# FORMULATION AND EVALUATION OF DICLOFENAC MATRIX TABLET USING NATURAL POLYMER

A THESIS SUBMITTED TO

*Assam Science & Technical University(ASTU) , Guwahati, Assam*

*In the partial fulfilment for the award of degree of*

***MASTER OF PHARMACY* (M.Pharm)**

**IN**

***(PHARMACEUTICS)***

***UNDER THE SUPERVISION OF***

***Dr.Biswajit Das, M.Pharm, Phd***

***Asstt. professor, Deptt.of Pharmaceutics***

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***KAMRUP, ASSAM***

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## ***CERTIFICATE***

This is to certify that the topic incorporated in this thesis entitled ***"Formulation and evaluation of Diclofenac sodium matrix tablet using natural polymer"*** being submitted by **Anindita Deb**, Roll no. **1405211002**, Regd. No. **098205214** in partial fulfillment of the requirement for the award of Degree of Master of pharmacy in Pharmaceutics of **Girijananda Chowdhury Institute of Pharmaceutical Science (GIPS), affiliated to ASTU, Guwahati, Assam** is a bonafied assignment which has been carried out under my direct supervision and guidance during the academic session 2015.

**I wish her all success in life.**

**Dr. Suvakanta Dash**
**Principal**
GIPS

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**Dr. A. B Ahmed**
**Assistant professor**
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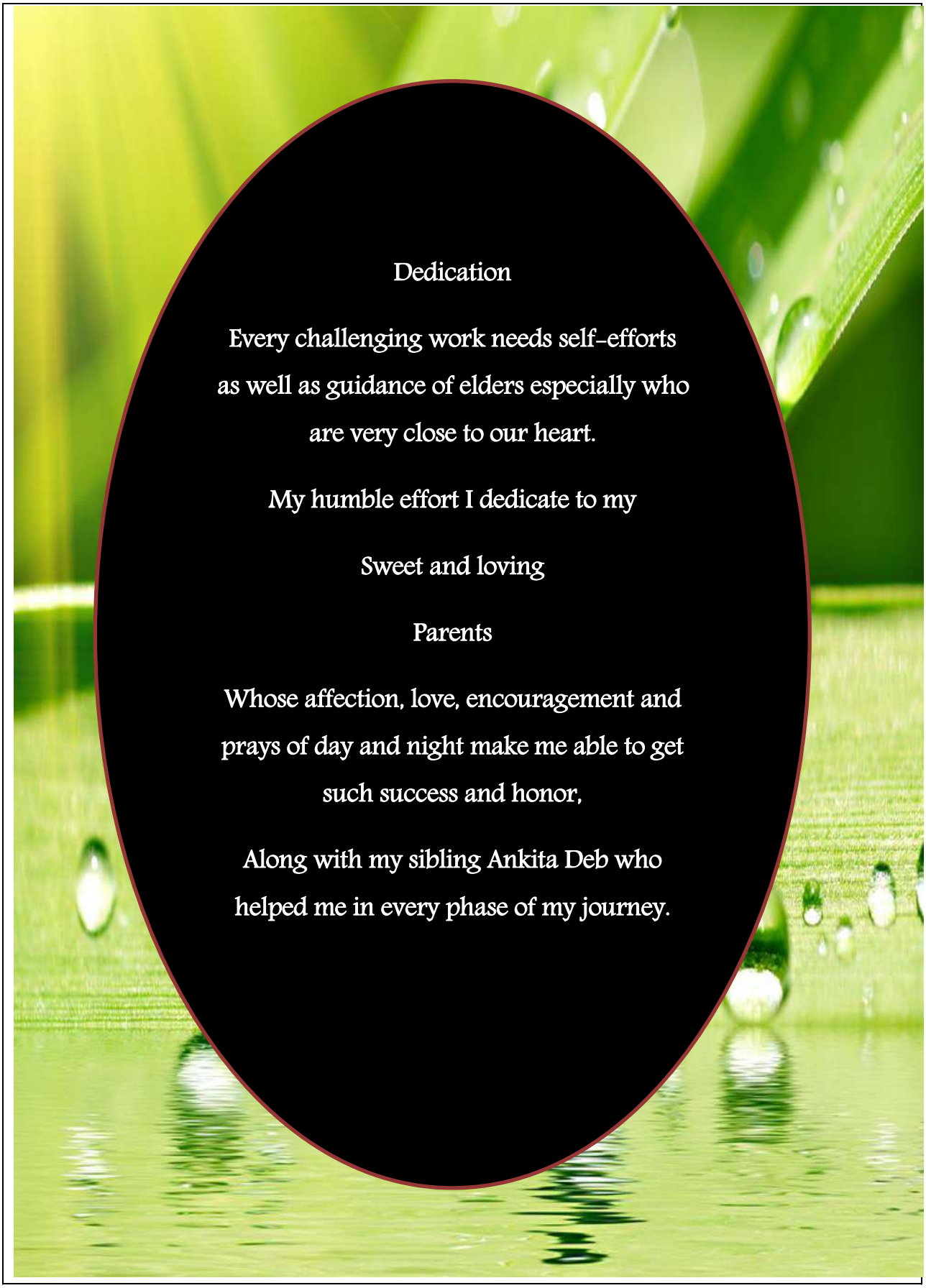
## ***DECLARATION***

I hereby declare that the thesis entitled **"*Formulation and evaluation of Diclofenac sodium matrix tablet using natural polymer*"** a bonafied and genuine research work carried out by me under the supervision of **Dr Biswajit Das,M.Pharm,Phd, Assistant prof., Department of pharmaceutics, Girijananda Chowdhury Institute of Pharmaceutical Science (GIPS), affiliated to ASTU, Guwahati, Assam**.The work embodied in the thesis is original and has not been submitted in part or full for the award of degree, diploma, associate ship or fellowship of any other university or institution.

**Anindita Deb**

**Roll no-1405211004**

**Regd. No.- 098205214**



Dedication

Every challenging work needs self-efforts as well as guidance of elders especially who are very close to our heart.

My humble effort I dedicate to my

Sweet and loving

Parents

Whose affection, love, encouragement and prays of day and night make me able to get such success and honor,

Along with my sibling Ankita Deb who helped me in every phase of my journey.

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*Finally, I owe to my family, my mother Ratna Deb, my father Anjan Kumar Deb & my sibling Ankita Deb a for making me capable of reaching up to this height of education by providing all forms of care, financial support and affection.*

**Date:** **(ANINDITA DEB)**

**Place:**

## LEGEND OF PUBLICATION

1. **MANUSCRIPT COMMUNICATION FOR PUBLICATION**

- **Pharmacological activities of Baheda (*Terminalia bellerica)*: A review.**

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- **Pharmacological activities of Baheda (*Terminalia bellerica)*: A review.**

  **Author's name:- *Anindita Deb, Sikha Barua, Dr. Biswajit Das at**

  **One day National seminar on Emerging Trends in Pharmaceutical education and research , 7$^{th}$ May, 2016**

  **Girijananda Choudhury Institute of Pharmaceutical Sciences, Guwahati-17, Assam, India.**

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# LIST OF ABBREVIATION

| | |
|---|---|
| BP | British Pharmacopoeia |
| USP | United State Pharmacopoeia |
| $^{0}$ C | Degree centigrade |
| CPS | Centipoise |
| Eg | Example |
| FDA | Food and drug administration |
| Fig | Figure |
| DSC | Differential Scanning Calorimetry |
| FT-IR | Fourier transport-infrared |
| GIT | Gastro intestine tract |
| gm | Gram |
| hr | Hours |
| HPMC | Hydroxyl propyl methyl cellulose |
| MCC | Micro Crystalline Cellulose |
| PVP | Poly Vinyl Pyrrolidone |
| CH | Chitosan |
| Mg | Milli gram |
| µg | Micro gram |
| µm | Micrometer |
| Rpm | Rotation Per Minute |
| UV | Ultra Visible |
| SEM | Scanning Electron Microscopy |
| XRD | X-Ray Diffraction |
| i.e | That is |
| SR | Sustained release |
| M | Meter |
| TBG | *Terminelia bellarica* gum |
| %w/v | *%weight by volume* |

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# CHAPTER 1

# INTRODUCTION

## 1. INTRODUCTION:

*Drugs can be administered through various routes; however, of all the routes of administration, oral route of administration is the most convenient for administering and for dosage adjustments. Important reason for their popularity is their convenience of application and the ease of preparation on an industrial scale* [1].

### *1.1 Oral drug delivery system:*

*Oral drug delivery is the most widely utilized route of administration among all the routes [nasal, ophthalmic, rectal, transdermal and Parental routes] that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe [in respect to Parentral route] due to its ease of administration, patient acceptance, and costeffective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:*

*1) Drugs with short half-life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.*

*2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult.*

*3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.*

*In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.* [2]

### 1.2 Controlled Drug Delivery system:

*Controlled drug delivery occurs when a polymer is combined with a drug or active agent such that the release from the bulk material is pre-designed. Controlled and Sustained*

*Release, both has been used in consistent and confusing manner. Both represent separate delivery process. Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Sustained release system generally don't attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters [3].*

### 1.2.1 Advantages of Controlled Drug Delivery System[4]

*The advantages of controlled drug delivery system are as follows:-*

- It helps in the maintenance of drug levels within a desired range.
- It is helpful in the delivery of "difficult" drugs: slow release of water-soluble drugs, fast release of lowsolubility drugs.
- It reduces dosing and increases patient compliance.
- It eliminates over or under dosing
- It prevents of side effects
- Reduction in Health care cost
- It improves efficiency in treatment:
- It reduces adverse side effects and improves tolerability

### *1.2.2 Mechanism of Controlled Drug Release Systems [1]*

#### *1.2.2.1 Diffusion Controlled System:*

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug J (in amount / area - time), across a membrane in the direction of decreasing concentration is given by Fick's law.

$$J = -D \frac{dc}{dx}$$

Where, D = diffusion coefficient in area/ time dc/dx = change of concentration 'c' with distance 'x'

Diffusion systems are characterized by release rate of drug is dependent on its diffusion through inert water insoluble membrane barrier. There are basically two types of diffusion devices.

**A. Reservoir Type:**

In the system, a water insoluble polymeric material encloses a core of drug, which controls release rate. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet .Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media. The polymers commonly used in such devices are Ethyl cellulose and Poly-vinyl acetate.

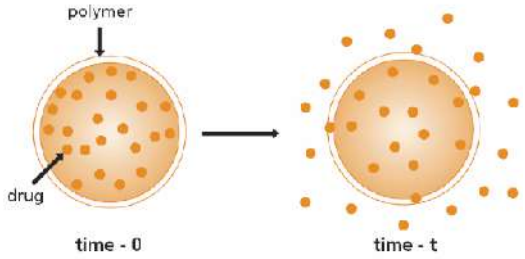



***Fig 1.1: Schematic Representation of Reservoir Diffusion Controlled Drug Delivery Device***

*The rate of drug released (dm/dt) can be calculated using the following equation*

$$\frac{dm}{dt} = ADK\frac{\Delta C}{l}$$

*Where, A = Area, D = Diffusion coefficient, K = Partition coefficient of the drug between the drug core and the membrane, l = Diffusion pathlength and ΔC= Concentration difference across the membrane.*

***Advantage**: By this system Zero order delivery is possible, release rates variable with polymer type.*

***Disadvantages**: System must be physically removed from implant sites. If system fails, high molecular weight compound generally increases cost per dosage unit & potential toxicity.*

**B. Matrix Type:**

A solid drug is homogenously 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.

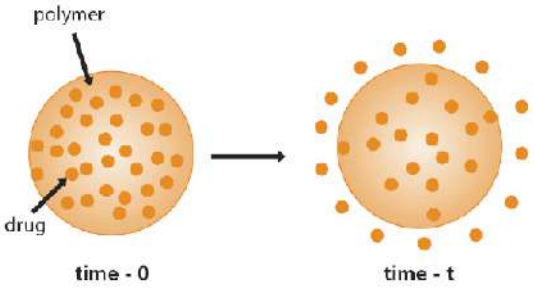



***Fig 1.2: Schematic Representation of Monolithic (matrix) Diffusion Controlled Drug Delivery System.***

***Advantages****: Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.*

***Disadvantages:*** *Cannot provide zero order release, removal of remaining matrix is necessary for implanted system.*

### *1.2.2.2. Dissolution Controlled Systems*

Drugs having high aqueous solubility and dissolution rate, shows challenge in controlling their dissolution rate. Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by

$$\frac{dm}{dt} = \frac{\mathrm{ADS}}{\mathrm{h}}$$

*Where, S = Aqueous solubility of the drug. A = Surface area of the dissolving particle or tablet. D = Diffusivity of the drug and h = Thickness of the boundary layer.*

**A. Encapsulation Dissolution Controlled Systems.**

*The drug particles are coated or encapsulated by microencapsulation techniques with slowly dissolving materials like cellulose, poly ethylene glycols, polymethacrylates, waxes etc. the dissolution rate of coat depends upon the solubility and thickness of the coating.*

*Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at late times will be achieved from those with thicker coating.*

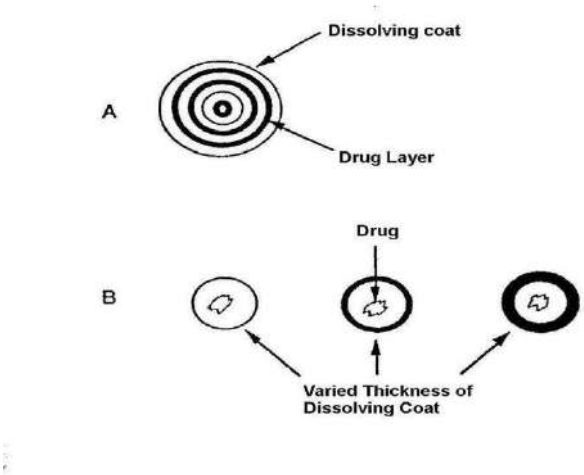



***Fig1.3: Encapsulation Dissolution Controlled Systems***

**B. Matrix Dissolution Controlled Systems** :

*In matrix systems the drug is homogeneously dispersed throughout a rate controlling medium. They employ waxes such as beeswax, carnauba wax, hydrogenated castor oil etcwhich control drug dissolution by controlling the rate of dissolution fluid penetration into the matrix by altering theporosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate. The drug release is often first order from such matrices. The wax embedded drug is generally prepared by dispersing the drug in molten wax and solidifying and granulating the same.*

***1.2.2.3. Dissolution and Diffusion Controlled Release Systems**:*

*The drug core is enclosed in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane which permit entry of aqueous medium into the core and hence drug dissolution and diffusion of dissolved drug out of the system. An example of obtaining such a coating is using a mixture of ethyl cellulose with poly vinyl pyrrolidiene or methylcellulose.*

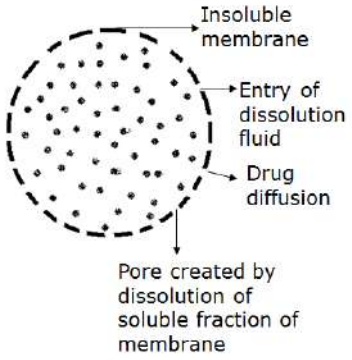



***Fig 1.4: Dissolution and Diffusion Controlled Release System***

### *1.2.2.4. Water Penetration Controlled Systems*[6]

*In water penetration controlled delivery systems, rate control is obtained by the penetration of water into the system. They are*

**A. Swelling Controlled Systems**

*Swelling controlled release systems are initially dry and when placed in the body absorbs water or other body fluids and swells. Swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment.*

**B. Osmotically Controlled Release Systems**

*These systems are fabricated by encapsulating an osmotic drug core containing an osmotically active drug (or a combination of an osmotically inactive drug with an osmotically active salt eg.NaCl) within a semi permeable membrane made from biocompatible polymer, e.g. cellulose acetate. A gradient of osmotic pressure is they created, under which the drug solutes are continuously pumped out of tablet through small delivery orifice in tablet coating over a prolonged period of time through the delivery orifice. This type of drug system dispenses drug solutes continuously at a zero order rate. Release of drug is independent on the environment of the system.*

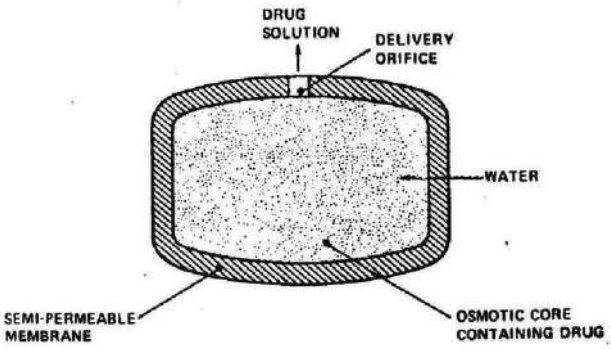



***Fig 1.5: Osmotically Controlled Release System***

***1.2.2.5 Methods using Ion Exchange:***

*This system is designed to provide the controlled release of an ionic or ionizable drug. It is prepared by first absorbing an ionized drug onto the ion-exchange resin granules such as codeine base with amber lite, and then after filtration from the alcoholic medium, coating the drug resin complex granules with a water permeable polymer, e.g. a modified copolymer of polyacrylic and methacrylic ester, and then spray drying the coated granules to produce the polymer coated drug resin preparation. The drug is released by exchanging with appropriately charged ions in the GIT. The drug is then diffuse out of the resin.*

$$Resin^{+} - Drug^{-} + X^{-} \longrightarrow Resin^{+} - X^{-} + Drug^{-}$$

*Where X- are ions in the GI tract*

*The rate of diffusion control by: the area of diffusion, diffusion path length and rigidity of resin. Thus, drug release depends on the ionic environment (pH, electrolyte conc.) and the properties of resin.*

***Advantage*** *- for those drugs which are highly susceptible to degradation by enzymatic processses since it offers a protective mechanism by temporarily altering the substrate.*

