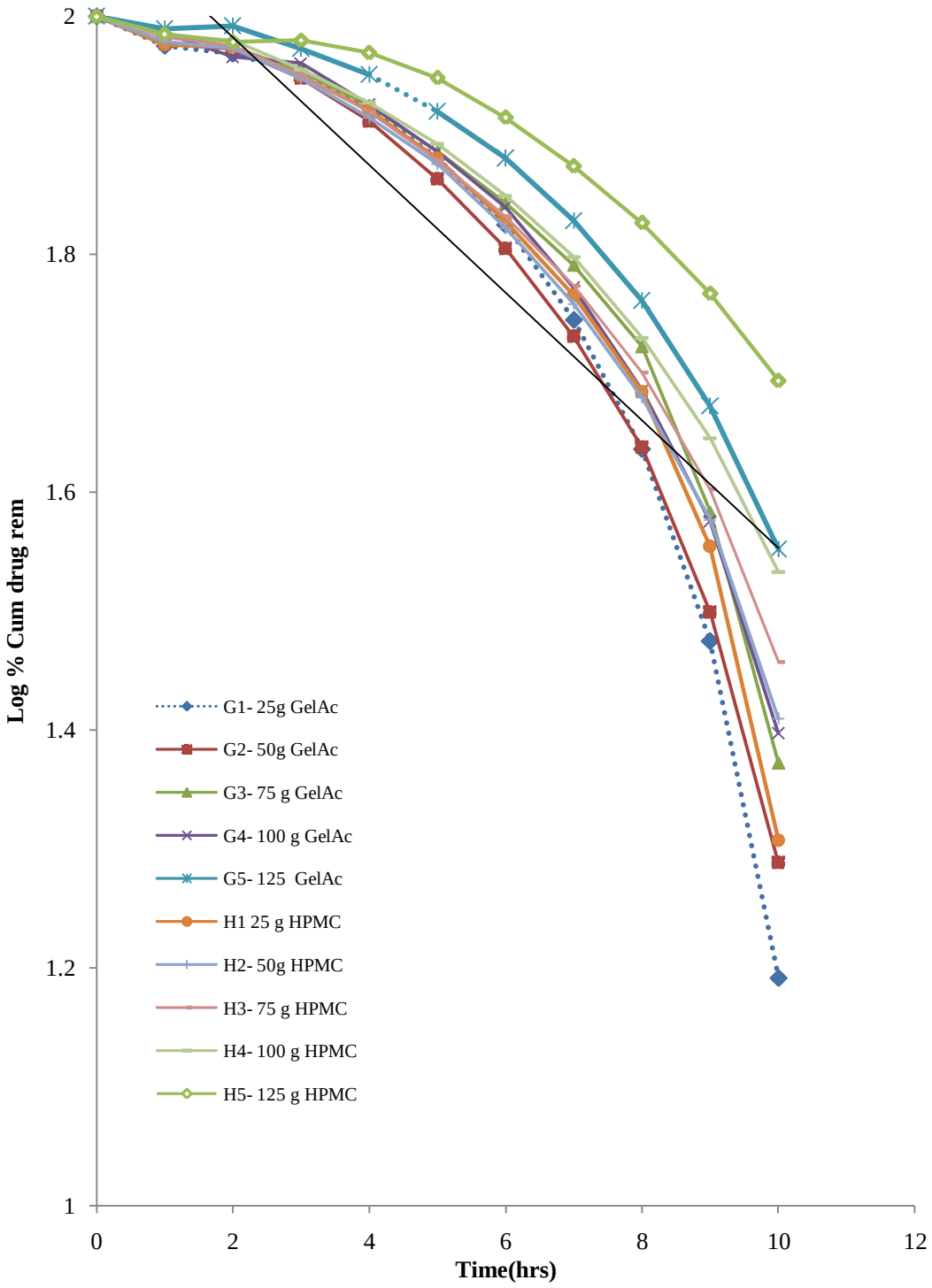


Figure 4: 10 First order plot(log % cummulative drug remaining versus) timefor formulations G1- H5

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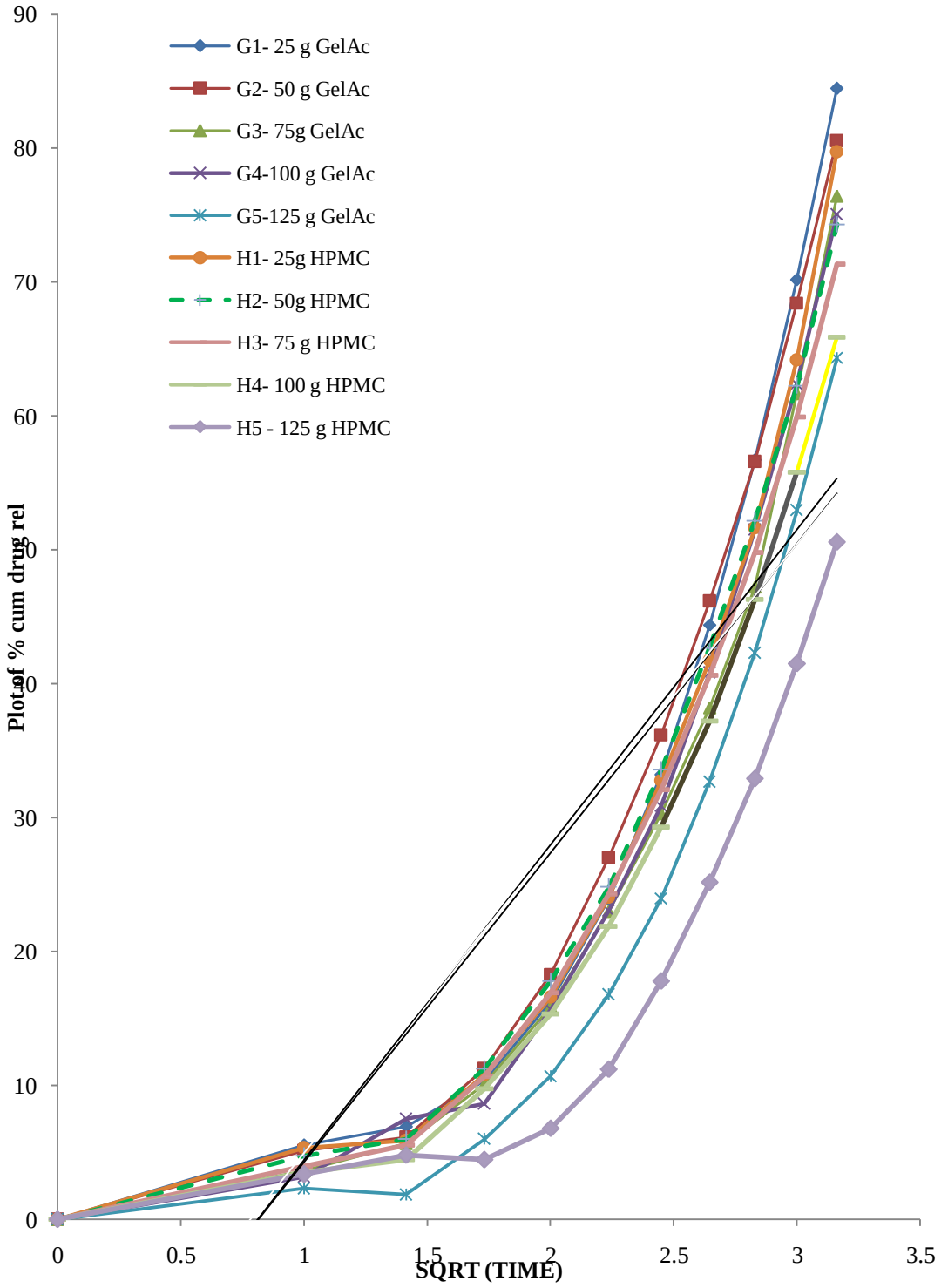


