Ca^{2+} ION CROSSLINKED INTERPENETRATING POLYMER NETWORK MATRIX TABLET OF HYDROLYSED METHACRYLAMIDE GRAFTED GELLAN GUM AND TAMARIND SEED GUM FOR SUSTAINED RELEASE OF DICLOFENAC SODIUM

Submitted by MAHANAM BRATA PAUL

B. Pharm. (J.U)

EXAM ROLL NO: **M4PHA1616**

REGISTRATION NO: 112064 of 2010-2011

Under the guidance of
Prof. (Dr.) Lakshmi Kanta Ghosh

2014-2016

Thesis submitted in partial fulfilment of the requirements for the

DEGREE OF MASTER OF PHARMACY

Department of Pharmaceutical Technology

Faculty of Engineering and Technology

JADAVPUR UNIVERSITY

Kolkata-700032

Ca^{2+}ION CROSSLINKED INTERPENETRATING POLYMER NETWORK MATRIX TABLET OF HYDROLYSED METHACRYLAMIDE GRAFTED GELLAN GUMAND TAMARIND SEED GUM FOR SUSTAINED RELEASE OF DICLOFENAC SODIUM

Submitted by

MAHANAM BRATA PAUL

B.Pharm. (J.U)

***EXAM ROLL NO:* M4PHA1616**

REGISTRATION NO: 112064 of 2010-2011

Under the guidance of

Prof. (Dr.) Lakshmi Kanta Ghosh

Division of Pharmaceutics

DEPARTMENT OF PHARMACEUTICAL TECHNOLOGY

Faculty of Engineering and Technology

JADAVPUR UNIVERSITY

Thesis submitted in partial fulfilment of the requirements for the

DEGREE OF MASTER OF PHARMACY

Department of Pharmaceutical Technology

Faculty of Engineering and Technology

JADAVPUR UNIVERSITY

Kolkata-700032

Session: 2014-2016

FORWARDING CERTIFICATE

*This isto certify that MahanamBrata Paul, B.Pharm.(**Examination Roll No:*** **M4PHA1616,** ***Registration No:112064 of 2010-2011****) has carried out his research work entitled as*"**Ca^{2+} ION CROSSLINKED INTERPENETRATING POLYMER NETWORK MATRIX TABLET OF HYDROLYSED METHACRYLAMIDE GRAFTED GELLAN GUM AND TAMARIND SEED GUM FOR SUSTAINED RELEASE OF DICLOFENAC SODIUM**" *under my direct supervision in the division of Pharmaceutics at the Department of Pharmaceutical Technology,Jadavpur University.He has incorporated his findings into this thesis submitted by him in partial fulfilment of requirements for the award of the degree ofMASTER OF PHARMACY.*

I am satisfied that he has carried out this work with proper care and attention to my entire satisfaction.

Supervised by

....

Prof. (Dr.) Lakshmi Kanta Ghosh
Division of Pharmaceutics
Department of Pharmaceutical Technology
Faculty of Engineering and Technology
Jadavpur University
Kolkata-700032

....

Prof. (Dr.) Biswajit Mukherjee
Head of the Department,
Department Pharmaceutical Technology
Faculty of Engineering andTechnology
Jadavpur University Kolkata-700 032
Kolkata – 700 032

....

Prof.(Dr.)Sivaji Bandyopadhyay
Dean,
Faculty of Engineering andTechnology
Jadavpur University

Declaration of Originality and Compliance of Academic Ethics

*I hereby declare that this thesis contains literature survey and original research work by me (**MahanamBrata Paul**), as part of my Master of Pharmacy studies.*

All information in this document have been obtained and presented in accordance with academic rules and ethical conduct.

I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name	***: MahanamBrata Paul***
Roll Number	***:* M4PHA1616**
Thesis Title	***: Ca^{2+} ION CROSSLINKED INTERPENETRATING POLYMER NETWORK MATRIX TABLET OF HYDROLYSED METHACRYLAMIDE GRAFTED GELLAN GUM AND TAMARIND SEED GUM FOR SUSTAINED RELEASE OF DICLOFENAC SODIUM***

Signature with Date :