***Limitation*** *- The release rate is proportional to the conc. of the ions present in the vicinity of administration site. So variable diet, water intake & intestinal contents affects the release rate of drug.*

*They are mainly of 2 types - cation exchange and anion exchange resin.*

**A. Cationic Drugs**

A cationic drug forms a complex with an anionic ionexchange resin e.g. a resin with a SO3- group. In the GI tract Hydronium ion (H+) in the gastrointestinal fluid penetrates the system and activates the release of cationic drug from the drug resin complex.

$$H^+ + Resin\text{-}SO3\text{-}Drug^+ \longrightarrow Resin\text{-}SO3\text{-}H^+ + Drug^+$$

**B. Anionic Drugs**

*An anionic drug forms a complex with a cationic ion exchange resin, e.g. a resin with a [N (CH3)3+] group. In the GI tract, the Chloride ion (Cl-) in the gastrointestinal fluid penetrates the system and activates the release of anionic drug from the drug resin complex.*

$$Cl^- + Resin\text{-}[N(CH_3)_3^+]\text{-}Drug^- \longrightarrow Resin\text{-}[N(CH_3)_3^+]\text{-}Cl^- + Drug^-$$

***1.2.2.6 Chemically Controlled Release Systems*** [7]

*Chemically controlled release systems are the systems that change their chemical structure, when exposed to biological fluid. Mostly, biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically safe and progressively smaller moieties. It is of two types and they are Erodible systems and Pendent chain system*

***1.2.2.6.1 Erodible Systems****: In erodible systems, the mechanism of drug release occurs by erosion. Erosion may be two types and they are*

**A. Bulk Erosion**

*In bulk erosion process, polymer degradation may occur through bulk hydrolysis*

- When the polymer is exposed to water hydrolysis occurs
- Hydrolysis degrades the large polymers into smaller biocompatible compounds
- These small compound diffuse out of the matrix through the voids caused by swelling
- Loss of the small compounds accelerates the formation of voids thus the exit of drug molecules
  e.g.polylactide, polyglycolic acid

**B. Surface ErosionProcess:**

*In surface erosion process, polymers like polyorthoesters and polyanhydridesetcoccurs degradation only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the delivery system.*

- When the polymer is exposed to water hydrolysis occurs
- Hydrolysis degrades the large polymers into smaller biocompatible compounds
- These small compound diffuse from the interface of the polymer
- Loss of the small compounds leads to drug loss

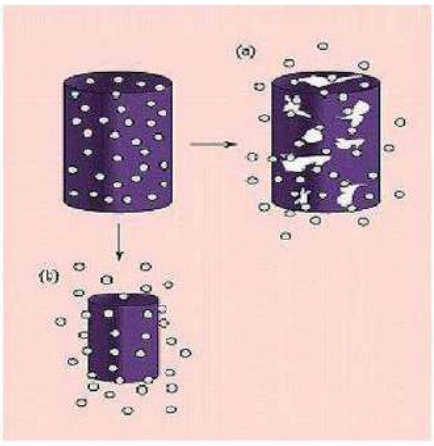



***Fig1.6: Bulk Erosion and Surface Erosion***

#### 1.2.2.6.2 Pendent Chain System

*Pendent chain systems consist of linear homo or copolymers with the drug attached to the backbone chains. The drug is released from the polymer by hydrolysis or enzymatic degradation of the linkages. Zero order can be obtained and the cleavage of the drug is the rate controlling mechanism. Example for polymers used in pendent chain systems like n-(2hydroxy propyl)methacrylamide etc.*

### *1.2.2.7 pH Independent Formulations*

*The gastrointestinal tract present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length of prolongation, further the chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH*

*dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH independent drug release. A buffered controlled release formuation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug.*

### *1.2.2.8 Hydrogels*

*Hydrogels are water swollen three dimensional structures composed of primarily hydrophilic polymers. They are insoluble because of chemical or physical cross-links. The physical cross-links include crystallites, entanglements or weak associations like hydrogen bonds or vanderwaals forces. These crosslinks provide the physical integrity and network structure. Hydrogels provide desirable protection of labile drugs, peptides and proteins.*

### *1.2.2.9 Altered Density Formulations*

*Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract like High density approach and Low density approach.*

## *1.3 Matrix tablets[9]:-*

Matrix tablets is a promising approach for the establishment of extended-release drug therapy as tablets offer the lowest cost approach to sustained and controlled release solid dosage forms. Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". These systems release drug in continuous manner by dissolution-controlled and diffusion-controlled mechanisms. Under gastric pH conditions, matrix tablet slowly erodes. However at a pH corresponding to the upper small intestine, the tablet disintegrates rapidly to reduce coated particles, which in turn slowly releases drug. Two different release mechanisms are operative, either of which is zero-order erosion and decreasing surface area, and dissolution of coated particles, but the overall tablet release profile comprising the two mechanisms in sequence is nearly linear for most of the dose in the tablet. The result in the ability to control active pharmaceutical ingredient's blood level's

in a narrow range, above the minimum effective level and below toxic level. This type of sustained-release tablet has clearly shown the potential of the tablet as a reliable sustained release dosage form with good release profile precision. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression .

### *1.3.1 Advantages offered by matrix tablets:*

*There are many advantages of matrix tablets some of them are as follows:*

- It maintains therapeutic concentrations over prolonged periods.
- It avoids the high blood concentration.
- Reduction in toxicity by slowing drug absorption.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Better drug utilization.
- Minimize drug accumulation with chronic dosing.
- Can be made to release high molecular weight compounds.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in GIT.
- Reduction in health care cost.
- Usage of less total drug.
- Improvement of the ability to provide special effects. Ex: Morning relief of arthritis through bed time dosing.
- Improved patient compliance.

### 1.3.2 Disadvantages of Matrix Tablets:

*There are many dis-advantages of matrix tablets some of them are as follows:*

- The remaining matrix must be removed after the drug has been released.
- Greater dependence on GI residence time of dosage form.
- Increased potential for first-pass metabolism.

- Delay in onset of drug action.
- Release rates are affected by food and the rate transit through the gut.
- Release rate continuously diminishes due to increased diffusional resistance and decrease in effective area at the diffusion front.

## 1.4 Polymer

The word polymer is derived from greek words, poly= many and mers= parts or units of high molecular mass each molecule of which consist of a very large number of single structural units joined together in a regular manner. In other words polymers are giant molecules of high molecular weight, called macromolecules, which are build up by linking together of a large number of small molecules, called monomers. The reaction by which the monomers combine to form polymer is known as polymerization. The polymerization is a chemical reaction in which two or more substances combine together with or without evolution of anything like water, heat or any other solvents to form a molecule of high molecular weight. The product is called polymer and the starting material is called monomer.

Today, the whole world is increasingly interested in natural drugs and excipients. In recent years, plant derived polymers have evoked tremendous interest due to their diverse pharmaceutical applications such as diluent, binder, disintegrants in tablets, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels and bases in suppository, they are also used in cosmetics, textiles, paints and paper-making. These polymers such as natural gums and mucilage are biocompatible, cheap and easily available and are preferred to semi synthetic and synthetic excipients because of their lack of toxicity, low cost, availability, soothing action and non-irritant nature. A large number of plant-based pharmaceutical excipients are available today. Ability to produce a wide range of material based on their properties and molecular weight, natural polymers became a thrust area in majority of investigations in drug, muscle fibers, polysaccharides, enzymes and gummy exudates are the natural polymers being used effectively in formulating the variety of pharmaceutical products. Chitosan, Carrageenan, acacia, agar, Ispaghula, karaya this are natural polymers most widely used in pharmaceutical and cosmetics product development [10].

### 1.4.1 Natural polymer

Natural polymers occur in nature and can be extracted. They are often water-based. Examples of naturally occurring polymers are silk, wool, DNA, cellulose and proteins.Ability to produce a wide range of material based on their properties and molecular weight, natural polymers became a thrust area in majority of investigations in drug delivery systems . Natural gums can also be modified to meet the requirements of drug delivery systems and thus can compete with the synthetic excipients available in the market.[11]

Carbohydrate polymers are extensively used in recent years in biomedical and pharmaceutical applications due to their biocompatibility. The polysaccharides represent one of the most abundant industrial raw materials and have been the subject of intensive research due to their sustainability, biodegrability and biosafety. A polymer is a large molecule (macromolecules) composed of repeating structural units. These subunits are typically connected by covalent chemical bonds. Both synthetic and natural polymers are available among which natural polymers are mostly used in pharmaceutical application because they are economical, readily available and non toxic. They are capable of chemical modification, potentially biodegradable and with a few exceptions, also biocompatible.

*The specific application of plant-derived polymers in pharmaceutical formulations include their use in the manufacture of solid monolithic matrix systems, implants, films, beads, microparticles, nanoparticles, inhalable and injectable systems as well as viscous liquid formulations. Within these dosage forms, polymeric materials have fulfilled different roles such as binders, matrix formers or drug release modifiers, film coating formers, thickeners or viscosity enhancers, stabilizers, disintegrants, solubilisers, emulsifiers, suspending agents, gelling agents and bioadhesives.*

#### *1.4.1.1 Advantages of natural polymer*

*There are many advantages of natural polymer as follows:-*

- Biodegradable – Naturally occurring polymers produced by all living organisms. They showno adverse effects on the environment or human being.
- Biocompatible and non-toxic– Chemically, nearly all of these plant materials are carbohydrates in nature and composed of repeating monosaccharide units. Hence they are non-toxic.
- Economic - They are cheaper and their production cost is less than synthetic material.

- Safe and devoid of side effects – They are from a natural source and hence, safe and without side effects.
- Easy availability – In many countries, they are produced due to their application in many industries.

***1.4.1.2 Disadvantages of natural polymer***

*The disadvantages of natural polymer are as follows:-*

- Microbial contamination – During production, they are exposed to external environment and hence, there are chances of microbial contamination.
- Batch to batch variation – Synthetic manufacturing is controlled procedure with fixed quantities of ingredients while production of natural polymers is dependent on environment and various physical factors.
- The uncontrolled rate of hydration—Due to differences in the collection of natural materials at different times, as well as differences in region, species, and climate conditions the percentage of chemical constituents present in a given material may vary.
- Slow Process – As the production rate depends upon the environment and many other factors, it can't be changed. So natural polymers have a slow rate of production.
- Heavy metal contamination – There are chances of Heavy metal contamination often associated with herbal excipients.

***1.5 Plant profile [11]:***

*TerminaliabellericaRoxb (combretaceae) is found widely throughout the Indian subcontinent, Sri Lanka, South- East Asia, Bangladesh as a medicinal plant. Plant and plant parts are used in the traditional system of medicines like Ayurveda, Siddha, Unani& Chinese medicine. The plant is constituted of Glucoside, Tannins, Gallic acid, Ethyl Gallate, Chebulinic acid.*

***1.5.1 Synonyms***

*Assam - Bhomora, Bhomra, Bhaira;*

*Eng - BelericMyrobalan;*

*Guj - Bahedam, Beheda;*

*Hindi - Bahera;*

*Kan - Shanti, Shantikayi, Tare, Tarekayi;*

*Mal - Tanni, Tannikai;*

*Mar - Beheda;*

*Ori - Beheda, Bhara;*

*Sansk - Vibhita, Aksa, Aksaka, Bibhitaki;*

*Tam - Thanakkai, Tanri, tanrikkai, Tani;*

*Tel - Tannikkaya, Vibhitakami, Tani;*

***1.5.2 Plant description***

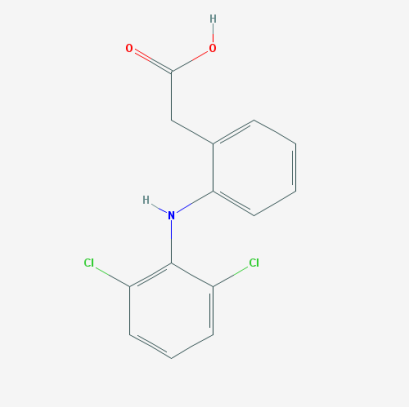
*Terminalia bellerica is a large deciduous tree to 50 m tall and a diameter of 3 m with a rounded crown. The frequently buttressed bole at the base is branchless up to 20 m. The bark is bluish or ashy-grey covered with numerous fine longitudinal cracks, the inner bark yellowish. Leaves are large, glabrous, alternate, broadly elliptic to obovate-elliptical, 4-24 cm x 2-11 cm, base rounded to cuneate, rufous-sericeous but soon glabrescent, with 6-9 pairs of secondary veins. Secondary and tertiary venation prominent on both surfaces, clusteredtowards the ends of branchlets. Petiole is 2.5-9 cm long. Young leaves copper-red, soon becoming parrot green, then dark green. Flowers solitary, small, 3-15 cm long, greenish white, simple, axillary spikes; calyx tube densely sericeous or tomentulose; flowers appear along with new leaves and have a strong honey-like smell. Fruit is sub-globular to broadly ellipsoid, 2-4 x 1.8-2.2 cm, densely velutinous or sericeous, light-yellow, obscurely 5-angled and minutely brown tomentosa. The generic name 'Terminalia' comes from Latin word 'terminus' or 'terminalis' (ending), and refers to the habit of the leaves being crowded or borne on the tips of the shoots.*

***1.5.3 Phytoconstituents***

*Glucoside (bellericanin), Gallo-tannic acid, Coloring matter, resins and a greenish yellow oil . Ellagic acid, gallic acid, lignans (termilignan and thannilignan), 7-hydroxy 3'4' (methylenedioxy) flavone and anolignanB .Tannins, ellagic acid, ethyl gallate, galloyl glucose and chebulagic acid, phyllemblin, β-sitosterol, mannitol, glucose, fructose and rhamnose.*

***1.6. Drug profile:***

***DICLOFENAC***




***Chemical name:*** *2-(2, 6-dichloranilino) phenylaceticacid.*

***1.6.1 Synonyms:-****Dichlofenal, Diclofenac, Diclofenac Potassium, Diclofenac Sodium, Diclofenac Sodium, Diclonate P, Diclophenac.*

***1.6.2 Chemical and Physical Properties:***

| | |
|---|---|
| *Molecular Weight* | *296.14864 g/mol* |
| *Molecular Formula* | *$C_{14}H_{11}Cl_2NO_2$* |
| *XLogP3* | *4.4* |
| *Hydrogen Bond Donor Count* | *2* |
| *Hydrogen Bond Acceptor Count* | *3* |
| *Rotatable Bond Count* | *4* |
| *Exact Mass* | *295.016684 g/mol* |
| *Monoisotopic Mass* | *295.016684 g/mol* |
| *Topological Polar Surface Area* | *49.3 A^2* |
| *Heavy Atom Count* | *19* |
| *Formal Charge* | *0* |
| *Complexity* | *304* |
| *Isotope Atom Count* | *0* |
| *Defined Atom Stereocenter Count* | *0* |
| *Undefined Atom Stereocenter Count* | *0* |
| *Defined Bond Stereocenter Count* | *0* |
| *Undefined Bond Stereocenter Count* | *0* |
| *Covalently-Bonded Unit Count* | *1* |

***Color:-****Crystals from ether-petroleum ether.*

***Melting Point**:- 156-158**deg C***

***Solubility:-**Water Solubility -2.37 mg/L (at 25 °C)*

***Vapor Pressure:-**6.14X10-8 mm Hg at 25 deg C (est)*

***LogP:-** log Kow = 4.51*

***pKa** :- 4.15*

***Dissociation Constants:-**pKa = 4.15*

***Comercial Dosage forms***

*TABLETS: - 25mg, 50mg, 100mg*

### *1.6.3 Pharmacokinetic Properties*

- **Absorption:-**Diclofenac is rapidly and efficiently absorbed after conventional oral, rectal or intramuscular administration. After intramuscular administration peak plasma concentrations are attained after 10 to 30 minutes. With the enteric-coated formulation peak concentrations are reached after 1.5 to 2.5 hours, and this is delayed by food to 2.5 to 12 hours. After a single 50mg dose of these formulations, mean peak plasma concentrations of unchanged diclofenac are 0.7 to 1.5 mg/L. No clear peak concentrations are found after a single 100mg dose of sustained release diclofenac, although the mean concentration was about 0.1 mg/L at 2 hours. Peak plasma concentrations and area under the plasma concentration-time curve are linearly related to dose over the range of 25 to 150mg, regardless of administration route, and no accumulation occurs after repeated doses.
- **Distribution:-**Like other NSAIDs, diclofenac is highly (≥ 99.5%) protein bound. The mean total volume of distribution is 0.12 to 0.17 L/kg and that of the central compartment is 0.04 L/kg. The drug efficiently penetrates inflamed synovial fluid where high concentrations are maintained compared with plasma concentrations. Diclofenac and its metabolites cross the placenta in animals, and small amounts may be found in the breast milk of women.
- **Metabolism:-**Diclofenac undergoes significant first-pass metabolism and only 60% of the drug reaches systemic circulation unchanged following oral administration. It is eliminated principally by hepatic metabolism and subsequent urinary and biliary excretion of glucuronide and sulphate conjugates of the metabolites. The principal metabolite in humans is 4′-hydroxydiclofenac, which possesses negligible anti-inflammatory activity compared with the parent drug; the amount excreted in urine accounts for 20 to 30% of the dose and that in bile for 10 to 20%. In healthy

volunteers, mean plasma clearance of diclofenac is 16 L/h, and the mean elimination half-life of the terminal phase is 1.1 to 1.8 hours. The mean elimination half-life after a radiolabelled dose is about 30 hours for the tracer.

- **Excretion:**-Age and renal or hepatic impairment do not appear to have any significant effect on plasma concentrations of unchanged diclofenac, although metabolite concentrations may be increased by severe renal impairment.