Figure 4:11 Higuchi plot (Plot of % cum drug released versus square root of time) for formulations G1- H5

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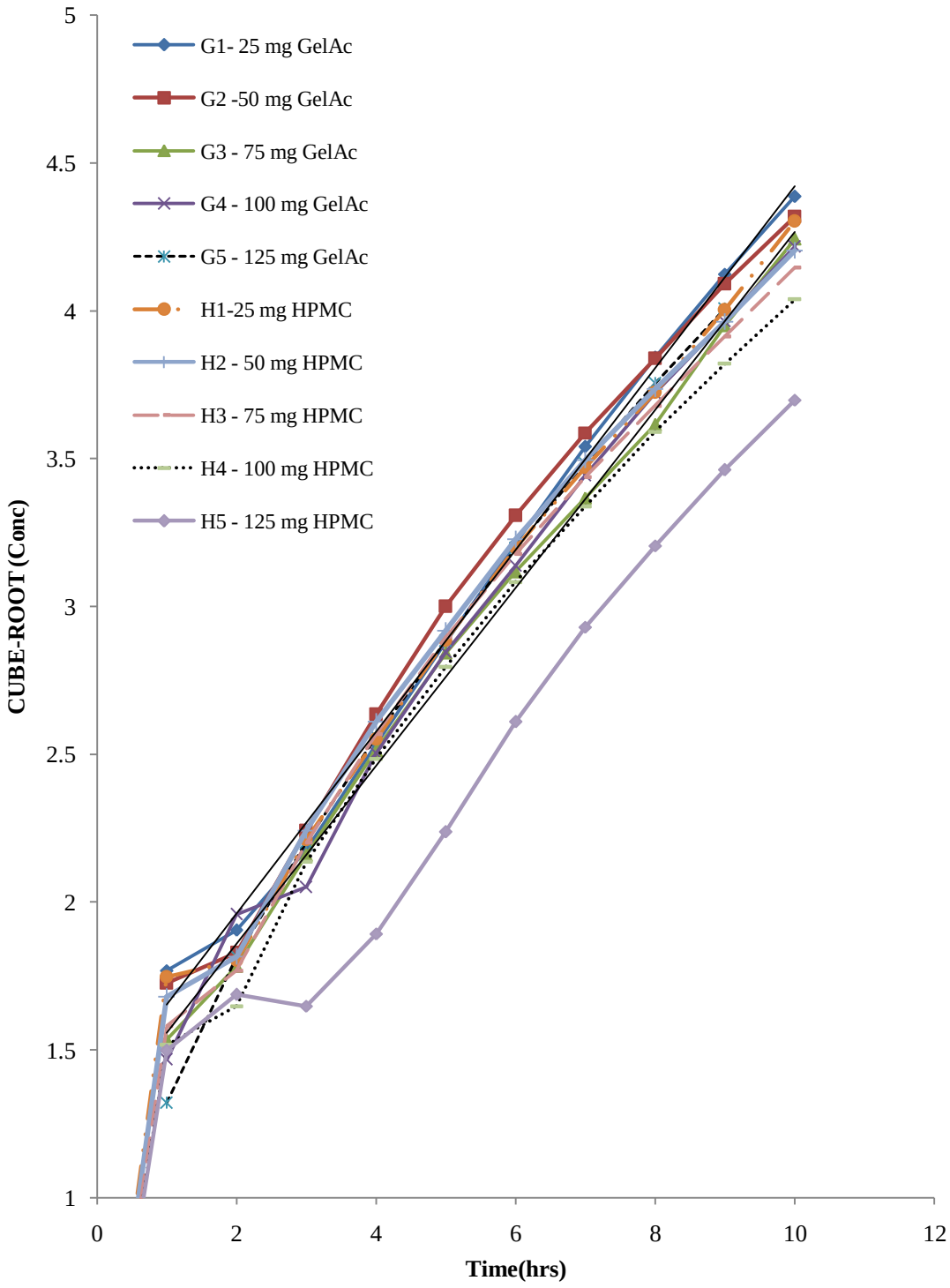


Figure 4: 12 Hixson-crowell plot (cube root % cumulative drug released versus time)for formulations G1- H5