CERTIFICATE OF APPROVAL

This is to certify that ***MahanamBrata Paul(Examination Roll No:* M4PHA1616*, Registration No: 112064 of 2010-2011)*** has carried out the research work on the subject entitled**"Ca^{2+} ION CROSSLINKED INTERPENETRATING POLYMER NETWORK MATRIX TABLET OF HYDROLYSED METHACRYLAMIDE GRAFTED GELLAN GUM AND TAMARIND SEED GUM FOR SUSTAINED RELEASE OF DICLOFENAC SODIUM"** under the supervision of ***Prof. (Dr.) Lakshmi Kanta Ghosh*** in the Department of Pharmaceutical Technology, Jadavpur University, Kolkata. He has incorporated his findings in the thesis submitted by him in partial fulfillment of the requirements for the degree of ***Master of Pharmacy.*** He has carried out the research work independently with proper care and attention to our entire satisfaction.

Supervised by

....

Prof. (Dr.) Lakshmi Kanta Ghosh
Division of Pharmaceutics
Department of Pharmaceutical Technology
Faculty of Engineering and Technology
Jadavpur University
Kolkata-700032

....

Prof. (Dr.)Biswajit Mukherjee
Head of the Department,
Department of Pharmaceutical Technology
Faculty of Engineering andTechnology
Jadavpur University
Kolkata – 700 032

Prof.(Dr.)Sivaji Bandyopadhyay
Dean,
Faculty of Engineering andTechnology
Jadavpur University
Kolkata-700 032

Acknowledgement

I take this opportunity to humbly acknowledge the contributions of my supervisor, Prof. (Dr.) L. K. Ghosh, Division of Pharmaceutics, Department of Pharmaceutical Technology, Jadavpur University, Kolkatafor his invaluable guidance and constant encouragement to materialize this piece of work and I express my heartfelt gratitude and thankfulness for his encouragement all through.

This acknowledgement will be incomplete if I do not express my sincere thanks to the team of our Pharmaceutics–II laboratory, Department of Pharmaceutical Technology, Jadavpur University. I extend my thanks to my seniors;Dr.Gouranga Nandi,Mr. Koushik Sen Gupta, Mr. Abhijit Changder, Dr.ManasBhowmik,Mrs.SanchitaDas,Mrs.MoumitaDas,Dr.PabitraMondal,Mrs.DebjaniSarkar, Miss.Swapnoleena Sen,Mr. Ashoke Mukherjee and my lab mate Mr.ProsenjitHudati and my junior Miss Riyashree Pal, other batch mates of different laboratories and my hostel roommates and lab assistants for their help & guidance throughout my thesis work.

I also thankful to the DSA instrumental lab for providing sophisticated instrumental support,department of pharmaceutical technology,Jadavpur University.

I place on record, my thanks to Jadavpur University and Department of Pharmaceutical Technology authorities to allow me to use their material and instrumental facilities.

I would like to express my gratitude towards Department of Metallurgical and Material Science, Jadavpur University, Kolkata, for their kind co-operation which helped me in completion of this project.

I express my thanks to UGC, Ministry of Human Resource and Development, Government of India, for providing me financial assistance in the form of fellowship.

At last, but not the least, I express my sincere regards to my family for their inspiration and motivation throughout my studies and all they have done for me during my studies.

'THANKS AGAIN TO ALL OF MY WELL WISHERS'

Dedicated To my beloved family,my guide

And my friends.

CONTENTS

		Page No.
1.	*INTRODUCTION*	*1 – 21*
	1.1. Aspects of novel drug delivery system	*1*
	1.2. Benefits of Novel Drug Delivery System	*1*
	1.3. Conventional drug therapy	*2*
	1.4. The sustained release concept	*2*
	1.5. IPN	*5*
	1.6. Brief introduction of Grafting	*8*
	1.7. References	*17*
2.	*NATURAL GUMS AND MUCILAGES*	*22–28*
	2.1. Introduction	*22*
	2.2. Advantages of natural gum in pharmaceutical uses	*23*
	2.3. Disadvantages of natural polymers in pharmaceutical uses	*23*
	2.4. Disadvantages of synthetic polymers in pharmaceutical use	*24*
	2.5. Classification of natural gums and mucilages	*24*
	2.6. Modification of natural gums and mucilage	*26*
	2.7. References	*26*
3.	*LITERATURE REVIEW*	*29 – 35*
	3.1. Introduction	*29*
	3.2. References	*34*
4.	*DRUG & EXCIPIENT PROFILES*	*36 – 63*
	4.1. Drug profile	*36*
	4.2. Excipients profiles	*47*
	4.3. References	*62*
5.	*AIMS AND OBJECTIVES*	*64– 66*
6.	*MATERIALS & METHODS*	*67 – 78*
	6.1. Drug used	*67*
	6.2. List of Chemical used	*67*
	6.3. List of Instrument handled	*68*
	6.4. Methods	*69*
	6.5. References	*78*
7.	*RESULTS AND DISCUSSION*	*79 – 98*
	7.1. Evaluation of Drug	*79*
	7.2. Synthesis and hydrolysisof Pmaa-g-GG	*81*
	7.3. Evaluation ofhPmaa-g-GG	*82*
	7.4. Tablet Characteristics	*90*
	7.5. In vitro drug release study and release mechanism	*90*
8.	*SUMMARY & CONCLUSION*	*99*