***1.6.4 Uses:***

*Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID). This medicine works by reducing substances in the body that cause pain and inflammation. Diclofenac is used to treat mild to moderate pain, or signs and symptoms of osteoarthritis or rheumatoid arthritis. The Cataflam brand of this medicine is also used to treat menstrual cramps. Diclofenac oral powder (Cambia) is used to treat a migraine headache attack. Cambia will only treat a headache that has already begun. It will not prevent headaches or reduce the number of attacks.*

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# CHAPTER 2

# LITERATURE REVIEW

## *2. LITERATURE REVIEW*

*The present study aimed to formulate and evaluate matrix tablet of Diclofenac sodium using natural polymer. The natural polymer used was obtained from Terminelia bellarica gum and characterized accordingly to be used in the formulations as matrix former. To perform with the study some of literatures were being surveyed. Those are as follows:-*

### *2.1 Reviews on Matrix tablets using natural polymers:*

***A. Seetha Devi et.al,*** *prepared and evaluated diclofenac sodium controlled release matrix tablets using natural polymer. The tablets were prepared by wet granulation technique and were evaluated for various parameters. In vitro release studies were carried out and found thatformulation containing Drug:Polymer (1:1.5) showed maximum release of 99.8%. all the formulations undergo Non-Fickian diffusion or Enomalous diffusion mechanism. Analysis of drug release rate from matrix system indicatedthat drug was released by Super case II transport mechanism.*

***P. Bharghava et. al,*** *formulated sustained release matrix tablets of Diclofenac sodium using Gum acacia and okra gum as release modifier. The tablets were undergone for various parameters. The invitro releasewas performed in phosphate buffer pH 7.4 for 24hrs. they found that the drug release from matrix tablet prepared by using natural polymer can be sustained for more than 12hrs and the drug release vary with concentration of polymer in m atrix tablets.*

***A.S. Rathore et.al.*** *Discussed about the difficulties method in the formulation of matrix tablets by the pharmaceutical technologists, that developing oral sustained release matrix tablet with constant release rate has always been a challenge. Most of drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. Hydrophilic polymers have become product of choice as an important ingredient for formulating sustained release formulations.*

***C. Sekhar et.al.*** *formulated suatained release matrix tablets of Didanosine by using natural gums like xanthan gum and guar gum. They prepared the granules by wet granulation method analysed those granules to determine the loose bulk density, tapped bulk density, angle of repose and Compatibility index. Their result showed that as the concentration of gum increases, swelling index also increased proportionally.*

***P. Pawan et.al.*** *formulated and evaluated matrix tablet of diclofenac sodium using natural mucilage of Abelmoschus esculentus as a release retardant. The mucilage was extracted from the fruit of Abelmoschus esculentus using acetone. The mucilage was characterized for physiochemical and powder characteristics. The matrix tablets were formulated using*

*different drug polymer ratio. The developed formulations of tablets were evaluated for pre-compression and post-compression parameters. Swelling index reveals that with increasing mucilage concentration there is increased swelling. With increase in mucilage concentration the drug release from the matrix tablets got retarded. Their final result showed matrix tablet of Diclofenac sodium using natural mucilage of Abelmoschus esculentus as a release retardant could be employed for retardant drug release.*

***L. P. Hingmire et.al.*** *attempted to increase therapeutic efficacy, reduce frequency of administration, and improve patient compliance, by developing sustained release matrix tablets of diclofenac sodium using natural polymers such as Xanthan gum, locust bean gum, sodium alginate. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness,thickness, swelling index & in vitro dissolution using paddle method, and swelling index. Their result showed formulation containing combination of locust bean gum and Xanthan gum (6:4) showed sustained release of drug for 12hours with release of 98.95 %. Optimized formulation was subjected to accelerated stability studies.*

***R. Malvia et.al****. attempted to formulate sustained release matrix tablets of Diclofenac sodium using gum acacia and tamarind gum as release modifier. Six batches of sustained release matrix tablets of Diclofenac sodium were prepared by using different drug: polymer ratios for both gum acacia and tamarind gum. Results showed that the drug release from matrix tablets prepared by using natural polymers can be sustained for more than 12 hrs and the drug release vary with concentration of polymer in matrix tablets.*

***V. Kamalakkannan et.al****. develop sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and natural gums like gumkodangogu. drug and polymer for control the release of drug up to desired time, the release rates were modulated by combination of two different rates controlling material and triple mixture of three different rate controlling material. After evaluation of physical properties of tablet, the in vitro release study was performed in0.1 N HCl . The effect of polymer concentration and polymer blend concentration were studied. .Dissolution data was analyzed by Korsmeyer-Peppas power law expression and modified power law expression. It was observed that matrix tablets contained polymer blend of kodangogu/HPMC were successfully sustained the release of drug upto 10 hrs.*

***M.K. Senapati et.al.*** *fabricated matrix tablets of phenylpropanolamine using karaya gum and guar gum, alone or in combination with other excipients. The tablets were evaluated for physical characteristics like hardness, weight variation, friability, swelling index and drug content. In vitro release of drug was performed in 0.1N HCl (pH 1.2) for 2 h and the rest of*

*dissolution in phosphate buffer (pH 6.8). The effect of water-soluble (lactose) and water-insoluble (dicalcium phosphate) excipients on drug release was evaluated. All the physical characteristics of the fabricated tablets were within acceptable limits. The tablets with karaya gum exhibited greater swelling indices than those with guar gum. All the batches provided drug release over a period of 6 h. The level of matrix former in the tablets affects drug release. Incorporation of lactose or dicalcium phosphate influenced drug release, but at lower polymer levels only. A combination of karaya gum and guar gum exhibited more sustained release than individual gum.*

***S. Jain et.al,*** *fabricated suatained release tablets of furosemide using pectin, guar gum and xanthan gum. The tablets were evaluated for physical characteristic like hardness, weight variation, fraibilty, and drug content. In-vitro release of drug was performed in PBS pH 7.2 for fifteen hours. All the physical characters of the fabricated tablet were within acceptable limits. The tablet with guar gum exhibited greater swelling index than those with pectin and xanthan gum. A better controlled drug release (80.74%) was obtained with the matrix tablet (G4) made-up of the guar gum than with the pectin and xanthan gum. It is cleared through the dissolution profile of furosemide from matrix tablets prepared using different natural polymers were retarded approx 15 hrs.*

***G.N.K.Ganesh et.al,*** *fabricated sustained release tablets of Diclofenac Sodium using Cashew nut tree gum, HPMC and Carbopol . The tablets were evaluated for preformulation studies like angle of repose, bluk density, compressibility index and physical characteristics like hardness, weight variation, fraibilty and drug content. In-vitro release of drug was performed in PBS pH 7.2 for twelve hours. All the physical characters of the fabricated tablet were within acceptablelimits. The tablet with HPMC(Batch B-I) and Carbopol(Batch C-I) exhibited greater drug content than those with cashew nut tree gum and other batches of HPMC and carbopol. A better sustained drug release (50.65%) was obtained with the matrix tablet (Batch C-III) made-up of the carbopol than with the cashew nut tree gum and HPMC. It is cleared through the dissolution profile of Diclofenac sodium from matrix tablets prepared using different polymers were indicated an increase in the polymer ratio retarded the drug release to a greater extent.*

***D. Bhowmik et.al****, studied that Controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time. Continuous oral delivery of drugs at predictable and reproducible kinetics for predetermined period throughout the course of GIT. Controlled release drug delivery employs drug-encapsulating devices from which therapeutic agents may be released at controlled rates for long periods of*

*time, ranging from days to months. Such systems offer numerous advantages over traditional methods of drug delivery, including tailoring of drug release rates, protection of fragile drugs and increased patient comfort and compliance.*

***N. Patel et.al,*** *studied that Oral drug delivery is the most convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness to drugs when administered by oral conventional method in the form of tablets and capsules. An appropriately designed controlled release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target site. Oral Sustained release (SR) / Controlled release (CR) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetic and pharmacodynamics properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance.*

***J.R. Patel et.al,*** *attempted to increase the solubility of this model drug by formulating Matrix tablet using HPMC, Ethyl cellulose, PVP and Carbopol-934 polymer to control the release of drug with a view to develop controlled release dosage. They found good physical integrity free from any drug- polymer interaction and the results provided a method of achieving controlled drug action through uniform drug release.*

***2.2 Reviews on Plant derived pharmaceutical excipients:***

***A.M. Avachat et.al.*** *discussed about the majority of the plant-derived polymeric compounds out of which polysaccharides, resins and tannins are most extensively studied and used. They studied about their sources, extraction procedure, chemical constituents, uses and some recent investigations as excipients in novel drug delivery systems.*

***S. Jana et.al****. investigated biodegradable polymers are widely being studied as a potential carrier material for site specific drug delivery because of its non-toxic, biocompatible in nature. Natural polysaccharides have been investigated for drug delivery applications as well as in biomedical fields.Modified polymer has found its application as a support material for gene delivery, cell culture, and tissue engineering. Now a day, the polymer is being modified to obtain novel biomaterial for controlled drug delivery applications. This review provides an*

*overview of the different modified polymer derivatives and their applications with special attention being put on controlled drug delivery and biomedical engineering.*

***V.S. Kulkarni et.al.*** *discussed various natural polymers, their advantages over synthetic polymers and role of natural polymers in designing novel drug delivery systems.*

***I.J Ogaji et.al.*** *discussed the current applications of natural polymeric materials in pharmaceutical formulations. The pharmaceutical applications of some of the traditional and commercially available natural polymers were discussed. Emerging potential pharmaceutical excipients of natural origins were also discussed. The increasing research interests in this group of materials are indications of their increasing importance. It is believed that as technology and testing techniques advance, more understanding of their physicochemical nature would be gained that can enable them to be tailored for wider Pharmaceutical applications than their synthetic counterparts.*

***S. Jain et.al.*** *fabricated sustained release tablets of furosemide using pectin, guar gum and xanthan gum. The tablets were evaluated for physical characteristic like hardness, weight variation, fraibilty, and drug content. In-vitro release of drug was performed in PBS pH 7.2 for fifteen hours. All the physical characters of the fabricated tablet were within acceptable limits. The tablet with guar gum exhibited greater swelling index than those with pectin and xanthan gum. A better controlled drug release (80.74%) was obtained with the matrix tablet (G4) made-up of the guar gum than with the pectin and xanthan gum. It is cleared through the dissolution profile of furosemide from matrix tablets prepared using different natural polymers were retarded approx. 15hrs.*

***N.M. Saraswathi et.al.****attempted attempts to provide comprehensive information on phytopharmacological properties of Terminalia belarica for further research.*

***B. Das et.al****. evaluated the polysaccharides obtained from Terminelia bellerica gum for its safety and potency towards pre formulation studies as pharmaceutical excipients. Their objective was to expound the physicochemical, thermal and functional properties of polysaccharides obtained from Terminelia belarica gum.*

***M.V. Kumudhavalli et. al,*** *enumerates the phytochemical and pharmacological evaluation of Terminalia bellerica. Attempted to isolate and characterized ellagic acid on the basis of IR and GCMS studies.*

***L.A. Refahy et.al,*** *studied the antioxidant activity via reducing power and Dot-blot methods, while cytotoxic activity was evaluated toward human cancer cell line; HepG-2 using Sulphorhodamine-B assay. The 70% methanolic extract was defatted via diethyl ether then undergoes fractionation using (petroleum ether, CH Cl , EtOAc and n-BuOH). The reducing*

*power was 22 expressedas (OD values) which ranged from (0.448 to 2.75 at 200 µg/ml), with respect to the ascorbic acid (2.85). On the other hand, the results of HepG-2 assay showed that 70% methanol extract have cytotoxic activity with IC 20 µg/ml (IC = 19.35 µg/ml) which falls within the National Cancer Institute criteria followed by ethyl 50 50 acetate and n-butanol fraction with IC = 24.5 and 28.6 µg/ml respectively. The high reducing power and 50 cytotoxic activities of n-BuOH fraction encourage us to subject it to chromatographic isolation. A bioassayguided fractionation and chemical investigation of the Terminalia bellerica resulted in the isolation of benzoic acid derivative which identified as 4-hydroxy-(2-methylbutanol) benzoic acid with reducing power activity (1.25).*

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# CHAPTER 3

# AIM AND OBJECTIVE

## 4. INTRODUCTION

*Plants have been used as medicines from the ancient times. Throughout the world medicinal plants are widely and successfully used. A plant with active medicinal constituents is used to treat diseases in the traditional systems like Ayurveda, Siddha and Unani. In Asia, the uses of medicinal plants are well established and are well documented. The plants those are recognized internationally mostly come from this region. Plants, plant parts and plant products those are used for the preparation of medicines serve us to uplift the economical status of the country and they are the natural wealth of a country. Medicinal plants has got significant role in saving the lives of rural area people. In India, 45,000 plant species have been identified and out of which 15-20 thousands plants are found to have good medicinal value. Study says about 6000 traditional plants are used in Indian traditional and herbal medicines.*[1] *Plant derived polysaccharides have evoked tremendous interest due to their diverse pharmaceutical applications such as diluent, binder, disintegrant in tablet formulation, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels and bases in suppository.*[2] *Polymers are considered ideal for formulating immediate and sustained release preparations due to their high stability, safety, non-toxic, hydrophilic and gel gorming nature.*

*Terminalia bellerica also referred to as, Beleric Myrobalan belonging to family Combretaceae is a large deciduous tree with a thick brownish gray bark with shallow longitudinal fissures, attaining a height of between 20 and 30 meters. It is found growing wild troughout the Indian subcontinent, Srilanka, and South East Asia, upto 1200 meters in elevation, in a wide variety of ecologies.*[3] *Terminalia bellerica is used in traditional medicine due to the wide spectrum of pharmacological activities associated with the biologically active chemicals present in this plant. The phytoconstituents isolated from various parts of the plant include alkaloid, coumarin, flavones, steroids (β-Sitosterol), lignans (termilignan, thannilignan), tannins (gallic acid, ellagic acid), glycosides (fructose, sucrose, galactose), terpenoid (belleric acid and chebulagic acid), saponin (bellericoside and bellericanin).*[4] *It is found to be having antimicrobial activity, antioxidant activity, antihypertensive activity and many more. In this study I selected this polymer as a matrix forming additive.*

### 4.1 Materials and methods

#### *4.1.1 Materials*

*Terminalia bellarica gum (TBG) was obtained from forest of Assam,district- cachar. USP I tapper of a USP tap density tester (Electro lab, model ETD-1020), vortex mixer (LablineEquipments, India), Bench centrifuge (Remi, India), Brookfield viscometer (LVDV-E) (Brookfield Engineering Labs, Stoughton- USA), Perkin Elmer 2400 Semis II CHN analyzer, differential scanning calorimeter (JADE DSC, Perkin Elmer, and USA), Siemens D5000 Xraydiffractometer(Siemens, Munich, Germany), IR spectrometer (Bruker Alpha FTIR). All other chemicals and solvents used were of analytical grade***.***

***4.1.2 Methodology***

***4.1.2.1 Extraction, purification and characterization of polysaccharides***

***4.1.2.1.1 Extraction:-***

*Driedgums were collected from the trunk bark of Terminalia bellarica plant and separated from fungal affected parts. The dried gums collected were then transformed into small pieces using hammer. Dried pieces were then dried in a oven dryer at a temperature maintained between 40°C to 50°C for continuous 72hrs. the obtained mass were then followed by grinding in a mill to obtain dry powder. The dried powder was then passed through sieve no #55 and stored in an air tight container. 1kg powder was weighed and extracted with boiling water three times. The aqueous extract was filtered through whatman filter paper. The filtrate was then concentrated in a rotary evaporator under reduced pressure, and then centrifuged at 3000rpm for 15mins. The supernatant was precipitated with three volumes of acetone, and stored overnight at 4°C. The precipitate was collected and washed again three times with acetone to get crude polysaccharide.*[5]

***4.1.2.1.2 Characterization:-***

***4.1.2.1.2.1 Solubility test:-***

*The purified polysaccharide obtained from Terminalia belarica gum (TBG) was evaluated for solubility in water, acetone, chloroform, and ethanol in accordance with the B.P specification.*[6]

***4.2.2.1.2.2 Composition of polysaccharides:-***

*Considering glucose as standard the total sugar content was estimated by the phenol-sulfuric acid analysis. Tests like Molisch tests, Fehling's test and iodine test was performed to determine the total carbohydrate content. Uv- visible spectra and Barfoed test were undergone to determine the protein presence.*[7]

***4.2.2.1.2.3 Loss on Drying***

*500 mg of polysaccharide (TBG) was weighed and placed in a clean and neat china dish. It was kept in hot air oven at 105°C until a constant weight was obtained. The china dish was removed from the oven and again the weight of the polysaccharide powder was determined.The moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage.*[7]

***4.2.2.1.2.4 Total ash and acid insoluble ash***

*2 g of polysaccharide (TBG) was weighed accurately in a previously ignited and tarred silica crucible. The material was then ignited by gradually increasing the heat to 500-600°C until it appeared white indicating absence of carbon. It is then cooled in a dessicator and total ash in mg per gm of air dried material is calculated. To the crucible containing total ash, 25ml of 2M HCl was added and boiled gently for 5 minutes, and then about 5ml of hot water was added and transferred into crucible. The insoluble matter was collected on an ash less filter paper. This was then washed with hot water until filtrate is neutral and the filter paper along with the insoluble matter was transferred into crucible and ignited to constant weight. The residue was then allowed to cool and then weighed.The percentage of acid insoluble ash was calculated from the weight of the sample taken.*[7]

***4.2.2.1.2.5 Determination of pH***

*This was done by shaking a 1 % w/v dispersion of the sample in water for 5 min and the pH determined using adigital pH meter. The data present here is for triplicate determination.*[7]

***4.2.2.1.2.6 Angle of Repose***

*The polysaccharide (TBG) powder (10 g) was accurately weighed and carefully introduced into a funnel clamped to a stand with its tip 10 cm from a plane paper surface. The powder was allowed to flow freely unto the paper surface. The height of the cone, H formed after complete flow and the radius of the cone, R were measured and used to calculate the angle of repose using the following equation:*

$$\textit{Angle of repose } \theta = \tan^{-1}( h/r)$$

*Where θ =Angle of Repose h= Weight of powder heap r=*
*Radius of powder heap*

***4.2.2.1.2.7 Bulk and tapped densities***

*Polysaccharide (TBG) was accurately weighed (10 gm) into a 100 ml measuring cylinder and without disturbing the cylinder the volume of powder was read to give the bulk volume. The measuring cylinder was then clamped to the USP I tapper of a USP tap density*