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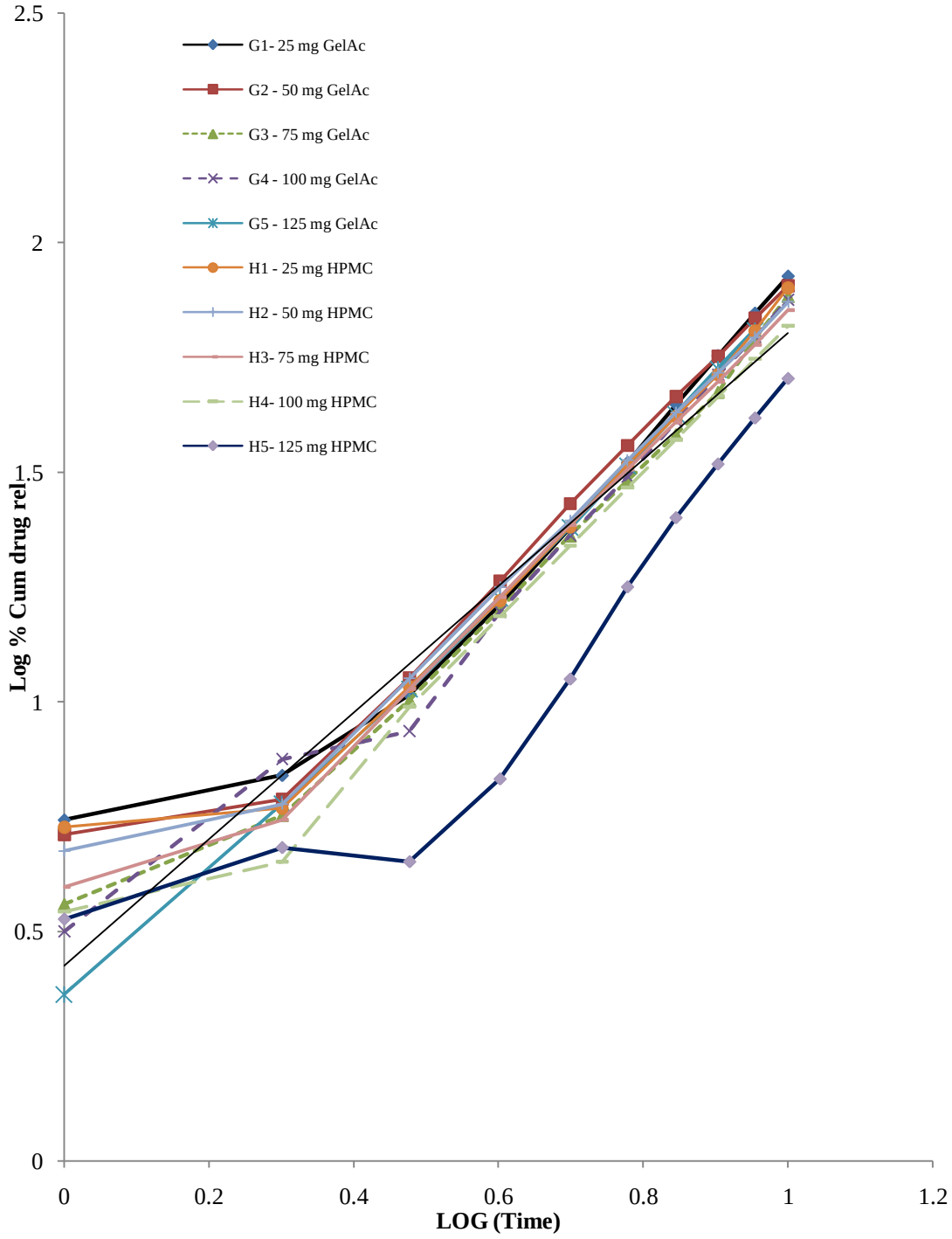


Figure4: 13 Korsmeyer Peppas plot(Plot of log % cumulative drug released versus log time) for formulations G1 –H5

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TABLE 4:7Correlation coefficient (r^2) and release exponent (n) values for different kinetic models of diclofenac sodium matrix tablets containing GelAc and HPMC as release retardant

KINETIC MODEL		G1	G2	G3	G4	G5	H1	H2	H3	H4	H5
Zero Order	**r^2**	0.939	**0.963**	0.942	0.952	0.922	0.930	0.966	0.966	0.964	0.904
First Order	**r^2**	0.803	0.858	0.826	0.860	0.856	0.825	0.883	0.891	0.902	0.86
Higuchi	**r^2**	0.762	0.798	0.769	0.780	0.728	0.714	0.805	0.805	0.799	0.714
Hixson Crowell	**r^2**	0.922	0.916	0.928	0.927	0.969	0.916	0.911	0.916	0.922	0.923
Korsmeyer Peppas	**r^2**	0.913	0.926	0.953	0.956	0.974	0.942	0.963	0.974	0.968	0.867
	'n' value	1.284	1.316	1.377	1.402	1.526	1.280	1.297	1.348	1.386	1.27
Predominant Kinetics		ZO	ZO	ZO	ZO	HC	ZO	ZO	ZO	ZO	ZO

KEY: G1- G5: formulation 10 – 50 % GelAc, respectively H1- H5: formulation 10 – 50 % HPMC respectively.

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4.9 Evaluation of Optimised Batch (G2) with Standard (H2)

Tables 4.7 and 4.8 compares the result obtained from physicochemical evaluation and dissolution profiles of the optimisedbatch G2 with the standard H2 containing HPMC. From the data obtained there is no significant difference (P>0.05).

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TABLE 4:8 Comparison of Evaluation parameters of optimum **batch** G2 with standard H2

Parameter evaluated	Batch G2	H2
Thickness (mm)	4.364	4.459
crushing strength (kgF)	12	10.33
Friability (%)	0	0.38
Weight Variation	pass	pass
Swelling Index (8 h)	160	240
Content uniformity (%)	100	98.55
DR2h (%)	6.127	5.5336
DR8h (%)	47.233	46.772
t 20 % (h)	7.12	7.67
P-value	0.7	

KEY: G2 and H2 formulation with 20 % GelAc and HPMC respectively.

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Table 4:9Comparison of dissolution profile **of** optimumbatch G2 with standard H2

Time (h)	G2	H2
1	5.138	4.74
2	6.126	5.99
3	11.265	11.26
4	18.314	17.79
5	27.009	24.84
6	36.166	33.60
7	46.179	42.69
8	56.588	52.17
9	68.445	62.25
10	80.567	74.31
P-value	0.8	

KEY: G2 and H2 formulation with 20 % GelAc and HPMC respectively.

CHAPTER FIVE

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5.0 DISCUSSION

Presently pharmaceutical industries are focusing on development of sustained release formulations due to its inherent advantages (Singh *et al*, 2012)

Gelatin and acacia were successfully co-precipitated with a yield of about 92.39 %. The high yield could be as a result of little impurities. GelAc had an off-white colour, and is odourless which makes it acceptable meaning it will not infer an offensive odour to the final product. ThepH is neutral as such no chemical reaction was expected between GelAc and other excipients or the API. Upon characterization of the powder property GelAc had a goodflow property of 25.44 ^{o} angle of repose. The angle of repose for pharmaceutical powders ranges between 25-45 ^{o}, the lower values indicate a better flow (Staniforth and Aulton, 2007). The free flowing properties of granules were further confirmed by Carr's index and Hausner's ratio which were 1.11 and 9.921% respectively. The Hausner's ratio and Carr's index have been widely used to estimate the flow property of powders. A Hausner's ratio of less than 1.2 is indicative of good flow whereas a value of 1.5 or higher suggests poor flow (Wells, 1988). Carr's index values of 5-10, 12-16, 18-21, and 23-28 indicate excellent, good, fair and poor flow properties of the material respectively. The result of physicochemical and flow properties suggest that GelAc has a good to excellent flow property.

High percent of GelAc was retain on sieve size 300µm, the granular sized particles may be due to the presence of acacia and its adhering nature causing a formation of agglomerates, the gelling capacity of gelatin and acacia may also be responsible for the swelling capacity of the co-precipitate. The particle size could be responsible for the free flowing nature of GelAc.

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The infra-red spectrum analysis of gelatin, acacia and gelatin-acacia co-precipitate (GelAc) was performed to study structural modifications and interaction between them. The characteristic peaks of gelatin and acacia remained the same upon FT-IR investigation of gelatin-acacia co-precipitate. The results suggested the absence of chemical reactivity between gelatin and acacia when they undergo co-precipitation, it can be said no new compound was formed during the co-precipitating process.

FT-IR spectra of diclofenac (pure drug), drug with GelAc, was illustrated and characteristic peaks were observed at different wave numbers. The major peaks are identical to functional group of Diclofenac sodium. Hence, it was confirmed that there was no incompatibility between drug and GelAc.

The tablets were prepared by wet granulation method. Tablets from all formulations were subjected to several inprocess evaluations. All tablet formulations passed the British Pharmacopoeia (2012)uniformity of weighttest. The B.P. (2012) states that for tablets having mean weight of greater than 250mg, not more than 2 tablets are permitted to deviate from the mean by greater than ± 5% and no tablet by more than ±10%. The significance of this test is to ensure that tablets in each batch of formulation fall within the official size range as any significant deviation could affect chemical content. Generally, excessive weight variation is attributed to poor granule flow during compression, improper die filling or presence of air in the granule bed (Ayorinde*et al.*,2012). The average percentage weight variation for 20 tablets was within official limits ranging from 0. 249 ± 0.004 g to 0.253 g ± 0.005 g for HPMC and 0.250 ±0.008 g to 0.254 ±0.005 g for GelAc. All batches passed the weight variation test and this can be attributed to good flow properties resulting in adequate die filling.

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All formulations had high crushing strength values with minimal or no friability. The friability was found to be 0 to 0.4% for HPMC and 0 to 0.51 % for GelAc, which is less than 1% as per the pharmacopoeial limit. High concentrations of GelAc in matrix tablet also affected the friability. The cohesiveness of GelAc which results to high crushing strength can also account for the low friability. The minimal friability obtained confirms the suitability of the wet-granulation process for the preparation of matrices (Mehta *et al.,* 2013). The low friability value also showed that tablets have sufficient strength to tolerate transportation stress and tablets ability to withstand transportation and mechanical shock during handling. (Silvina, 2002).

Diclofenac tablets should contain 90–110% diclofenac of the drug content on assay (USP, 2007). The percentage content of diclofenac sodium ranged from 94.2 % to 101 % for HPMC and 97 % to 101.4 % for GelAc. The results indicate that all the batches had acceptable contents of the active ingredient and all fell within the pharmacopoeial limit. Indicating good uniformity of content among all the different batches. It is essential for tablet formulations to pass the drug content test as good mechanical properties of tablets alone cannot make up for insufficient drug content.

The swelling index is used to characterize the hydrophilic character of formulations. Swelling can be described as the increase in weight, volume or length (Abdulsamad *et al.,* 2014). Majority of excipients employed in the preparation of the matrix tablets are hydrophilic in nature and in aqueous media the tablets absorb water, swell and increase in size. The swelling index is an indication of the ability of the material used to absorb water while maintaining the integrity of the tablets. Swelling index of each formulation was calculated mathematically, formulation containing higher concentration of GelAc

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and HPMC showed the highest swelling index, this could be due to the swelling ability of GelAc thus the higher the concentrations the greater the swelling index. Furthermore, the relationship between swelling index at 8 h was calculated foreach batch of the formulation. Each showed a direct influence on swelling index depending onconcentration of polymer. As time increases, weight gain by tablet was increased and the swelling index was increased. It has been observed that the cumulative percent drug release decreases with increasing concentration of gum and swelling index. The reason attributed to this fact is slow erosion of the gelled layer from the tablets containing higher amounts ofgum (Atif *et al*., 2013).

Influence of pH

It is known that the release rate of drugs from hydrophilic matrices containing HPMC, is affected by changing the pH (Silvina *et al*., 2012). Thus, the dissolution rate was investigated at pH 1.2 and 6.8. For all the formulations, the release rate of diclofenac sodium was extremely low at acidic pH, after 2 hours only less than 10% of drug was released. All the batches of GelAc described in this work displayed a similar behaviour with low release at pH 1.2 and a higher release at pH 6.8, showing a faster drug dissolution rates, in agreement with previous studies as reported by (Silvina *et al.*, 2002)

Release kinetics is an essential aspect of drug formulation and development.Kinetic data are also employed in setting *in vivo–in vitro* correlation (IVIVC) of dosage forms (Thakkar et al., 2009). The release kinetics was evaluated by fitting the drug release data to five kinetic models. All the formulations were subjected to *in-vitro* dissolution studies. From dissolution study it revealed that as concentration of GelAc increases the rate of drug release from tablet decreasedthe same was observed with HPMC, the decreased release rate with increase in HPMC concentration has also been reported by

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others and has been proposed by Alderman, 1984(as cited in Muhammed and Barbara, 2015).

This may be because an increase in matrix concentration leads to an increase in the viscosity of the gel as well as the formation of gel layer with a longer diffusional path which may in turn cause a decrease in the effective diffusion co - efficient of the drug and therefore a reduction in the drug release rate (Hingmire, 2013). GelAc is shown to have a similar release behaviour as HPMC. It was observed that difference between HPMC and GelAc on the drug release rate were not significant ($p > 0.05$) as they tend to overlap, due to the similar behaviour of the polymers under the same conditions.

The kinetic model with the highest correlation coefficient value (r^2) was selected as the model that best described the dissolution data. In most of the cases it was observed that the release kinetics of diclofenac sodium from the matrix tablet followed the mixed release kinetics of Zero order(r^2values of 0.922 to 0.963 for GelAc tablets and 0.904 to 0.966 for HPMC tablets) and Hixson- Crowell release kinetics (r^2 values of 0.916 to 0.969 for GelAc tablets and 0.911 to 0.923 for HPMC) but Zero order release kinetics predominates. Drug release from diclofenac sodium tablets using GelAc as release retardant followed zero order profile, which indicates the drug release via diffusion mechanism from hydrophilic matrices for all the batches except for formulation G5 which followed the Hixson-Crowell model. It maybe concluded that drug released is bydiffusion within the matrix. Batch G2 with 50 g GelAc had the highest correlation coefficient value at 0.9628.