*tester (Electro lab, model ETD-1020).The volume of the powder was read after every 25 taps up to a total of 275 taps when volume of powder was constant. This represents the tapped volume of the powder. The bulk density and tapped density was calculated using the following equations.*

$$\textbf{Bulk Density} = \frac{\textbf{weight of the sample}}{\textbf{Bulk volume}}$$

$$\textbf{Tapped density} = \frac{\textbf{Weight of the sample}}{\textbf{Tapped volume}}$$

***4.2.2.1.2.8 Compressibility index***

*The compressibility index was calculated as follows*

$$\textbf{Compressibility (C \%)} = \frac{\textbf{Tapped density} - \textbf{Bulk density}}{\textbf{Tapped density}}$$

***4.2.2.1.2.9 Hausner ratio***

*Hausner ratio is a measure of flowability of the TBG polysaccharide and is calculated using the following equation. A low Hausner ratio means that thepolysaccharide powder has a high flowability. Hausner ratio above 1.25 indicates poor flow.*

$$\textbf{Hausner ratio (H)} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}}$$

***4.2.2.1.2.10 Swelling Index***

*This was done by taking 1.0 g quantity of in a 15 ml plastic centrifuge tubes and the volume occupied was noted. Ten milliliters of distilled water was added to it and the content was mixed on a vortex mixer (LablineEquipments, India) for 2 min. The mixture was allowed to stand for 10 min and immediately centrifuged at 1000 rpm on a bench centrifuge (Remi, India). The supernatant was carefully decanted and the volume of sediment was measured.[9]The swelling index was computed using the following equation.*

$$\textbf{S= (V2 - V1) / V1 x 100}$$

*Where S is the % swelling capacity, V2 is the volume of the hydrated or swollen material and V1 is the volume of the material prior to hydration. The experiment was repeated by using 0.1 N HCl and Phosphate buffer 7.4 in water.*

***4.2.2.1.2.11 Viscosity of polysaccharide***

*The viscosity of a 1.0% w/v dispersion of the polysaccharide obtained from Terminaliabelaricagum (TBG) read at shear rates between 0.1 to 10.0 reciprocal seconds*

*and at 23$^{o}$C using a Brookfield viscometer (LVDV-E) (Brookfield Engineering Labs, Stoughton- USA). Spindle 62 was used and 3 minutes was allowed for stabilization of the readings before the viscosity was read.*

***4.2.2.1.2.12 Elemental Analysis***

*Elemental analysis of carbon, hydrogen and nitrogen was carried using a Perkin Elmer 2400 Semis II CHN analyzer. Accurately weighed 0.5 mg of sample was heated to 1150 °C and the corresponding element was determined by using thermal conductivity detector.* [10]

***4.2.2.1.2.13 Scanning Electron Microscopy***

*The dried sample of polysaccharide obtained fromTerminaliabelaricagum (TBG) was mounted on a metal stub and sputtered with gold in order to make the sample conductive, and the images were taken voltage of 15 KV at 100 x and500x magnifications respectively.*

***4.2.2.1.2.14 Differential scanning calorimetry***

*A differential scanning calorimeter (JADE DSC, Perkin Elmer, and USA) was used to study the thermal properties of the polysaccharide obtained from Terminaliabelarica gum (TBG). The polysaccharide was scanned in the temperature range of 50-2200C under an atmosphere of nitrogen. The heating rate was 200C/min, followed by a cooling cycle back to 300C at the same rate.*

***4.2.2.1.2.15 X-ray powder diffraction***

*X-ray diffraction (XRD) patterns of the polysaccharide obtained from Terminalia bellarica gum (TBG) were analyzed using a Siemens D5000 Xray diffractometer(Siemens, Munich, Germany). Powder sample, packed in rectangular aluminium cells, illuminated using CuKα radiation (λ = 1.54056 Å) at 45 kV and 40 mA. Samples were scanned between diffraction angles of 5° to 40°C 2θ. Scan steps of 0.1 were used and the dwell time was 15.0 Sec. A nickel filter was used to reduce the Kβ contribution to the X-ray signal. The'd' spacing was computed according to Bragg's law of diffraction.*

***4.2.2.1.2.16 Fourier transform-infra red***

*The Fourier transform-infra red (FT-IR) spectrum of the sample was recorded in an IR spectrometer (Bruker Alpha FTIR). Triplicate measurements were made, and the spectrum with the clearest identifiable peaks was chosen.*

**4.2 Result and discussion:-**

*Polysaccharides from Terminelia bellerica gum were purified using water and precipitated with acetone. The percentage yield of the polysaccharide obtained from the TBG was found to be 8.5%.*

***4.3.1 Characterization of selected polysaccharide:-***

*The purity of polysaccharide was determined by undergoing phytochemical tests such as test for alkaloids, steroids, flavonoids, saponins, tannins and phenols whose outcome found to be absent. The purity was confirmed as only carbohydrate was found to be present. Then the polysaccharide was characterized by various organoleptic properties such as colour, odour, taste, touch and texture.*

| *Parameter* | *Terminelia bellarica Gum* |
|---|---|
| *Colour* | *Brown* |
| *Odour* | *Odourless* |
| *Taste* | *Tasteless* |
| *Shape* | *Irregular & Fibrous* |
| *Touch & texture* | *Hard & rough* |

***Table 4.1:- Organoleptic properties of powdered polysaccharide***

*Swelling index of the TBG was found to be which reveals high swelling index as the swelling index results high. The ability of swelling of any polysaccharide is based on its water retention capacity.*

*The pH of the 1%w/v TBG was found to be 7. The melting point of TBG was found to be 195◦C. Moisture content of TBG was found to be 3.10% which results good stability for pharmaceutical dosage forms.*

*The solubility behavior of the TBG polysaccharide was carried out which shows that the polysaccharide is soluble in warm water, sparingly soluble in cold water, whereas insoluble in etanol,methanol, acetone, chloroform & ether.*

*The ash values are measured as high values of ash indicates low level of purity and adulteration of sand and other earthy matter such as carbonates. Here the total ash values for TBG polysaccharide was found to be 3.6 and the acid insoluble ash value was found to be 0.10±0.04 which indicates high level of purity as the values were found to be very low.*

*The microbial test for the TBG polysaccharide was performed and the count was found to be within limit thus microbial contamination is not a risk factor for the product degradation.*

*The properties such as bulk density, tapped density, compressibility index, hausner's ratio, kawatika analysis snd angle of repose are refered to as properties of the powder to adhere together for better compressibility in a pharmaceutical formulation. Compressibility index (I) values up to 15%usually result in good to excellent flow properties and value above 25% are often sources of poor tableting qualities. The bulk density, tapped density, compressibility index and hausner's ratio of TBG were found to be 0.56g/cc, 0.72g/cc, 22% and 1.28 respectively. The values are found to be within limit and are believed to serve for good flow properties and compressibility. The angle of repose was found to be 28 which indicates good floe properties.*

| ***Parameters*** | ***Results*** |
|---|---|
| *Swelling index (%v/v) water*<br>*0.1N HCL*<br>*Phosphate buffer 6.8* | *205±0.04*<br>*245±0.02*<br>*315±0.03* |
| *Loss on drying (%w/w)* | *3.10* |
| *Total ash (%w/w)* | *3.6* |
| *Acid insoluble ash (%w/w)* | *0.10±0.04* |
| *pH* | *7* |
| *Angle of repose ( Degree)* | *28* |
| *Bulk density (g/cc)* | *0.56* |
| *Tapped density (g/cc)* | *0.72* |
| *Compressibility index (%)* | *22* |
| *Hausner ratio* | *1.28* |

***Table 4.2: Results for flow properties of powdered polysaccharides***

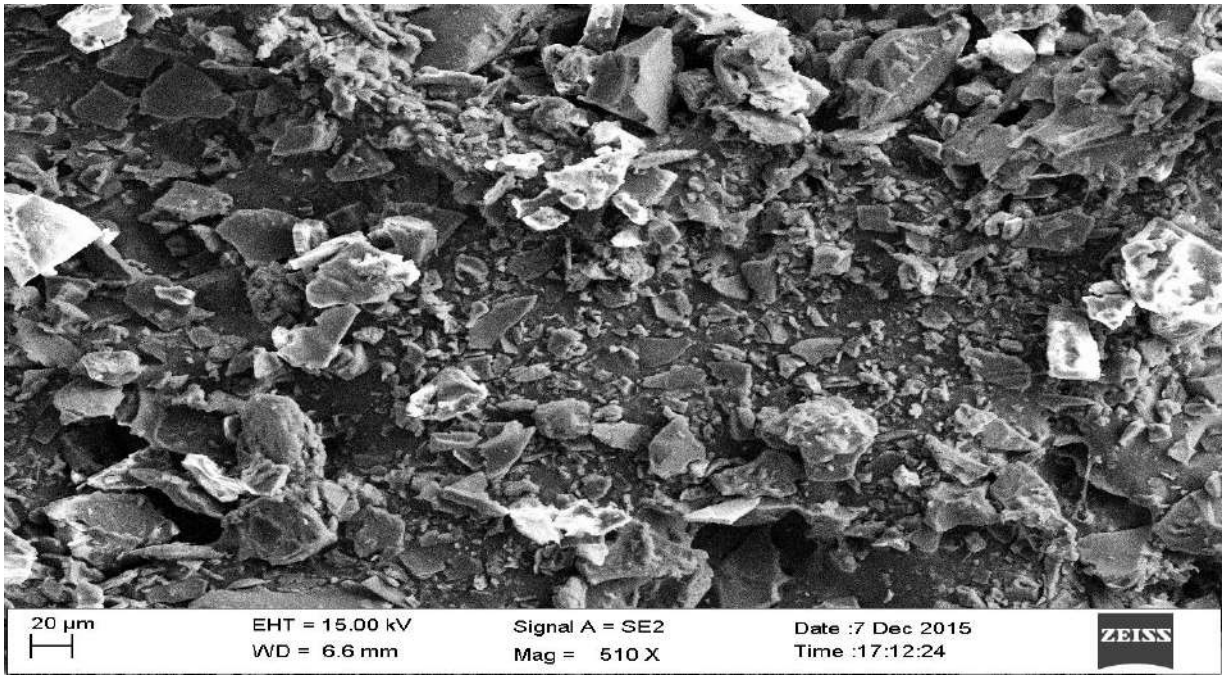


***Figure4.1:- SEM for Terminelia bellarica gum magnification 510x***

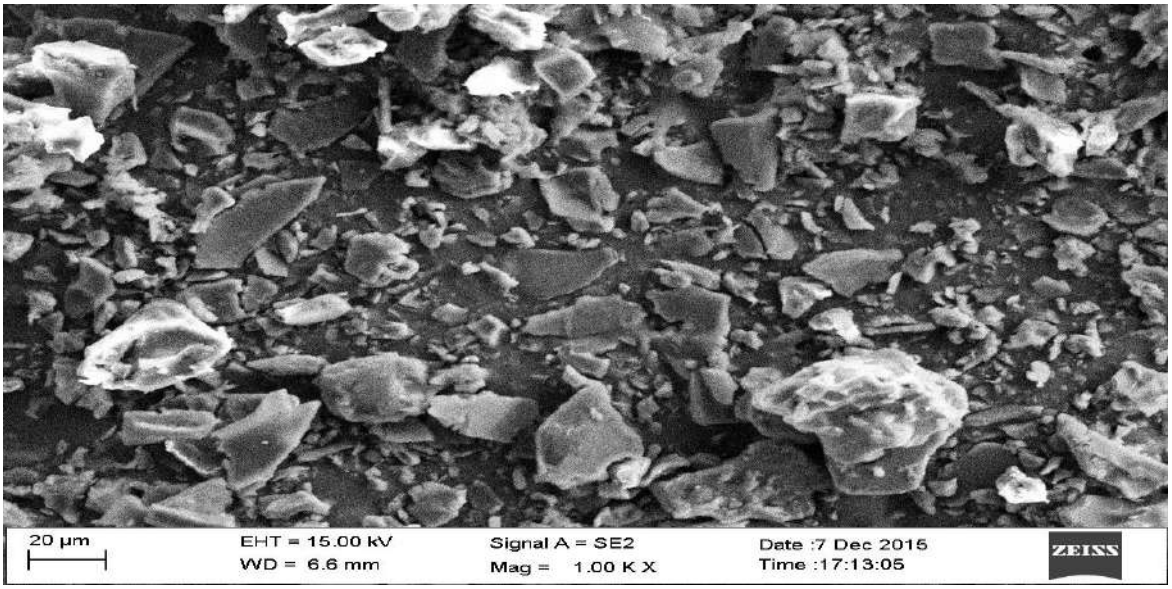


***Figure 4.2 :- SEM for Terminelia bellarica gum magnification 1.00KX***

*The SEM photographs of TBG have revealed that the polysaccharides are irregular and fibrous in shape.*

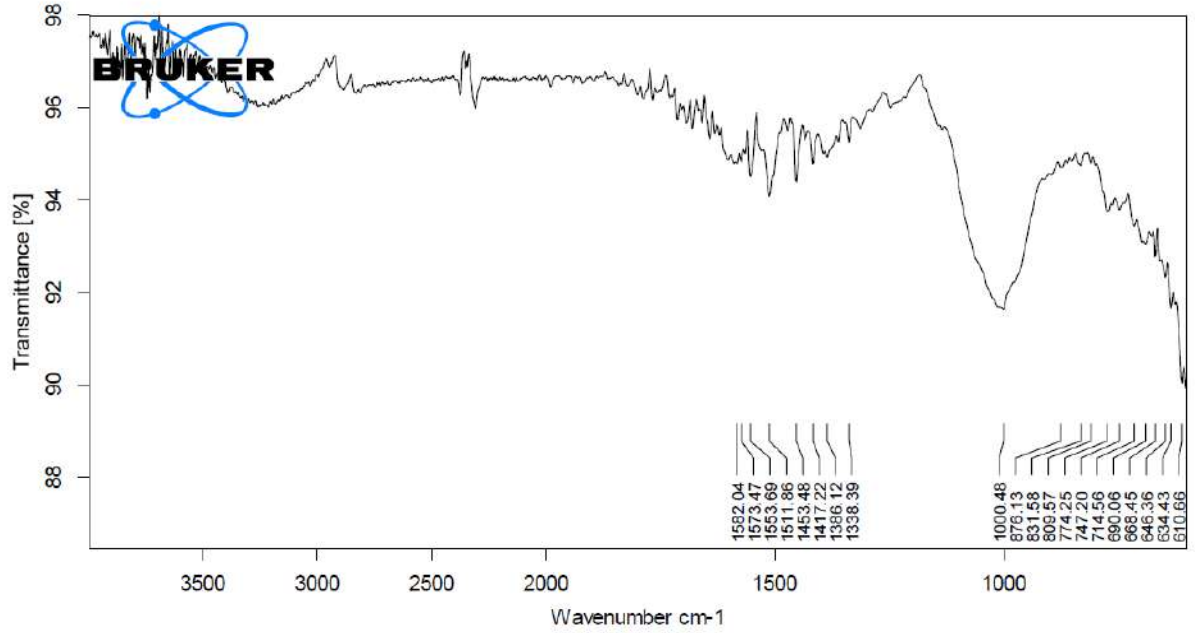


***Figure 4.3: FT-IR spectroscopy for Terminelia bellarica gum.***

*FTIR spectroscopy is a useful tool in identification as well as purity of a compound. The principal absorption peaks of tamarind seed polysaccharide were found to be 1553.69$^{-1}$cm, 1511.86$^{-1}$cm, 1453.48$^{-1}$cm and 1000.48$^{-1}$cm,*

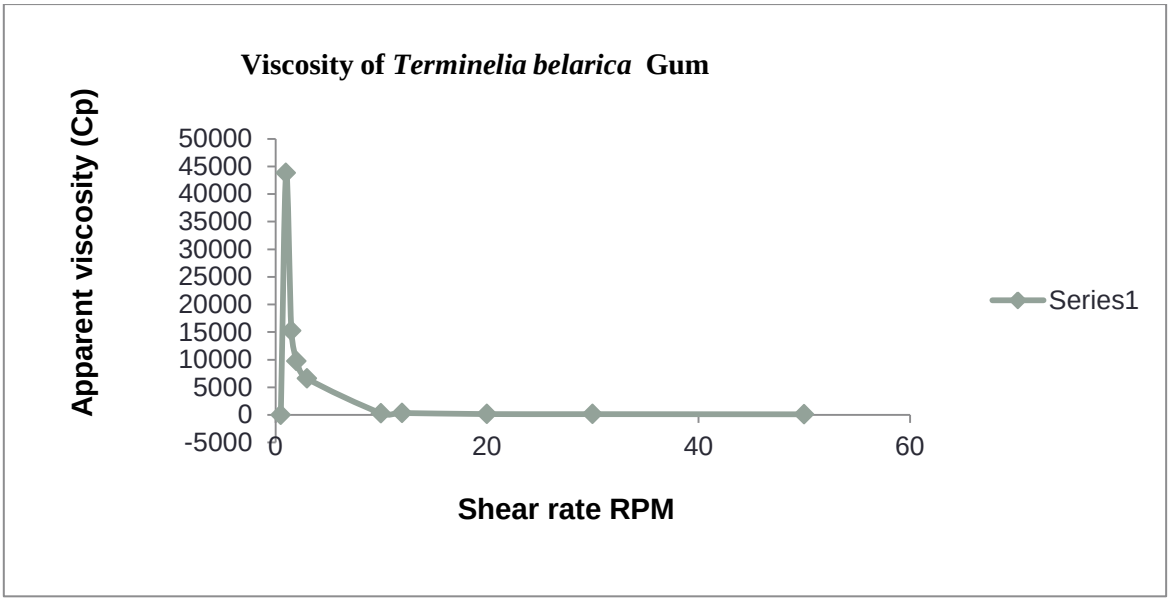


***Figure4.4 :- viscosity curve of Terminelia bellarica gum***

*Differential Scanning Calorimetry (DSC) measures the heat loss or gain, resulting from physical or chemical changes within a sample as a function of temperature. A sharp*