To confirm the exact mechanism of drug release from these tablets, the data were fitted into Korsemeyer Peppas equation with diffusion exponent ‘n’ valuesranging from 1.284 to 1.5256 for GelAc and 1.270 to 1.386 for HPMC,the value of the release exponent‘n’

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in the Korsmeyer-Peppas model was greater than one, which corresponds to a super case II transport mechanism, (the Super Case II model is characterized when n > 1)indicating an anomalous behaviour, suggesting that more than one mechanism may be involved in release kinetics (Singh *et al;*2012).This means the drug release rate does not change over time and involves polymer relaxation and chain disentanglement as was explained by Ahmed *et al*(2013). G2 was selected as the optimized batchas it had the highest correlation coefficient (r^2). According to 'n' values obtained from the Korsemeyer-Peppas plot, it can be concluded that the drug release is by case II transport (Barathi *et al.,* 2011; Charu*et al.,* 2014).

The data presented proved that the formulations are useful for a sustained release of diclofenac, as the percentage released after 8 h is nearly 70%, except for G5 which has a higher concentration of GelAc

Evaluation of optimised batch

Formulation H2 with similar formula as G2 was experimented against the optimized batch (G2). The values of dissolution profile of the optimised batch (G2) were compared with the response values of the standard batch (H2) and it showed that it had a similar dissolution profile.

CHAPTER SIX

6.0 SUMMARY, CONCLUSION AND RECOMMENDATION

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6.1 Summary

Gelatin-acacia was co-precipitated successfully to yield GelAc. The co-precipitate had good flow property on investigation. FT-IR spectra showed no interaction between drug and co-precipitate characteristic peaks of diclofenac sodium were maintained. Tablets were formulated by wet granulation method, and granules had excellent flow property. Tablet property of average weight variation, hardness, thickness and friability all fell within the official limit. The tablet generally had a high crushing strength and crushing strength increased with an increase in in polymer concentration. The drug generally had low release in SGF pH 1.2 and a higher release rate in SIF pH 6.8. The release rate decreased with an increase in GelAc concentration in the matrix tablet, this is probably due to formation of a gel layer which has a longer diffusional pathway. Formulation followed the zero order release pattern when subjected to kinetic modelling with an anomalous behaviour.

6.2 Conclusion

All characterized parameters of the formulated tablets and GelAc were found to be within the official limit.Results from the study shows that GelAc possesses the requisite physicochemical properties as a drug release retardant in sustaining the release of diclofenac sodium from the designed matrix tablet.

Varying concentration of GelAc was studied and the co-precipitate concentration was found to influence the drug release rate, as the quantity of co-precipitate increased, the drug release rates decreased. The use of GelAc was successful in achieving the sustained drug release of diclofenac sodium for 10 hours from the formulated tablets. Formulation G2 showed sustained drug release for 10 hours. The release kinetics of drug after a study of the kinetic model was best explained by zero order equation. The

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drug release from the tablets was sufficiently sustained and the mechanism of drug release as super case II transport from tablets was confirmed.

6.3 Recommendations

I.Further analytical work can still be carried out on the co-precipitate for a more comprehensive characterization.

II. Process optimization can be carried out on gelatin acacia co-precipitate, such as varying the ratio of gelatin to acacia, increasing or decreasing drying time and temperature.

III. Different grades of acacia can be co-precipitate with gelatin from different sources and the co-precipitate compared to ascertain if there would be any difference in the physicochemical profile.

IV. GelAc can be optimised for other dosage form formulation such as mucoadhesive dosage form.

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APPENDIX

Appendix 1: Particle size distribution of GelAc

SEIVE SIZE (μm)	WEIGHT	% FREQ	Column1
1000	0.32	0.64	640
710	6.55	13.1	9301

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300	29.48	58.96	17688
180	6.89	13.78	2480.4
125	2.82	5.64	705
PAN	3.02	6.04	0
TOTAL	49.08	98.16	30814.4

MEAN PARTICLE SIZE	308.144

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Appendix 2: Specification for weight variation of tablets as per USP

Average weight of tablets (mg)	% difference
130 or less	10
From 130 to 324	7.5
More than 324	5

Appendix 3: Swelling Index of diclofenac Matrix Tablets

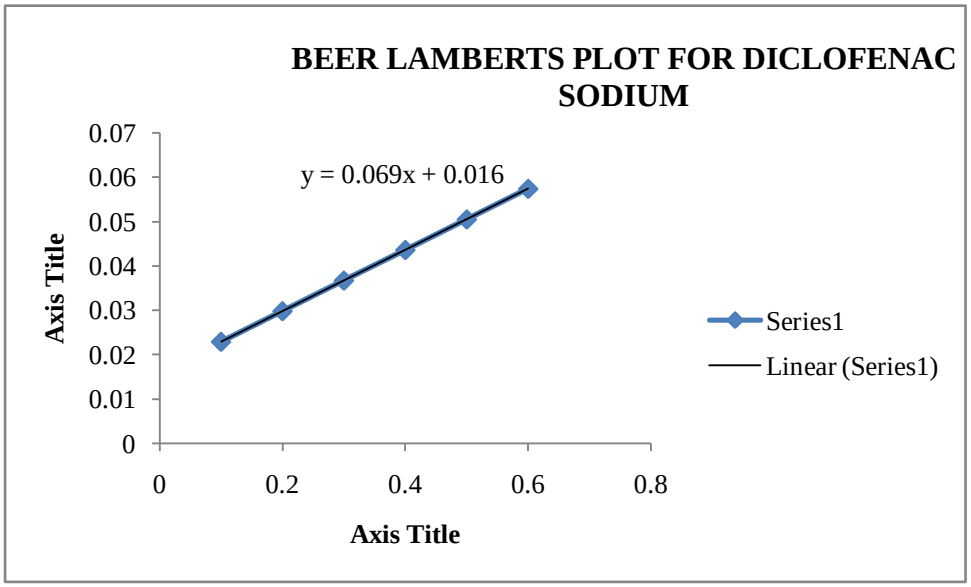
time (h)	G1	G2	G3	G4	G5	H1	H2	H3	H4	H5
2	70	96	102	124	145	60	144	192	184	212
4	82	122	122	132	152	112	180	220	228	236
6	112	132	144	154	172	164	212	248	260	284
8	146	158	179	183	200	180	240	272	368	380
10	154	166	199	191	218	236	284	344	380	408
12	168	182	200	206	236	292	360	392	408	424

KEY: G1,G2, G3, G4, G5: formulation with 25 g. 50 g, 75 g, 100 g, and 125 g GelAc, respectively H1, H2, H3, H4, H5: formulation with 25 g ,50 g ,75 g, 100 g, and 125 g HPMC respectively.

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Appendix 4:Calibration Curve for Diclofenac Sodium

Conc(ug/ml)	Absorbance(nm)
0.1	0.0229
0.2	0.0298
0.3	0.0367
0.4	0.0436
0.5	0.0505
0.6	0.0574



`

Appendix 5:*In-vitro* dissolution test data

H1

Time(h)	Abs	Amt (µg/ml)	Amt × 5	Amt/1000	% released	% Cum drug rel
0	0	0	0	0	0	0
1	0.405	5.6376812	28.188406	0.028188406	25.6258235	25.62582345
2	0.451	6.3043478	31.521739	0.03152174	28.6561265	28.65612648
3	0.051	0.5072464	2.5362319	0.002536232	2.30566535	30.96179183
4	0.184	2.4347826	12.173913	0.012173913	11.0671937	42.02898551
5	0.249	3.3768116	16.884058	0.016884058	15.3491436	57.37812912
6	0.285	3.8985507	19.492754	0.019492754	17.7206851	75.09881423
7	0.33	4.5507246	22.753623	0.022753623	20.685112	95.78392622
8	0.46	6.4347826	32.173913	0.032173913	29.2490119	125.0329381
9	0.636	8.9855072	44.927536	0.044927536	40.8432148	165.8761528
10	0.652	9.2173913	46.086957	0.046086957	41.8972332	207.773386

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H2

Time(h)	Abs	Amt (µg/ml)	Amt × 5	Amt/1000	% released	% Cum drug rel
0	0	0	0	0	0	0
1	0.229	3.0869565	15.434783	0.015434783	14.0316206	14.03162055
2	0.264	3.5942029	17.971014	0.017971014	16.3372859	16.3372859
3	0.096	1.1594203	5.7971014	0.005797101	5.27009223	21.60737813
4	0.101	1.2318841	6.1594203	0.00615942	5.59947299	27.20685112
5	0.115	1.4347826	7.173913	0.007173913	6.52173913	33.72859025
6	0.249	3.3768116	16.884058	0.016884058	15.3491436	49.07773386
7	0.254	3.4492754	17.246377	0.017246377	15.6785244	64.75625823
8	0.236	3.1884058	15.942029	0.015942029	14.4927536	79.24901186
9	0.325	4.4782609	22.391304	0.022391304	20.3557312	99.60474308
10	0.501	7.0289855	35.144928	0.035144928	31.9499341	131.5546772

`

H3

Time(h)	Abs	Amt (μg/ml)	Amt × 5	Amt/1000	% released	% Cum drug rel
0	0	0	0	0	0	0
1	0.311	4.2753623	21.376812	0.021376812	19.4334651	19.43346509
2	0.388	5.3913043	26.956522	0.026956522	24.5059289	24.50592885
3	0.118	1.4782609	7.3913043	0.007391304	6.71936759	31.22529644
4	0.183	2.4202899	12.101449	0.012101449	11.0013175	42.22661397
5	0.227	3.057971	15.289855	0.015289855	13.8998682	56.12648221
6	0.252	3.4202899	17.101449	0.017101449	15.5467721	71.67325428
7	0.33	4.5507246	22.753623	0.022753623	20.685112	92.35836627
8	0.415	5.7826087	28.913043	0.028913043	26.284585	118.6429513
9	0.477	6.6811594	33.405797	0.033405797	30.3689065	149.0118577
10	0.567	7.9855072	39.927536	0.039927536	36.2977602	185.3096179

`

H4

Time(h)	Abs	Amt (µg/ml)	Amt × 5	Amt/1000	% released	% Cum drug rel
0	0		0	0	0	0
1	0.221	2.9710145	14.855072	0.014855072	13.5046113	13.50461133
2	0.322	4.4347826	22.173913	0.022173913	20.1581028	20.15810277
3	0.111	1.3768116	6.884058	0.006884058	6.25823452	26.41633729
4	0.151	1.9565217	9.7826087	0.009782609	8.89328063	35.30961792
5	0.183	2.4202899	12.101449	0.012101449	11.0013175	46.31093544
6	0.316	4.3478261	21.73913	0.02173913	19.7628458	66.07378129
7	0.398	5.5362319	27.681159	0.027681159	25.1646904	91.23847167
8	0.464	6.4927536	32.463768	0.032463768	29.5125165	120.7509881
9	0.463	6.4782609	32.391304	0.032391304	29.4466403	150.1976285
10	0.543	7.6376812	38.188406	0.038188406	34.7167325	184.914361

`

H5

Time(h)	Abs	Amt (µg/ml)	Amt × 5	Amt/1000	% released	% Cum drug rel
0	0	0	0	0	0	0
1	0.123	1.5507246	7.7536232	0.007753623	7.04874835	7.048748353
2	0.235	3.173913	15.869565	0.015869565	14.4268775	14.42687747
3	0.094	1.1304348	5.6521739	0.005652174	5.13833992	19.56521739
4	0.123	1.5507246	7.7536232	0.007753623	7.04874835	26.61396574
5	0.132	1.6811594	8.4057971	0.008405797	7.64163373	34.25559947
6	0.153	1.9855072	9.9275362	0.009927536	9.02503294	43.28063241
7	0.179	2.3623188	11.811594	0.011811594	10.7378129	54.01844532
8	0.209	2.7971014	13.985507	0.013985507	12.7140975	66.73254282
9	0.229	3.0869565	15.434783	0.015434783	14.0316206	80.76416337
10	0.238	3.2173913	16.086957	0.016086957	14.6245059	95.3886693

`

G1

Time(h)	Abs	Amt (µg/ml)	Amt × 5	Amt/1000	% released	% Cum drug rel
0	0	0	0	0	0	0
1	0.1	1.2173913	6.0869565	0.006086957	5.53359684	5.533596838
2	0.121	1.5217391	7.6086957	0.007608696	6.91699605	6.916996047
3	0.068	0.7536232	3.7681159	0.003768116	3.42555995	10.34255599
4	0.106	1.3043478	6.5217391	0.006521739	5.92885375	16.27140975
5	0.132	1.6811594	8.4057971	0.008405797	7.64163373	23.91304348
6	0.157	2.0434783	10.217391	0.010217391	9.28853755	33.20158103
7	0.186	2.4637681	12.318841	0.012318841	11.198946	44.40052701
8	0.203	2.7101449	13.550725	0.013550725	12.3188406	56.71936759
9	0.22	2.9565217	14.782609	0.014782609	13.4387352	70.15810277
10	0.233	3.1449275	15.724638	0.015724638	14.2951252	84.45322793