*symmetric melting endotherm can indicate relative purity, whereas broad asymmetric curve suggests impurities or more than one thermal process. The endothermic peak usually indicates the loss of water present in the compound.*[11]

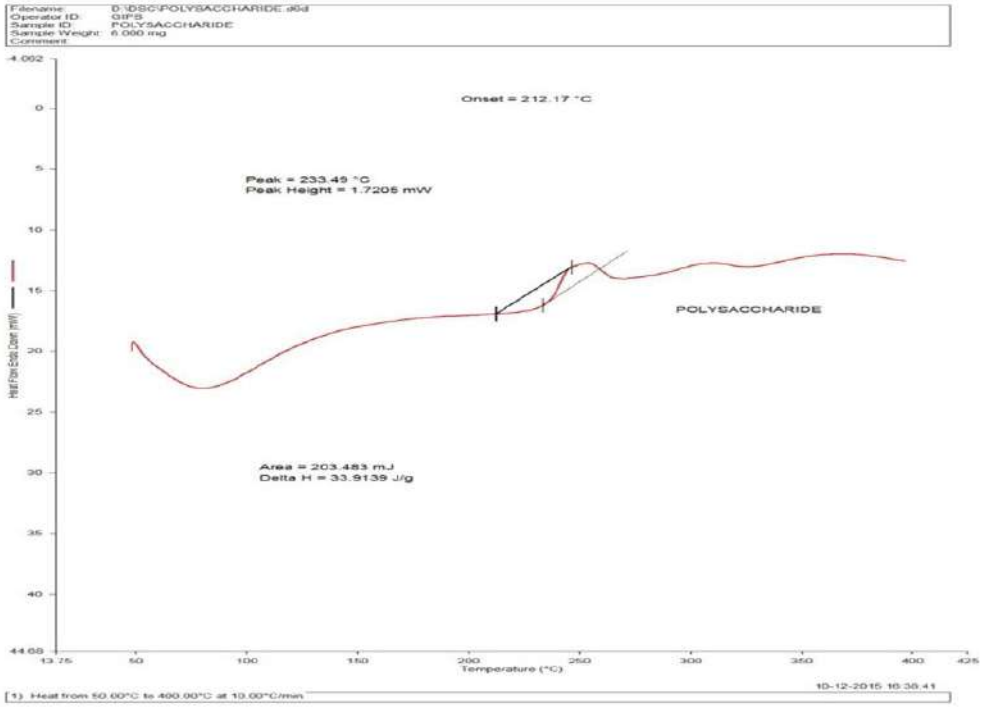


***Figure.4.5 :- DSC for Terminelia Bellarica gum***

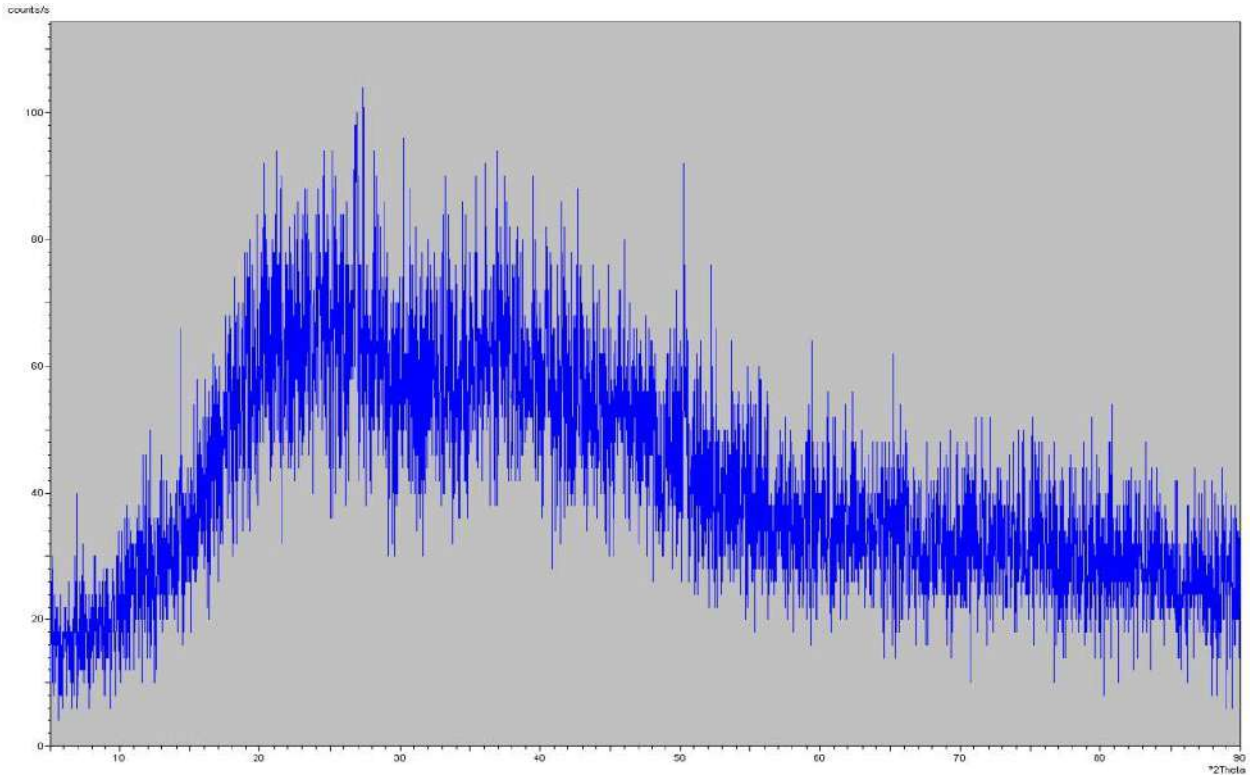


***Figure 4.6:- X-RAY Diffraction Spectroscopy of Terminalia bellarica gum.***

## *4.4 Definition of acute toxicity*

*Acute toxicity refers to those adverse effects occurring following oral or dermal administration of a single dose of a substance, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours.*

### *4.4.1 Need of acute toxicity study:-*

*Traditional use of herbal drugs may broadly be divided into three categories as follows:-*

- *Those are well known and have been widely used for many years.*
- *Those are not well known in the country but for which international experience is available.*
- *That represents a new compound hitherto not evaluated as to its safety and efficacy.*

*The first category mainly consists of foodstuff product (s), which has been in use for a long time as traditional herbal remedies, and the requirements are limited. In general, it these foodstuff products are generally safe for human and animal consumption and establishment of safety of these products is not so important. For the second category, views concerning the type of documents required to be presented may differ from country to country. So it is necessary that varieties of requirements will be elaborated for these products covering anything from reference in scientific literature confirming that the product is safe. To satisfy the demands for limited or shortened toxicological testing of these products, an investigation must be carried out on toxicity profile. The third group, where the authority is faced with a product not previously screened for its toxicological properties, toxicity studies of those product must have to be undertaken.*

*Terminalia bellerica has been used for centuries in the Indian traditional system of medicine.The dried fruit and other parts are being in use for medicinal purposessince decades.As discussed previously in this chapter section* ***4.4.1****., the need of the acute toxicity study. According to the traditional use of herbal drug classification the acute toxicity study of the Terminelia bellarica is not that important as this plant is already being used in tradition. In some of the research it has been already established that Terminalia bellerica polysaccharide obtained from gum have no acute toxicity effect. Some of the references are cited below in support of evidence.*

## *4.5 CONCLUSION:-*

*The research work was carried out successfully. The polysaccharides were isolated, extracted & characterized. The characterization was carried out for different physiochemical properties & powder properties. Other properties like pH, solubility, flow property, bulk density etc were found to be in the desired range. Analytical tests like X-Ray diffraction spectroscopy, Differential scanning calorimetry, Fourier Transform Infrared Radiation, Scanning electron microscopy were carried out and the results showed good property of the polysaccharide which can be further used as pharmaceutical excipients.*

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# CHAPTER 4

# EXTRACTION, PURIFICATION AND CHARACTERIZATION OF NATURAL GUM

## *5.1 INTRODUCTION*

*Matrix system is the most innumerable method used in the development of Sustained release formulations. It is the release system, which prolongs and control release of drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent. i.e. hydrophilic polymers.[1] Matrix systems are widely used in oral controlled drug delivery because of their flexibility (which results in obtaining desirable drug release profile), cost effectiveness and broad regulatory acceptance.[2]*

*Diclofenac Sodium is sodium 2-[(2, 6dichlorophenyl)-amino] phenyl acetate and is an acetic acid nonsteroidalantiinflammatory drug (NSAID) with analgesic and antipyretic properties. It is used to treat, dysmenorrhea, ocular inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and actinic keratosis[2].*

*The present investigation is aimed to formulate the sustained release matrix tablet of Diclofenac sodium with different concentration of Termineliabellaricagum polymer with other excipients.*

## *5.2MATERIALS AND METHODOLOGY*

### *5.2.1 Materials*

#### *5.2.1.1 Chemicals and reagents*

| **Sl no.** | **Materials** | **Manufacturer/ Supplier** |
|---|---|---|
| **1** | Diclofenac Sodium | Alkem laboratories, Baddi |
| **2** | HPMC- K-100 | Haylon |
| **3** | Microcrystalline cellulose | Merck specialist pvt ltd, Mumbai-18 |
| **4** | PVP-K-30 | Merck specialist pvt ltd, Mumbai-18 |
| **5** | Magnesium stearate | Balaji drugs, Mumbai- 37 |
| **6** | Talc | Himedia, Mumbai, India |
| **7** | Potassiumdihydrogenphosphate | Merck specialist pvt ltd, Mumbai-18 |
| **8** | Iso propyl alcohol | Balaji drugs, Mumbai- 37 |

#### *5.2.1.2 List of instruments*

| **Sl. no** | **Instrument** | **Company name** |
|---|---|---|
| 1 | Digital weighing balance | Denver Instrument, USA |

| | | |
|---|---|---|
| 2 | UV- Visible spectrophotometer | Shimaju, Model: UV 1800 240V |
| 3 | FT-IR | Alpha Bruker (Model no:10059736), Germany |
| 4 | Melting point apparatus | Macroscientific works 10A/UA, Jawahar Nagar, Delhi-11007 |
| 5 | Hot air oven | International commercial Traders, 18, Kolkata-700001 |
| 7 | Thermostate Water Bath | Jain Surgical Glass Warer (JSGW) |
| 8 | Rotary evaporator | BuchiRotaevapor R-3 |
| 9 | Tablet compression machine | Shakti Ahmedabad, India Eco Press, Parle Elizabeth tools Pvt ltd, India. |
| 10 | Hardness tester | Rolex Tablet hardness tester |
| 11 | Friability tester | Roche friabilitor |
| 12 | Dissolution test apparatus | DS8000, Lab India. |

### *5.2.2 METHODOLOGY*

#### *5.2.2.1 Physico- chemical properties of the drugs:-*

##### *5.2.2.1.1 Solubility determination:-*

*A minute quantity of the drug sample was taken in a test tube and solubility was determined by dissolving the drug in 1ml of various solvent like water, ethanol, methanol, 6.8 phosphate buffer etc.*[3]

##### *5.2.2.1.2 Melting point determination:-*

*Small quantity of the drug was taken in a capillary tube(fused at one end) and placed in a melting point apparatus and the temperature was noted at which the drug gets melted.*[4]

##### *5.2.2.1.3Estimation of diclofenac sodium in analytical sample:*[5]

##### *5.2.2.1.3.1Determination of absorption maxima($\lambda_{max}$) of diclofenac sodium in phosphate buffer ph 6.8:*

*100mg of drug was weighed and dissolved in 100ml of water in volumetric flask (stock solution). 10ml was taken from it and transferred in another 100ml of volumetric flask and diluted upto 100ml (standard working solution). The spectra of the solution was run in 200 to 400nm UV- visible spectrophotometer.*

***5.2.2.1.3.2 Preparation of standard curve of diclofenac sodium in phosphate buffer pH 6.8***

*100mg of drug was weighed and dissolved in 100ml of phosphate buffer in volumetric flask (stock solution). 10ml was taken from it and transferred in another 100ml of volumetric flask and diluted upto 100ml (standard working solution). From the above working solution 2ml, 4ml, 6ml, 8ml and 10ml was withdrawn and diluted upto 10ml in 10ml volumetric flask to get the concentration of 20µg, 40µg, 60µg, 80µg and 100µg respectively. The absorbance was determined for each solution using phosphate buffer as blank at 273nm in UV-visible spectrophotometer.*

***5.2.2.2 DRUG- EXCIPIENTS COMPATIBILITY STUDY:-***

***5.2.2.2.1 FT-IR Spectroscopy study:[6]***

*IR spectra of pure drug was obtained by directly placing the sample under the pressure head of the instrument. Infra-red spectra were recorded using FTIR (Bruker; ALPHA; Model No10059736) spectrometer and spectrums were recorded in region of 4500 to 500 cm-1.*

***5.2.2.2.2Differential scanning calorimetrystudy[9]:-***

*It is used to analyse thermal stress on drug and there mixture. Individual sample and 1:1 w/w physical mixture of drug were weighed and almost 5mg were taken in the DSC pan and scanned in the temperature range of 50 to 300°c in nitrogen environment. A heating rate of 10°c per minute was used, and the thermograms were reviewed for evidence of any interaction.TheElutes collected were concentrated under reduced pressure to an appropriate volume, and then dialyzed against distilled water. The remaining portion was lyophilized to afford total purified polysaccharide.*

***5.2.2.3 Preparation of Matrix tablet:***

*Diclofenac sodium tablets were prepared by wet granulation technique. Sustained release (SR) matrix tablets of Diclofenac sodium were prepared by using drug Diclofenacsodium , HPMC-K-100, lactose, PVP-K-30, microcrystalline cellulose and Termineliabellaricagum. Termineliabellaricagum were used as matrix forming polymer, while microcrystalline cellulose was used as filler to maintain the tablet weight. All ingredients were passed through a sieve #20, weighed and blended. The granules ( which are*

*obtained after wet granulation ) were compressed by a direct compression technique, using Kbr(IR press), with the help of 8mmflat faced punches.*

| **Ingredients** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
|---|---|---|---|---|---|---|---|---|---|
| **Diclofenac Sodium** | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| **Polymer** | 12.5 | 25 | 37.5 | 50 | 62.5 | 75 | 87.5 | 100 | 112.5 |
| **HPMC K100** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Lactose** | 127.5 | 55 | 50 | _ | 67.5 | 55 | _ | _ | 17.5 |
| **MCC** | _ | 50 | 42.5 | 70 | _ | 35 | 42.5 | 30 | _ |
| **PVP K 30** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Mg stearate** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Talc** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Total** | **250** | **250** | **250** | **250** | **250** | **250** | **250** | **250** | **250** |

***Table 5.1: Formulation of matrix tablets:-***

***5.2.2.4 EVALUATION OF TABLETS:***

***5.2.2.4.1Pre compression parameters[7]***

***5.2.2.4.1.1 Angle of repose:*** *Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is determined by using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone heighty (h) was obtained. The radius of the heap (r) was measured as angle of repose (θ) was calculated using the formula:*

$$\theta = \tan^{-1}(h/r)$$

***5.2.2.4.1.2 Bulk density:*** *Apparent bulk density (pb) was determined by pouring the blend in to a graduated cylinder. The bulk volume (vb) and weight of the powder (M) was calculated using the formula:*

$$Pb = M/Vb$$

***5.2.2.4.1.3 Tapped density:*** *The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (Pt) was calculated by using formula:*

$$Pt=M/Vt$$

***5.2.2.4.1.4 Compressibility index:*** *The simplest way for measuring of free flow of powder was compressibility, an indication of the ease with which a material can be induced to flow was given by compressibility index (I).*

$$I= (Vo-Vt/Vo) \times 100$$

*Where, Vo is the bulk volume and Vt is tapped volume.*

***5.2.2.4.1.5 Hausner's ratio:*** *Hausner's ratio was an indirect index of ease of powder flow. It was calculated by:*

$$Hausner\ ratio=Pt/Pd$$

*Where, Pt is tapped density and Pd is bulk density. Lower hausner'sratio(<1.25) indicates better flow properties than higher ones (> 1.25).*

***5.2.2.4.2 Post compression parameters***

***5.2.2.4.2.1 Weight variation[7]:***

*Twenty tablets were selected random and weighed individually. The individual weights were compared with average weight for determination of weight variation.*

***5.2.2.4.2.2 Friability[7]:***

*Twenty tablets from each batch were selected randomly and weighed. These preweighted tablets were subjected to friability testing using Roche friabilator for 100 revolutions. The tablets in the fibrilator undergo both abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability.*

$$F= (1-W0 - W)\ 100$$

*Where, W0 is weight of the tablets before and W is weight of the tablets after test.*

***5.2.2.4.2.3 Hardness[7]:***

*Five tablets from each batch were selected and hardness was measured using Monesanto hardness tester to find the average tablet hardness or crushing strength.*

***5.2.2.4.2.4 Content uniformity[7]:***

*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 60 min and filtered. 1mL of the filtrate was diluted to 100 mL with pH 6.8 phosphate buffer. Absorbance of this solution was measured at 273 nm using pH 6.8 phosphate buffer as blank and content of Diclofenac sodium was estimated.*

***5.2.2.4.2.5 In vitro drug release/Dissolution studies[7]:***

*The tablet samples were subjected to in-vitro dissolution studies using USP Type 2 dissolution apparatus at 37±2°C and 50 rpm speed. As per the official recommendation of USFDA, 900 ml of pH 6.8 Phosphate buffer was used as dissolution medium. Aliquot equal to 5 ml was withdrawn at specific time intervals 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 273 nm (Table 4) by comparing with the standard calibration curve*