`

G2

Time(h)	Abs	Amt (µg/ml)	Amt × 5	Amt/1000	% released	% Cum drug rel
0	0	0	0	0	0	0
1	0.094	1.1304348	5.6521739	0.005652174	5.13833992	5.138339921
2	0.109	1.3478261	6.7391304	0.00673913	6.12648221	6.126482213
3	0.094	1.1304348	5.6521739	0.005652174	5.13833992	11.26482213
4	0.123	1.5507246	7.7536232	0.007753623	7.04874835	18.31357049
5	0.148	1.9130435	9.5652174	0.009565217	8.69565217	27.00922266
6	0.155	2.0144928	10.072464	0.010072464	9.15678524	36.16600791
7	0.168	2.2028986	11.014493	0.011014493	10.0131752	46.17918314
8	0.174	2.2898551	11.449275	0.011449275	10.4084321	56.58761528
9	0.196	2.6086957	13.043478	0.013043478	11.8577075	68.44532279
10	0.2	2.6666667	13.333333	0.013333333	12.1212121	80.56653491

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G3

Time(h)	Abs	Amt (μg/ml)	Amt × 5	Amt/1000	% released	% Cum drug rel
0	0	0	0	0	0	0
1	0.071	0.7971014	3.9855072	0.003985507	3.62318841	3.623188406
2	0.102	1.2463768	6.2318841	0.006231884	5.66534914	5.665349144
3	0.083	0.9710145	4.8550725	0.004855072	4.41370224	10.07905138
4	0.104	1.2753623	6.3768116	0.006376812	5.79710145	15.87615283
5	0.124	1.5652174	7.826087	0.007826087	7.11462451	22.99077734
6	0.127	1.6086957	8.0434783	0.008043478	7.31225296	30.3030303
7	0.136	1.7391304	8.6956522	0.008695652	7.90513834	38.20816864
8	0.153	1.9855072	9.9275362	0.009927536	9.02503294	47.23320158
9	0.235	3.173913	15.869565	0.015869565	14.4268775	61.66007905
10	0.24	3.2463768	16.231884	0.016231884	14.7562582	76.41633729

`

G4

Time(h)	Abs	Amt (μg/ml)	Amt × 5	Amt/1000	% released	% Cum drug rel
0	0	0	0	0	0	0
1	0.064	0.6956522	3.4782609	0.003478261	3.16205534	3.162055336
2	0.13	1.6521739	8.2608696	0.00826087	7.50988142	7.509881423
3	0.033	0.2463768	1.2318841	0.001231884	1.1198946	8.629776021
4	0.123	1.5507246	7.7536232	0.007753623	7.04874835	15.67852437
5	0.128	1.6231884	8.115942	0.008115942	7.37812912	23.05665349
6	0.135	1.7246377	8.6231884	0.008623188	7.83926219	30.89591568
7	0.167	2.1884058	10.942029	0.010942029	9.94729908	40.84321476
8	0.178	2.3478261	11.73913	0.01173913	10.6719368	51.51515152
9	0.181	2.3913043	11.956522	0.011956522	10.8695652	62.38471673
10	0.208	2.7826087	13.913043	0.013913043	12.6482213	75.03293808

`

G5

Time(h)	Abs	Amt (µg/ml)	Amt × 5	Amt/1000	% released	% Cum drug rel
0	0	0	0	0	0	0
1	0.041	0.3623188	1.8115942	0.001811594	1.64690382	1.646903821
2	0.054	0.5507246	2.7536232	0.002753623	2.50329381	2.503293808
3	0.049	0.4782609	2.3913043	0.002391304	2.17391304	4.677206851
4	0.087	1.0289855	5.1449275	0.005144928	4.67720685	9.354413702
5	0.109	1.3478261	6.7391304	0.00673913	6.12648221	15.48089592
6	0.125	1.5797101	7.8985507	0.007898551	7.18050066	22.66139657
7	0.148	1.9130435	9.5652174	0.009565217	8.69565217	31.35704875
8	0.162	2.115942	10.57971	0.01057971	9.61791831	40.97496706
9	0.178	2.3478261	11.73913	0.01173913	10.6719368	51.64690382
10	0.189	2.5072464	12.536232	0.012536232	11.3965744	63.04347826

`

Appendix 6: Zero order release rate

Time (h)	% Cumulative drug released									
	G1	G2	G3	G4	G5	H1	H2	H3	H4	H5
0	0	0	0	0	0	0	0	0	0	0
1	5.534	5.14	3.62	3.16	2.31	5.34	4.74	3.95	3.49	3.36
2	6.917	6.13	5.67	7.51	1.84	5.86	5.99	5.53	4.48	4.81
3	10.343	11.26	10.08	8.63	5.99	10.80	11.26	10.67	9.75	4.48
4	16.27	18.31	15.88	15.68	10.67	16.60	17.79	16.93	15.35	6.79
5	23.913	27.01	22.99	23.06	16.80	24.04	24.84	24.31	21.87	11.20
6	33.202	36.17	30.30	30.90	23.98	32.74	33.60	32.08	29.31	17.79
7	44.401	46.18	38.21	40.84	32.67	41.77	42.69	40.65	37.22	25.16
8	56.719	56.59	47.23	51.52	42.29	51.65	52.17	49.80	46.31	32.94
9	70.158	68.45	61.66	62.38	52.96	64.16	62.25	59.95	55.80	41.50
10	84.453	80.57	76.42	75.03	64.36	79.71	74.31	71.34	65.88	50.59
r^2 value	0.939	0.9628	0.9421	0.9515	0.9304	0.9304	0.9658	0.9664	0.9641	0.9043

`

Appendix 7: First order release rate

Time(h)	Log % Cumulative drug remaining									
	G1	G2	G3	G4	G5	H1	H2	H3	H4	H5
0	2	2	2	2	2	2	2	2	2	2
1	1.975	1.977	1.984	1.986	1.990	1.976	1.979	1.982	1.985	1.985
2	1.969	1.973	1.975	1.966	1.992	1.974	1.973	1.975	1.980	1.979
3	1.953	1.948	1.954	1.961	1.973	1.950	1.948	1.951	1.955	1.980
4	1.923	1.912	1.925	1.926	1.951	1.921	1.915	1.919	1.928	1.969
5	1.881	1.863	1.887	1.886	1.920	1.881	1.876	1.879	1.893	1.948
6	1.825	1.805	1.843	1.840	1.881	1.828	1.822	1.832	1.849	1.915
7	1.745	1.731	1.791	1.772	1.828	1.765	1.758	1.773	1.798	1.874
8	1.636	1.638	1.722	1.686	1.761	1.684	1.680	1.701	1.730	1.826
9	1.475	1.499	1.584	1.575	1.672	1.554	1.577	1.603	1.645	1.767
10	1.192	1.289	1.373	1.397	1.552	1.307	1.410	1.457	1.533	1.694
r^2 value	0.8033	0.8597	0.826	0.8595	0.8619	0.8246	0.8828	0.891	0.9018	0.8595