***5.2.2.4.2.6 Drug release kinetics:[10]***

- **Zero-Order Kinetics:**

*Zero order as cumulative amount of Percentage drug released vs time*

***C = K0t***

*Where KQ is the zero-order rate constant expressed in units of concentration/time and t is the time in hours.*

- **First order kinetics:**

*First order as log cumulative percentage of log (%) cumulative drug remaining vs time*

***,LogC = LogC0-kt/ 2.303***

*Where Co is the initial concentration of drug, k is the first order constant, and t is the time.*

- **Higuchi Model:** Higuchi's model as cumulative percentage of drug released vs square root of time

***Q = Kt1/2***

*Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time*

- **KorsmayerPeppas equations:** Korsmeyerpeppas equation used to determine the mechanism of drug release form the polymer matrix of the tablet Log cumulative

percentage of drug. releasedVs Log time, and the exponent n was calculated through the slope of the straight line.

$$Mt/M_o = Ktn$$

***5.2.2.4.2.7 Selection of optimized formulation:[8]***

*The concentration of natural polymer in matrix tablet was optimized by study the properties of tablet and in vitro release profile. The effect of polymer concentration on release properties of matrix tablet was determined using different drug: polymer ratio. All the tablet parameter was evaluated for each formulation and mathematical kinetics model for release profile was compared. The formulation which provide best release pattern with better tablet parameter selected as optimized tablet.*

***5.2.2.4.2.8 Release profile of marketed tablet Voveran SR:[8]***

*In vitro release study of marketed tablet Voveran SR was carried out using mathematical kinetics model.*

***5.2.2.4.2.9 Comparison of optimized formulation with marketed tablet Vovren SR:[8]***

*The optimized formulation which provides best release profile along with all tablet parameter within standard limit was compared with marketed tablet Voveran SR 100 mg. The comparison is made whether the optimized formulation was provide better release profile or equivalent or less effective release pattern than marketed tablet Voveran SR 100.*

***5.3 RESULTS:***

***5.3.1 Organoleptic properties of Diclofenac sodium***

1. Nature — Amorphous solid powder
2. Colour — White powder
3. Odour — Odourless
4. Taste — Tasteless
5. Solubility-
    - In water — Freely soluble
    - In methanol — Soluble
    - In ethanol — Soluble
    - In phosphate buffer pH 6.8 — Freely soluble

**5.3.2 Melting point Determination:**

*The melting point of the drug was found to be 153°C which conforms the melting point as reported in official pharmacopoeia(B.P) which reveals that drug sample is retaining the desired property of purity.*

### 5.3.3 Compatibility studies of Drug and polysaccharide TBG by FT-IR Spectroscopy:

*FT-IR Spectroscopy studies of DS, DS with TBG polysaccharide and only TBG polysaccharide was carried out separately to find out the compatibility of the DS with polymer (TBG). The FT-IR spectra of pure DS showed characterisctics peak at for the presence of respectively which are also present in the combination of DS and polmer(TBG) indicating the compatibility of DS with TBG polymer.*

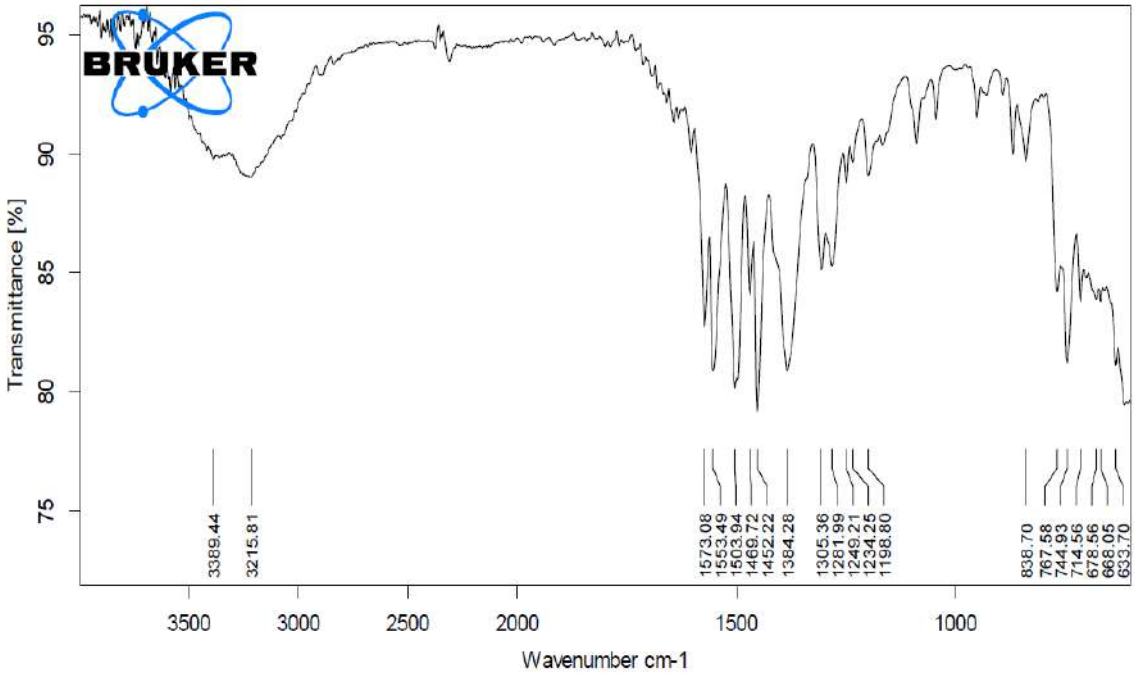


***Figure5.1 : FT-IR of drug Diclofenac sodium***

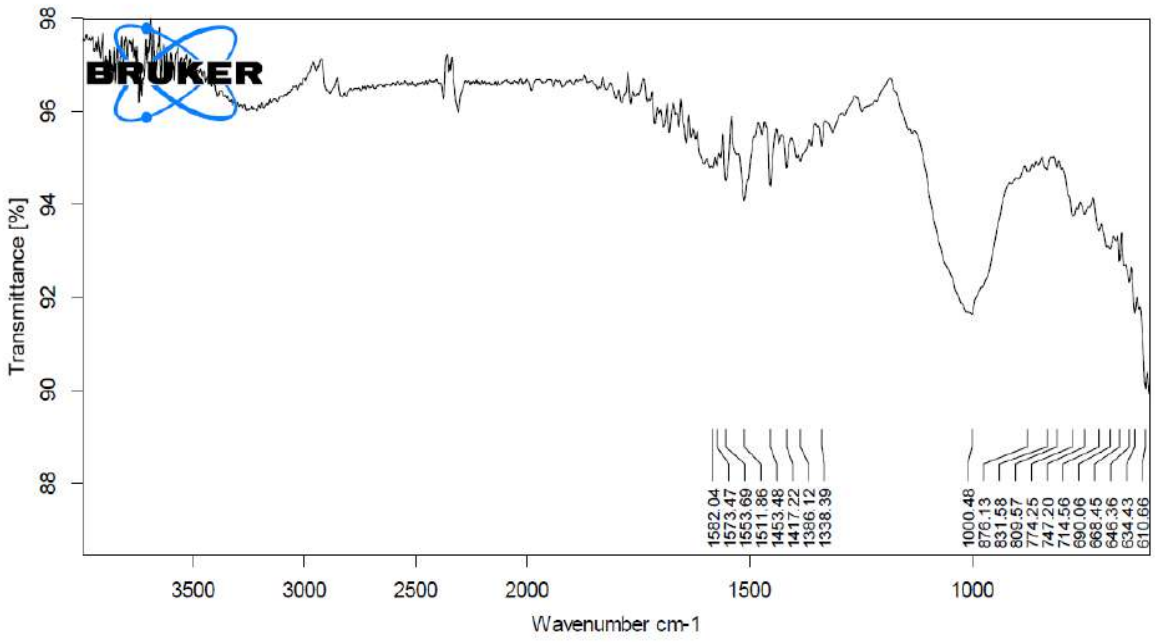


***Figure 5.2: FT-IR of polysaccharide (TBG)***

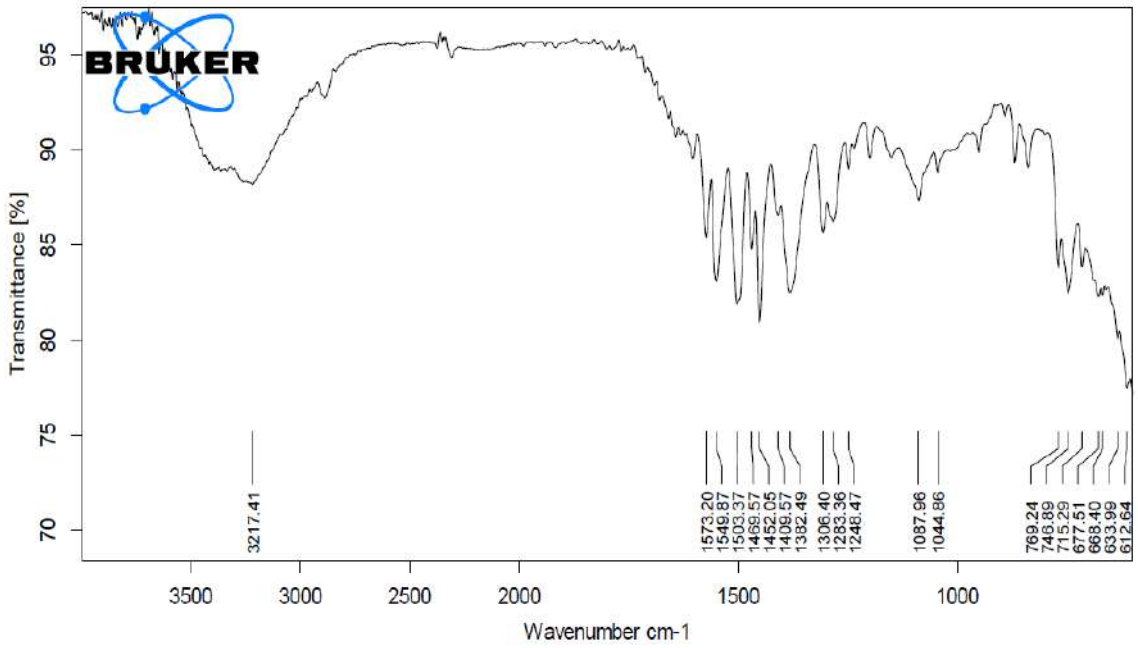


***Figure 5.3: FT-IR of drug( DS) with polysaccharide( TBG)***

### 5.3.4 Differential scanning calorimetry studies:

*Differential Scanning Calorimetry (DSC) measures the heat loss or gain, resulting from physical or chemical changes within a sample as a function of temperature. A sharp symmetric melting endotherm can indicate relative purity, whereas broad asymmetric curve*

*suggests impurities or more than one thermal process. The endothermic peak usually indicates the loss of water present in the compound.*[11]

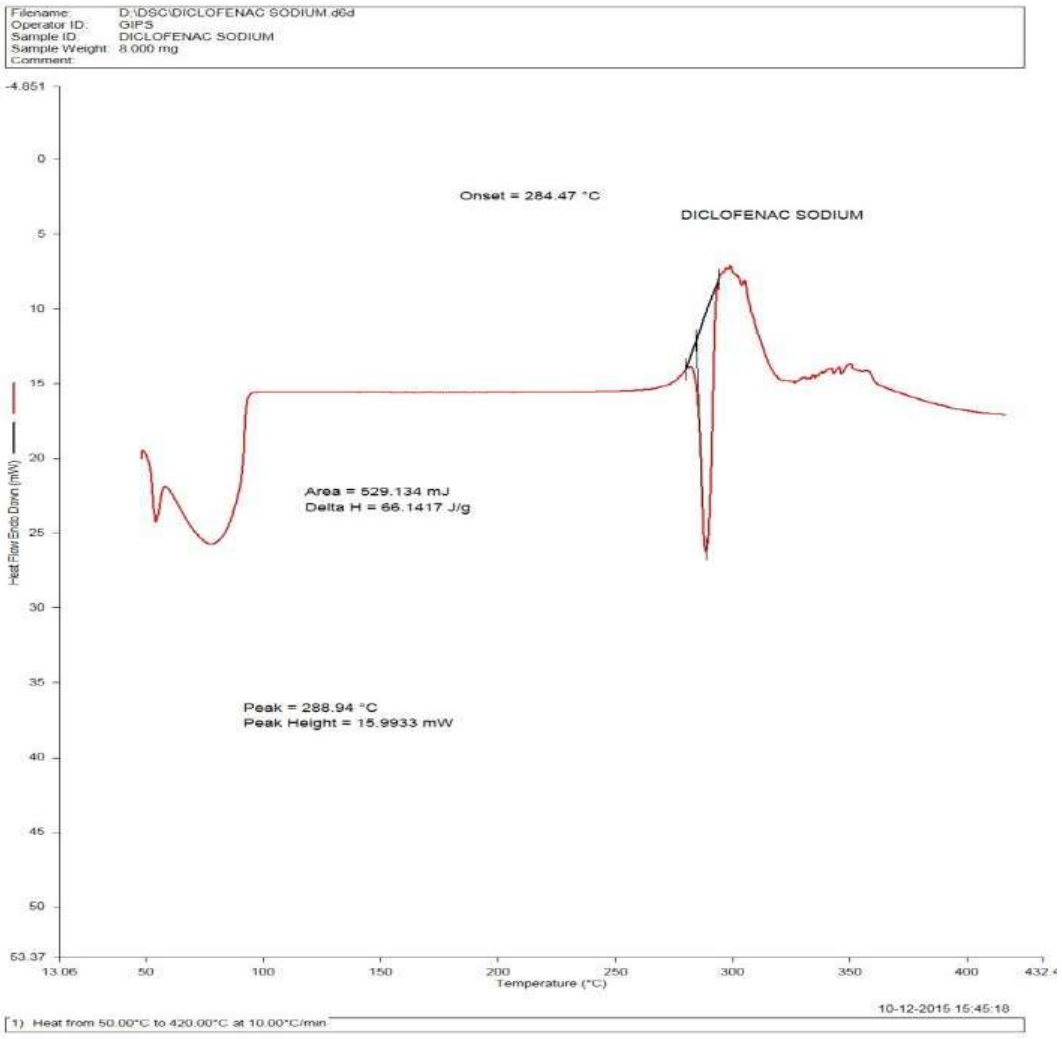


***Figure 5.4: DSC for Diclofenac sodium***

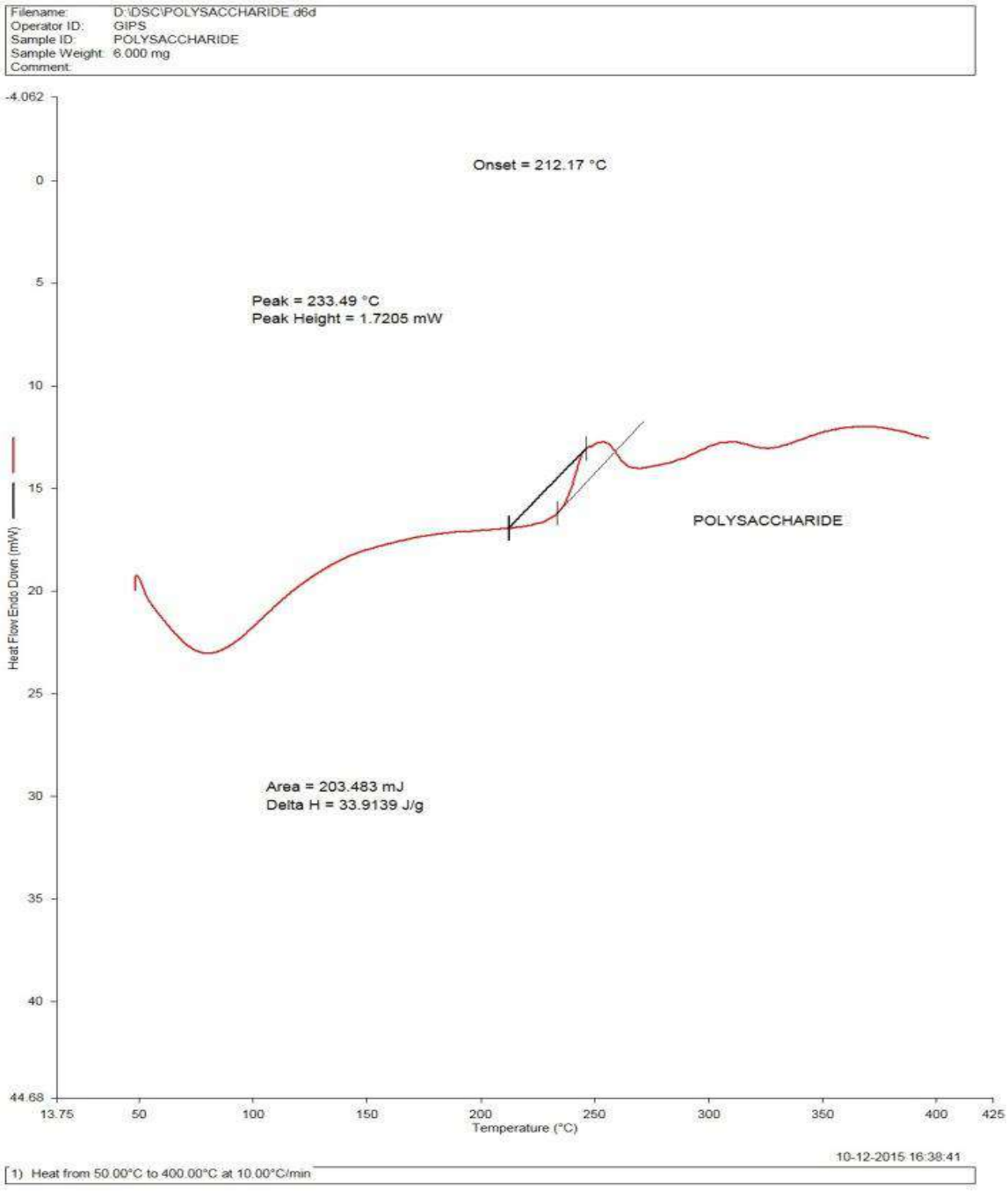


***Figure5.5: DSC for polysaccharide(TBG)***

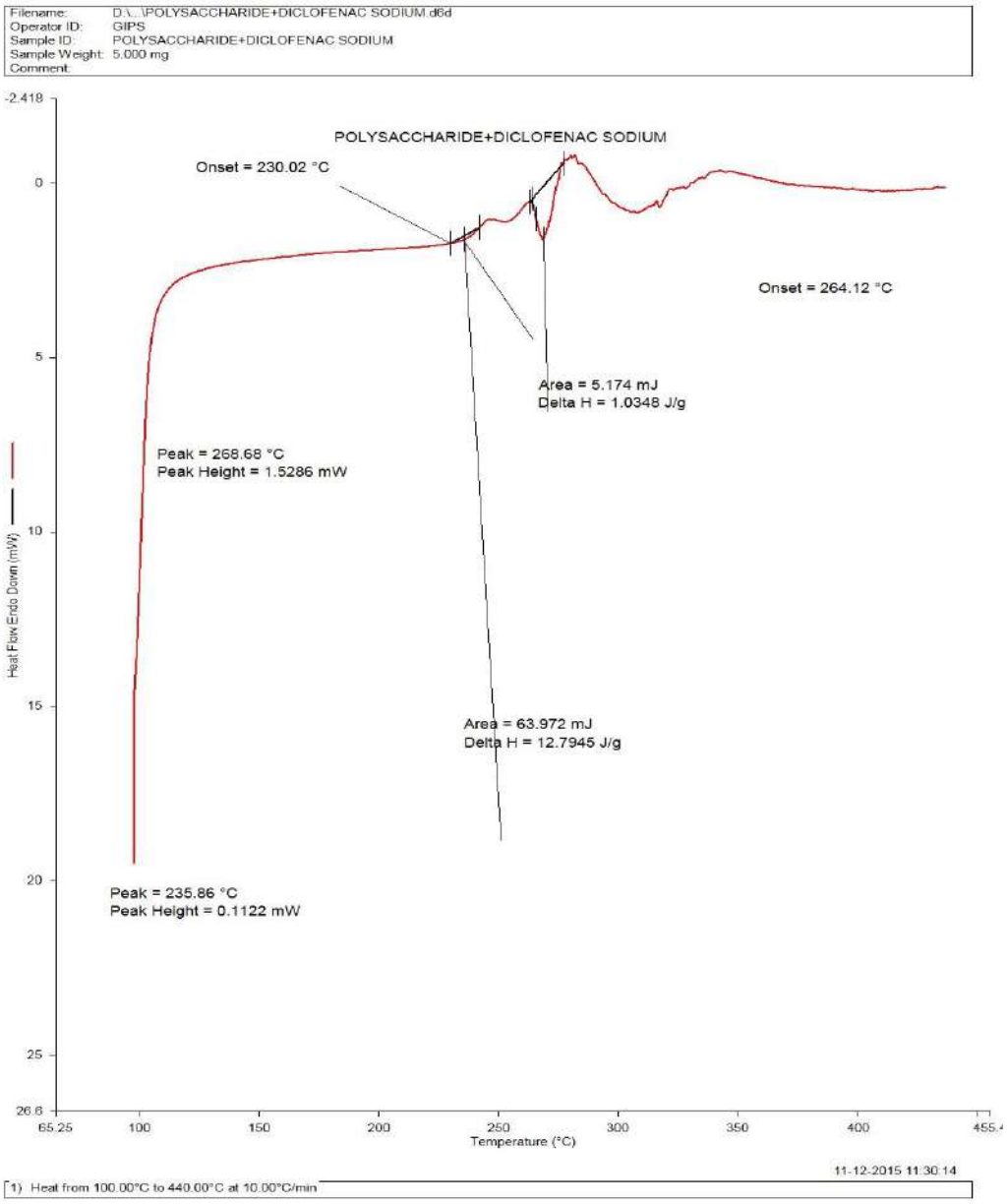


***Figure5.6 : DSC for Diclofenac sodium in combination with polysaccharide(TBG)***

*DSC result showed that the onset for drug Diclofenac was found to be 284.47 and for the Polysaccharide it was found to be 233.49. After mixing both the Diclofenac sodium and Polysaccharide the onset got shifted to 264.47 and 230.02. Thus it did not show very difference so its within the acceptable limit.*

### 5.3.5 Estimation of Diclofenac sodium in analytical sample:

*After scaning the appropriate aqueous dilute solution of Diclofenac sodium in the range of 200-400nm the $\lambda_{max}$ was found to be 273nm.*

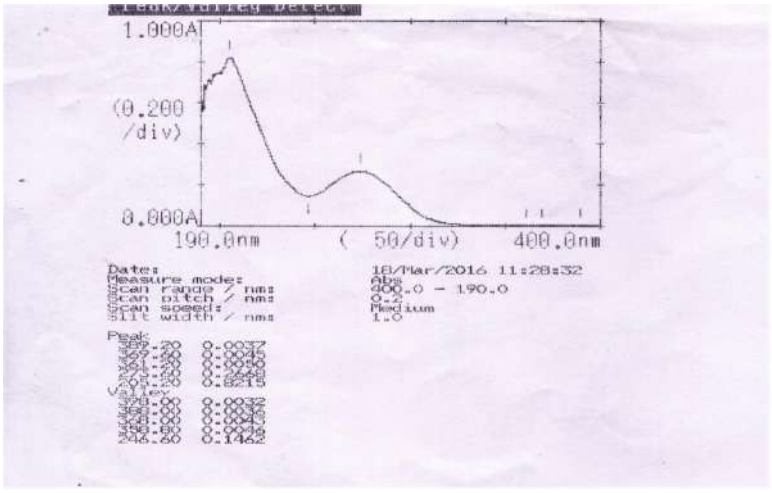


***Figure 5.7: Maximum absorption curve of Diclofenac Sodium***

*The UV spectra and calliberation curve of DS in the above mentioned solvent system were presented in figure.The data of the calliberation curve was presented in Table. The linearity of the curve was found between concentration ranges of 2-14µg/ml with regression equation of y= 0.0256-0.0086 and* $R^2$ *= 0.9945.*

| SL no. | Concentration(µg/ml) | Absorbance |
|---|---|---|
| 1 | *0* | 0 |
| 2 | *2* | 0.0368 |
| 3 | *4* | 0.0921 |
| 4 | *6* | 0.1416 |
| 5 | *8* | 0.1901 |
| 6 | *10* | 0.2571 |

***Table5.2 : Data for calibration curve of DS in phosphate buffer 6.8 at*** $\lambda_{max}$ ***273nm***

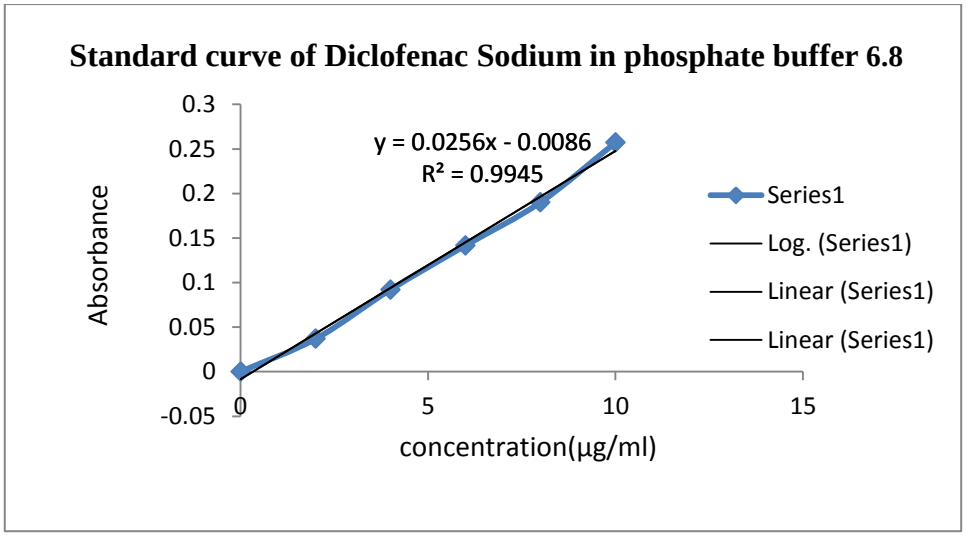


***Fig 5.8: Calibration curve of Diclofenac Sodium in phosphate buffer 6.8***

### *5.3.6 Evaluation of tablet:*

#### *5.3.6.1 Precompression parameters of granules:*

*Before preparing the batches of tablets several precompression parameters were evaluated for the granules used in formulation of tablets. Some of the precompression parameters evaluated were Angle of repose, Bulk density, Tapped density, Hausner ratio and Carr's index. The datas are tabulated below:-*

| Formulation code | Angle of repose ($\theta^0$) | Bulk density ($g/cm^3$) | Tapped density ($g/cm^3$) | Hausner ratio | Carr's index (%) |
|---|---|---|---|---|---|
| F-1 | 23.50 | 0.475 | 0.533 | 1.12 | 10.88 |
| F-2 | 23.61 | 0.478 | 0.532 | 1.11 | 10.15 |
| F-3 | 25.34 | 0.493 | 0.536 | 1.08 | 8.02 |
| F-4 | 24.78 | 0.486 | 0.545 | 1.12 | 10.82 |
| F-5 | 24.04 | 0.478 | 0.553 | 1.16 | 13.56 |
| F-6 | 25.30 | 0.472 | 0.559 | 1.18 | 15.56 |
| F-7 | 25 | 0.471 | 0.556 | 1.81 | 15.28 |
| F-8 | 26.05 | 0.474 | 0.536 | 1.13 | 11.57 |
| F-9 | 27.50 | 0.494 | 0.544 | 1.10 | 9.19 |

***TABLE 5.3: PRECOMPRESSION PARAMETERS OF TABLETS***

#### 5.3.6.2 Post compression parameters:

*The sustained release matrix tablets of Diclofenac sodium were prepared by wet granulation method. The results of physicochemical evaluation of prepared tablets were*

*shown Table. The tablets were evaluated for thickness, hardness, friability, weight variation, % of drug content.*

| **Formulation code** | **Thickness (mm)** | **Hardness (kg/cm$^2$)** | **Friability (%)** | **Weight variation** | **% of Drug content** |
|---|---|---|---|---|---|
| F-1 | 4.5±0.03 | 6.5±0.3 | 0.12±0.03 | 246±0.6 | 96.27±0.21 |
| F-2 | 4.2±0.06 | 6.8±0.2 | 0.19±0.05 | 247±0.5 | 96.59±0.24 |
| F-3 | 4.5±0.03 | 6.5±0.8 | 0.9±0.01 | 248±0.3 | 98.21±0.24 |
| F-4 | 4.8±0.04 | 7±0.1 | 0.13±0.09 | 249±0.01 | 97.62±0.12 |
| F-5 | 4.3±0.07 | 6.5±0.8 | 0.23±0.02 | 246±0.05 | 97.53±0.29 |
| F-6 | 4.5±0.06 | 6.6±0.9 | 0.26±0.01 | 246±0.04 | 96.19±0.32 |
| F-7 | 4.6±0.07 | 6.9±0.5 | 0.19±0.04 | 249±0.06 | 98.69±0.25 |
| F-8 | 4.7±0.04 | 6.2±0.3 | 0.21±0.08 | 248±0.04 | 97.56±0.23 |
| F-9 | 4.2±0.05 | 6±0.9 | 0.25±0.01 | 246±0.03 | 98.67±0.31 |

***Table5.4 : Physicochemical properties of tablets containing Diclofenac sodium***

### 5.3.7 In Vitro Drug Release Studies

*Maximum % cumulative drug release was observed in F1. Minimum % cumulative drug release was observed in F6. The concentration of polymer varies, the release of the drug. The data of percentage drug release of all formulation are shown in Table5.5 and the plots are shown in figure 5.9.*

| **Time (hrs)** | **Formulation code** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **F-1** | **F-2** | **F-3** | **F-4** | **F-5** | **F-6** | **F-7** | **F-8** | **F-9** |
| **0.5** | 19.34±0.42 | 14.52±0.21 | 15.85±0.19 | 12.72±0.16 | 9.05±0.23 | 8.02±0.13 | 10.66±0.23 | 5.31±0.17 | 10.55±0.35 |
| **1** | 43.70±.3 | 38.12± | 27.76± | 25.88± | 17.27± | 19.09±0. | 30.71±0. | 18.44± | 20.89± |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 6 | 0.46 | 0.23 | 0.20 | 0.08 | 36 | 18 | 0.26 | 22 |
| **1.5** | 59.99±0.31 | 57.56±0.47 | 39.89±0.19 | 37.23±0.22 | 33.66±0.17 | 40.41±0.31 | 59.65±0.24 | 42.07±0.29 | 38.06±0.17 |
| **2** | 75.86±0.58 | 64.75±0.82 | 55.92±0.15 | 45.13±0.19 | 59±0.13 | 54.68±0.25 | 62.35±0.28 | 52.99±41 | 53.45±0.35 |
| **3** | 82.2±20.91 | 78.06±0.22 | 62.59±0.21 | 47.18±0.08 | 66.06±0.17 | 56.72±0.27 | 66.88±0.19 | 66.17±0.33 | 57.53±0.41 |
| **4** | 90±0.11 | 87.19±0.45 | 65.84±0.25 | 53.71±0.10 | 71.30±0.25 | 62.64±0.19 | 71.32±0.36 | 71.78±0.15 | 64.83±0.39 |
| **5** | | 96.16±0.15 | 72.60±0.29 | 70.41±0.18 | 76.01±0.16 | 71.61±0.26 | 77.80±0.51 | 77.74±0.31 | 66.85±0.26 |
| **6** | | | 94.61±0.67 | 83.61±0.18 | 82.07±0.11 | 76.01±0.19 | 80.11±0.28 | 80.36±0.17 | 72.42±0.23 |
| **8** | | | | 92.36±008 | 89.16±0.42 | 81.19±0.23 | 85.16±0.31 | 83.22±0.22 | 78.03±0.77 |
| **10** | | | | | 96.06±0.17 | 86.01±0.12 | 89.25±0.16 | 86.45±0.27 | 87.95±0.22 |
| **12** | | | | | | 91.12 ±0.32 | 96.16±0.19 | 94.15±0.14 | 99.68±0.11 |

*Number of tablets n=3*

***Table 5.5: % Cumulative Drug Release***

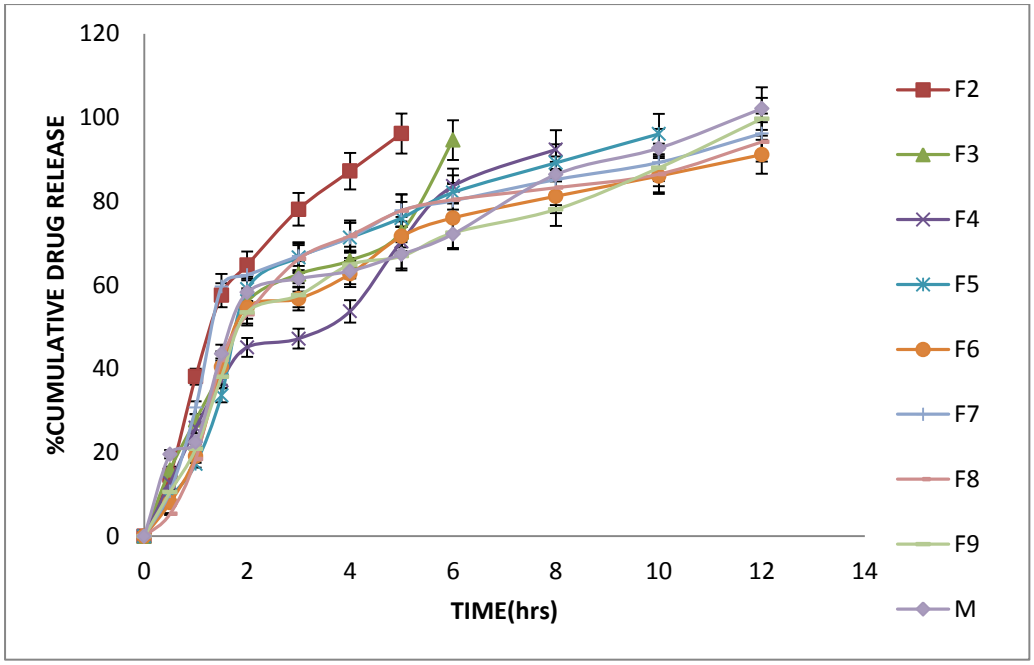


***Figure5.9 : Cumulative drug release***

*The in vitro dissolution studies were carried out for all the formulations from F1-F9 in USP apparatus type II using dissolution mediums phosphate buffer pH 6.8. The release data were noted for 12hrs for all the formulated batches. The result showed that with the varying concentration of polymer the release of drug showed sustained pattern. Formulation F1 containing 10% of polymer showed 4hrs to release 90% i.e approximately 100% of Drug. Similarly the formulations F2,F3,F4,F5 got released at 5,6,8,10hrs and F6,F7,F8,F9 showed sustained release release pattern till 12hrs approximately 96%. Thus with increase % of polymer, TBG polysaccharide with the release time was seen to be extended together with polymer as it is seen in the case of F6. It was confirmed that by increasing the concentration of polymer the release of drug is extended because of slower erosion and increased viscosity which kept the gel network intact for 12hrs with higher proportion of TBG polysaccharide.*