Appendix: 8 Higuchi release model

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SQRT (TIME)	% Cumulative drug released									
	G1	G2	G3	G4	G5	H1	H2	H3	H4	H5
0	0	0	0	0	0	0	0	0	0	0
1	5.534	5.138	3.623	3.162	2.306	5.336	4.743	3.953	3.491	3.360
1.414	6.917	6.126	5.665	7.510	1.845	5.863	5.995	5.534	4.480	4.809
1.732	10.343	11.265	10.079	8.630	5.995	10.804	11.265	10.672	9.750	4.480
2	16.271	18.314	15.876	15.679	10.672	16.601	17.787	16.930	15.349	6.785
2.236	23.913	27.009	22.991	23.057	16.798	24.045	24.835	24.308	21.871	11.199
2.449	33.202	36.166	30.303	30.896	23.979	32.740	33.597	32.082	29.315	17.787
2.646	44.401	46.179	38.208	40.843	32.675	41.765	42.688	40.646	37.220	25.165
2.828	56.719	56.588	47.233	51.515	42.292	51.647	52.174	49.802	46.311	32.938
3	70.158	68.445	61.660	62.385	52.964	64.163	62.253	59.947	55.797	41.502
3.162	84.453	80.567	76.416	75.033	64.361	79.710	74.308	71.344	65.876	50.593
r^2 value	0.7619	0.7983	0.7685	0.7796	0.7402	0.714	0.8049	0.8048	0.7994	0.714

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Appendix:9 Hixson-Crowell model

Time (h)	cube root % cumulative drug released									
	G1	G2	G3	G4	G5	H1	H2	H3	H4	H5
0	0	0	0	0	0	0	0	0	0	0
1	1.769	1.726	1.536	1.468	1.321	1.747	1.680	1.581	1.517	1.498
2	1.905	1.830	1.783	1.958	1.226	1.803	1.817	1.769	1.648	1.688
3	2.179	2.242	2.160	2.051	1.817	2.211	2.242	2.202	2.136	1.648
4	2.534	2.636	2.513	2.503	2.202	2.551	2.610	2.568	2.485	1.893
5	2.881	3.000	2.843	2.846	2.561	2.886	2.918	2.897	2.797	2.237
6	3.214	3.307	3.118	3.138	2.884	3.199	3.227	3.178	3.083	2.610
7	3.541	3.588	3.368	3.444	3.197	3.470	3.495	3.438	3.339	2.930
8	3.842	3.839	3.615	3.721	3.484	3.724	3.737	3.679	3.591	3.206
9	4.124	4.091	3.951	3.966	3.755	4.003	3.963	3.914	3.821	3.462
10	4.387	4.319	4.244	4.218	4.008	4.304	4.204	4.147	4.039	3.699
r^2 value	0.996	0.9911	0.997	0.993	0.990	0.916	0.9105	0.916	0.9216	0.9233

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Appendix: 10 Korsmeyer-Peppas model

Log % Cumulative drug released

LOG (Time)	G1	G2	G3	G4	G5	H1	H2	H3	H4	H5
0	0	0	0	0	0	0	0	0	0	0
0	0.743	0.711	0.559	0.500	0.363	0.727	0.676	0.597	0.543	0.526
0.301	0.840	0.787	0.753	0.876	0.266	0.768	0.778	0.743	0.651	0.682
0.477	1.015	1.052	1.003	0.936	0.778	1.034	1.052	1.028	0.989	0.651
0.602	1.211	1.263	1.201	1.195	1.028	1.220	1.250	1.229	1.186	0.832
0.699	1.379	1.432	1.362	1.363	1.225	1.381	1.395	1.386	1.340	1.049
0.778	1.521	1.558	1.481	1.490	1.380	1.515	1.526	1.506	1.467	1.250
0.845	1.647	1.664	1.582	1.611	1.514	1.621	1.630	1.609	1.571	1.401
0.903	1.754	1.753	1.674	1.712	1.626	1.713	1.717	1.697	1.666	1.518
0.954	1.846	1.835	1.790	1.795	1.724	1.807	1.794	1.778	1.747	1.618
1	1.927	1.906	1.883	1.875	1.809	1.902	1.871	1.853	1.819	1.704
r^2 value	0.936	0.954	0.974	0.97	0.997	0.941	0.963	0.973	0.968	0.867

KEY: G1,G2, G3, G4, G5: formulation with 25 g. 50 g, 75 g, 100 g, and 125 g GelAc, respectively H1, H2, H3, H4, H5: formulation with 25 g ,50 g ,75 g, 100 g, and 125 g HPMC respectively.

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APPENDIX 12: Interpretation of diffusional release mechanisms from polymeric films

RELEASE EXPONENT (N)	DRUG TRANSPORT MECHANISM	RATE AS A FUNCTION OF TIME
0.5	Fickian diffusion	$t^{-0.5}$
0.45 < n = 0.89	Non -Fickian transport	t^{n-1}
0.89	Case II transport	Zero order release
Higher than 0.89	Super case II transport	t^{n-1}

(Suvakanta Dash *et al.*,2010)

APPENDIX 13: Student T-test analysis

	Variable 1	*Variable 2*
Mean	37.455	49.54973333
Variance	3182.051	8000.42343
Observations	9	9
Pooled Variance	5591.237	
Hypothesized Mean Difference	0	
df	16	
t Stat	-0.34312	
P(T<=t) one-tail	0.367987	
t Critical one-tail	1.745884	
P(T<=t) two-tail	0.735974	
t Critical two-tail	2.119905	

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	Variable 1	*Variable 2*
Mean	35.5797	32.964
Variance	712.7785	591.3928
Observations	10	10
	652.0857	
Hypothesized Mean Difference	0	
df	18	
t Stat	0.229045	
P(T<=t) one-tail	0.410708	
t Critical one-tail	1.734064	
P(T<=t) two-tail	0.821416	
t Critical two-tail	2.100922	