***Drug release mechanism &release curve***

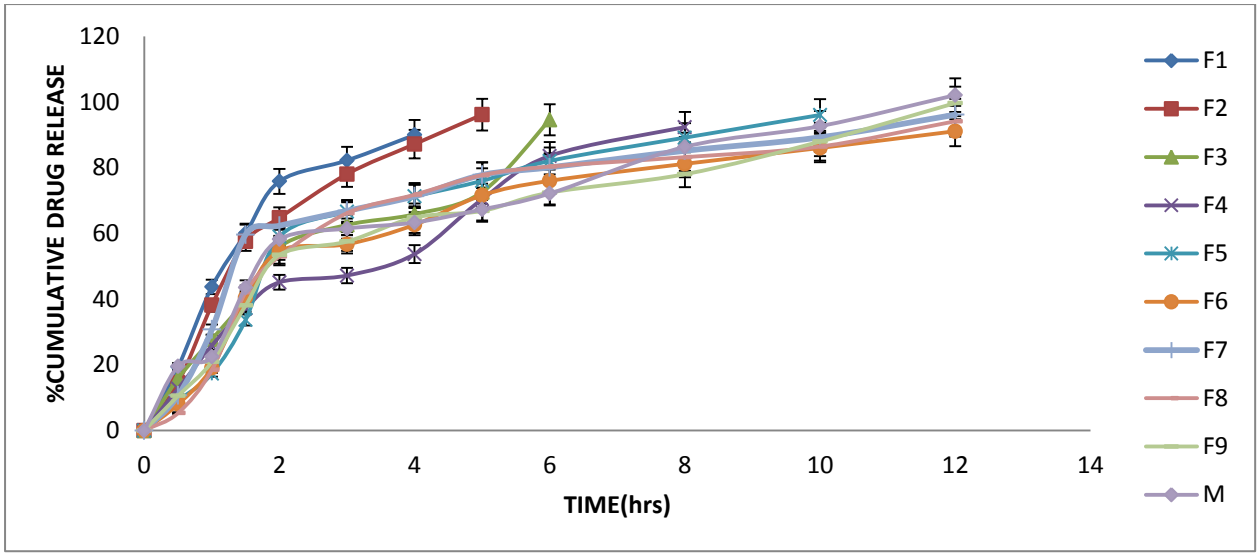


*Figure 5.10: zero order release kinetics of F1-F9 with Marketed formulation.*

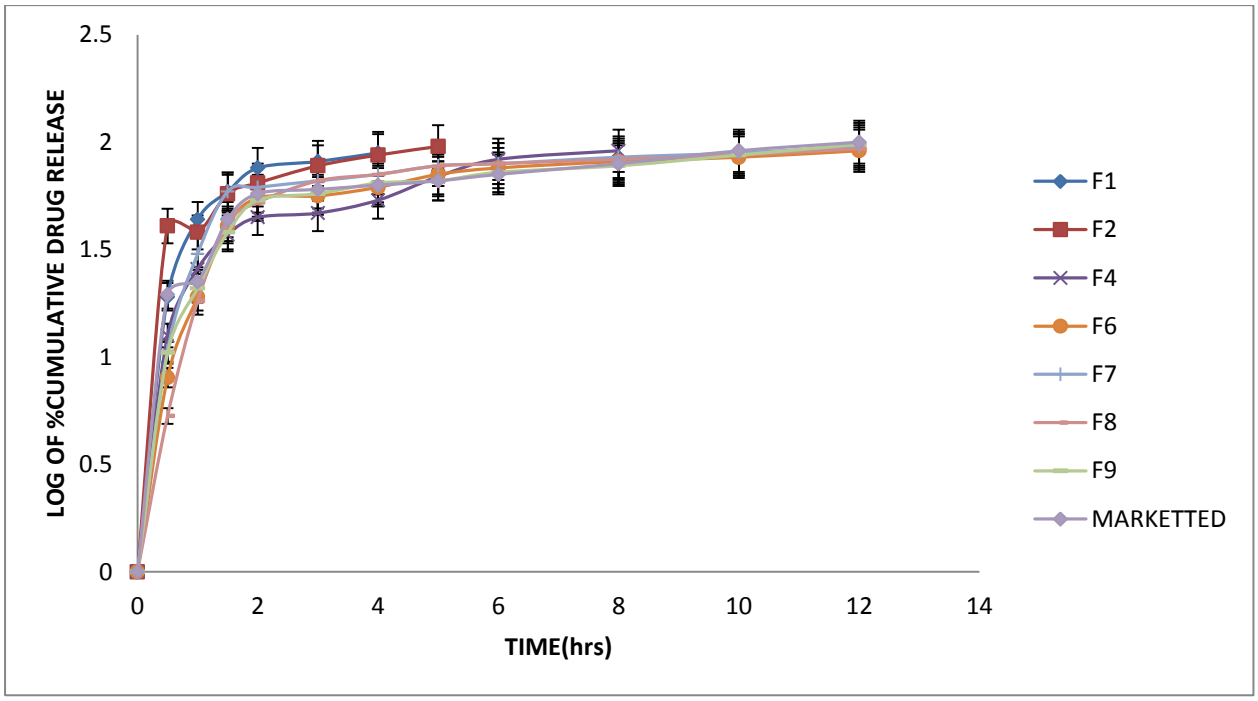


*Figure 5.11: First order release kinetics of F1-F9 with marketed formulaion.*

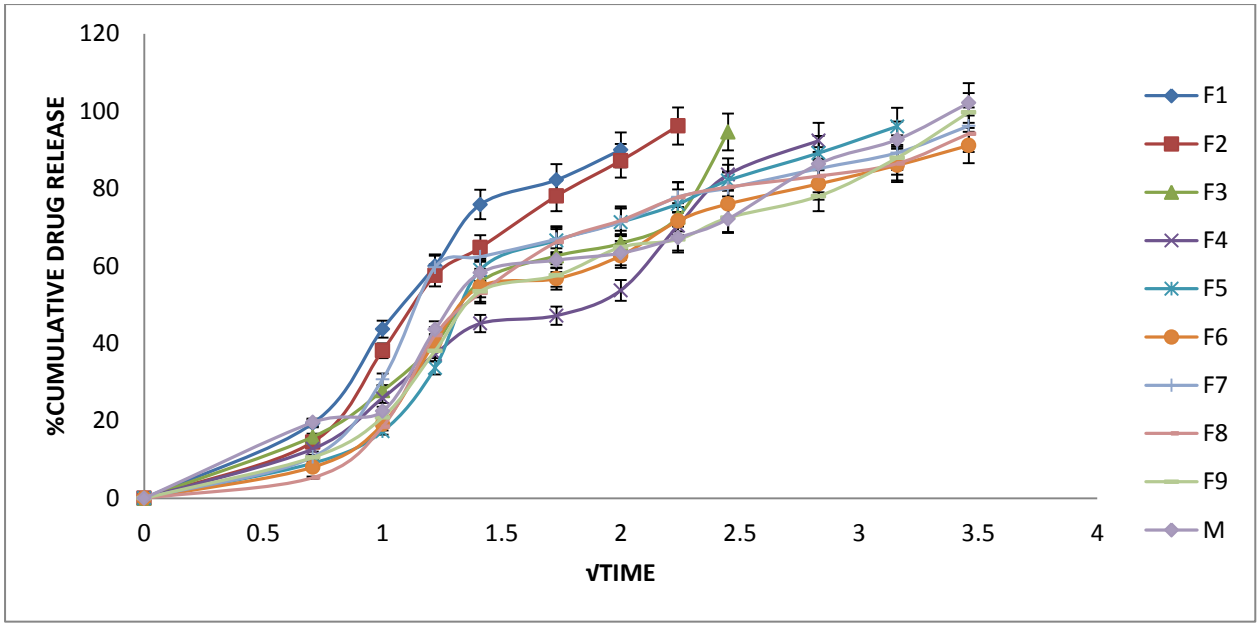


***Figure5.12 : Higuchi release kinetics of F1-F9 withmarketed formulation***

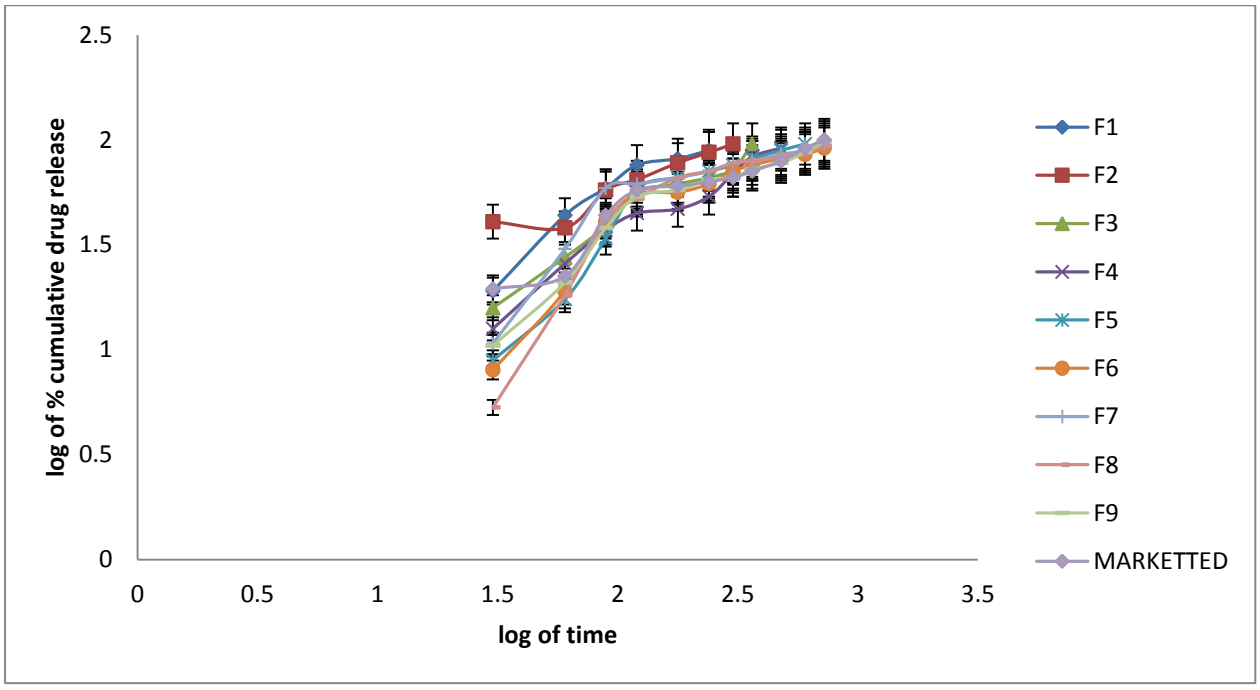


***Figure5.13 :Korsemeyerpeppas model of F1-F9 with Marketed formulation***

| *FA Code* | *Zero order* | | *First Order* | | *Higuchi Model* | | *Korsemeyer-Peppas Model* | |
|---|---|---|---|---|---|---|---|---|
| | $K_0$ | $R^2$ | $K_1$ | $R^2$ | $K_H$ | $R^2$ | $n$ | $R^2$ |
| *F1* | *18.766* | *0.8448* | *0.3643* | *0.5448* | *49.422* | *0.9568* | *0.7367* | *0.9292* |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *F2* | *16.358* | *0.8835* | *0.2463* | *0.4368* | *46.535* | *0.9661* | *0.4228* | *0.9078* |
| *F3* | *12.36* | *0.9182* | *0.2141* | *0.5377* | *37.535* | *0.9624* | *0.6734* | *0.9601* |
| *F4* | *12.144* | *0.9518* | *0.1641* | *0.5281* | *33.878* | *0.9714* | *0.6693* | *0.9621* |
| *F5* | *8.5112* | *0.7915* | *0.1314* | *0.4949* | *34.324* | *0.929* | *0.7762* | *0.8881* |
| *F6* | *6.2352* | *0.7808* | *0.0986* | *0.4429* | *28.65* | *0.9313* | *0.6844* | *0.8534* |
| *F7* | *5.5837* | *0.6962* | *0.0896* | *0.3711* | *28.04* | *0.8811* | *0.5637* | *0.7846* |
| *F8* | *6.4099* | *0.7175* | *0.1039* | *0.4439* | *30.00* | *0.9002* | *0.7818* | *0.8098* |
| *F9* | *6.5539* | *0.848* | *0.0965* | *0.4444* | *29.244* | *0.9564* | *0.6329* | *0.8947* |
| *Marketed* | *7.2864* | *0.8397* | *0.0892* | *0.4027* | *29.269* | *0.9598* | *0.5025* | *0.9099* |

. ***TABLE 5.6: Release kinetic data for evaluation of drug release mechanism***

*With an n value of 0.5, the equation becomes equal to the square root model described by Higuchi, which signifies that drug release from the matrix is governed by Fickian diffusion, for n value 0.5–1.0, anomalous non-fickian drug diffusion occurs i.e. combination of both diffusion or swelling as well as erosion mechanism. For n>1, non-Fickian case-II, erosion controlled or zero order release kinetics is followed. The R and n values of various batches of tablets are depicted in Table 5.6.*

*The $R^2$ value and model constant of corresponding mathematical model were given in the above table. From the zero order and First order plot it can be easily understood that with increase percentage of polymer, the more retardation of drug release occurred as seen in F1 to F8. Retardation decrease with less amount of polymer as in case of F5 to some extent and with 99% for F9. Best release was seen in case of F6. But linearity was observed with Higuchi equation indicating that drug release by diffusion through swellable matrix.. The n values of the formulations were found to be 0.9313. Thus as the n value of F6 falls in the range of 0.5-1.0, it followsanomalous non-fickian drug diffusion occurs i.e. combination of both diffusion or swelling as well as erosion mechanism in case of Higuchi model.*

*The $R^2$values for marketed formulation was also carried out as given in table 5.6. The marketed formulation was found to follow Higuchi model thus and the values falls in the range of 0.5-1.00 which indicates it follows*it

*followsanomalous non-fickian drug diffusion occurs i.e. combination of both diffusion or swelling as well as erosion mechanism in case of Higuchi model. Thus F6 was compared with marketed formulation and the release was found to be equivalent with that of standard marketed formulation.*

## 5.4 Conclusion:

*The research work was carried out successfully. The tablets were prepared by wet granulation technique using different drug polymer ratios. Before compression the granules were evaluated for precompression parameters and then the tablets were evaluated for postcompression parameters. The results were found satisfactory for some of the formulations. Then in-vitro release studies were carried out for 12hrs and the release studies showed release approximately 100%. From which formulation F6 with polymer concentration 30% was found to be optimized formulation as it showed better sustained release of drug. With the values obtained from drug release with time different release kinetics model equations were carried out and depicted in table 5.6., it was found that the optimized formulation F6 and marketed formulation both followed Higuchi model of release i.eanomalous non-fickian drug diffusion occurs i.e. combination of both diffusion or swelling as well as erosion mechanism as the values came within the range of 0.5-1.00.*

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# CHAPTER 6

# CONCLUSION AND SUMMARY

## *SUMMARY AND CONCLUSIONS*

*The aim of the present study was (1) To isolate and purify the polysaccharides from Terminalia bellerica Gum and investigate their physico-chemical properties for the suitability of use as pharmaceutical excipients (2) To evaluate the toxicity of the purified polysaccharide (3) To evaluate the sustained release properties by using both in vitro method.*

***Chapter 1*** *of the thesis deals with the background of the investigation and a brief introduction to oral controlled drug delivery system with respect to different theory of controlled release aspects. The role of matrix former polysaccharide isolated from gum and mucilage's in drug delivery system and the advantages and recent application of polysaccharide based drug delivery have been thoroughly discussed. Introduction to matrix tablets and polymer from natural origin has been discussed along with their uses in pharmaceutical excipients. Further, an introduction to Terminalia bellerica and the drug profile of diclofenac sodium have been presented.*

***Chapter 2*** *deals with the literature review based on matrix tablet formulation and their evaluation using natural polymer.*

***Chapter 3*** *deals with the major aim, objective and plan of the work. This includes a brief description of the approaches used to achieve the objectives.*

***Chapter 4*** *deals with the evaluation of Terminalia bellerica gum as pharmaceutical excipient. Polysaccharide isolated and purified by analytical methods. To characterize the polysaccharides by assessing particle size distribution in polysaccharide powder, flow properties such as bulk density, tapped density, compressibility index, Hausner ratio and angle of repose were studied. The microbial quality test was conducted to detect the load of different species of bacteria, yeast and moulds. Ash values, moisture content, solubility and pH were determined for the polysaccharide to evaluate their purity and suitability as excipient for pharmaceutical formulations. Elemental analysis, scanning electron microscopy (SEM), X-ray diffraction crystallography (XRD), differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FT-IR) techniques were used to characterize the polysaccharides.*

***Chapter 6*** *deals with the preparation and evaluation of controlled release matrix tablets by using Terminalia bellerica gum polysaccharide. The tablets were formulated by wet granulation method after evaluating drug-excipient interaction studies. Diclofenac*

*sodium was taken as a model drug to study the sustained release property of the isolated purified polysaccharide (TBGP). Nine different formulations were prepared (F5-F45) with different concentrations of polysaccharide. The tablets were evaluated for their physical properties like weight variation, hardness, friability and content uniformity. Dissolution study was conducted to characterize release mechanism from the matrix system and data were fitted to various kinetic models. The mucoadhesive property was evaluated different in vitro, ex vivo and in vivo models.*

*The drug-excipient interaction studies (FTIR and DSC) indicated no chemical interaction between diclofenac sodium and polysaccharides used in the experiment.*

*The tablets showed better release rate in phosphate buffer pH 6.8. the tablets were also undertaken via preformulation and postformulation parameters.The formulation were then studied using % cumulative drug release . The formulations were carried out for release kinetics studies for each and every formulations. The prepared formulations showed acceptable physicochemical properties and in-vitro dissolution study showed better controlled release for 12hrs amomg those 9 formulations F6 showed better sustained release pattern over marketed formulation. F6 follwed Higuchi release model, anomalous non-fickian drug diffusion occurs i.e. combination of both diffusion or swelling as well as erosion mechanism as the values came within the range of 0.5-1.00. Further in-vivo absortion studies need to be carried out in future to fully characterize the formulations.*