LIST OF SYMBOLS AND ABBREVIATIONS

Abbreviations/ Symbols	Meaning of abbreviations/ symbols
&	And
±	Plus or minus
%	Percentage
Avg.	Average
e.g.	For example
i.e.	That is
Soln.	Solution
nm	Nanometer
mg	Milligram
mm	Millimeter
ml	Milliliter
SL.	Serial Number
ARA	Amount remaining to be absorbed
DR	Drug release
CDR	Cumulative drug release
%CDR	Percent cumulative drug release
BP	British pharmacopoeia
IP	Indian pharmacopoeia
DSC	Differential scanning calorimetry
GIT	Gastrointestinal tract
GRT	Gastric residence time
GTT	Gastric transit time
GRDDS	Gastro retentive drug delivery system
Maa-g-GG	Methacrylamide grafted gellan gum
hPmaa-g-GG	Hydroxylated polymethacrylamide grafted gellan gum
IR	Infrared
FTIR	Fourier transform infrared spectroscopy
XRD	X-ray diffraction
PVP	Polyvinyl pyrolidine
mcg	Microgram
rpm	Revolution per minute
HPMC	Hydroxy propyl methyl cellulose
CAN	Cerric ammonium nitrate
USP	United states pharmacopoeia
UV	Ultraviolet
SR	Sustained release
No.	Number
ºC	Degree centigrade
%C	Percent conversion
%G	Percent grafting
λ_{max}	Maximum absorbance wavelenth

CHAPTER: 1

INTRODUCTION

1. INTRODUCTION:

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route of administration has received more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other routes [1].Oral controlled release dosage forms have been developed for the past three decades due to their considerable therapeutic advantages and applications. The high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms [2].Controlled Drug Delivery System provides drug release at a predetermined, predictable and controlled rate to achieve high therapeutic efficiency with minimal toxicity [3].

Development of a successful oral controlled release drug delivery dosage form requires an understanding of three aspects:

- The Anatomic and physiologic characteristic of gastrointestinal tract (GIT)
- Physiochemical, pharmacokinetic and pharmacodynamic characteristic of the drug and
- Dosage form characteristics

1.1.Aspects of novel drug delivery system[4-6]:

Patients with chronic diseases are increasing day by day. This situation necessitates the use of drugs for a longer period and taking a lot of medicines simultaneously, which may lead to a decrease in patient compliance. This problem is serious for drugs with short biological half-life because they must be taken more frequently. To overcome such problems, different types of novel drug delivery systems has been developed that are capable to release the drug gradually for a long time, thereby reduced the dose frequency. The drug delivery system should deliver a drug at a rate dictated by the needs of the body over a specified period of treatment. This idealized objective points to the two aspects most important to the drug delivery namely:

- Relates to targeting a drug to a specific organ or tissue.
- To controlling the rate of drug delivery to the target tissue.

1.2. Benefits of Novel Drug Delivery System[7]:

- Convenience in dosing
- Higher patient compliance
- Reduced adverse effects
- Improved efficacy

1.3.Conventional drug therapy[8, 9]:

To understand the importance of sustained release drug delivery in therapy, it is necessary to review some aspects of conventional dosage forms and drug delivery. In most cases of conventional dosage forms the dosing interval is much shorter than the half-life of the drug resulting in a number of limitations

- Depending on biological half-life of the drug, large peaks and valleys in the drug level will occur, unless the dosing interval is relatively short.
- Success by this approach depends on patient compliance with the dosing regimen. Numerous studies have documented that lack of compliance is an important reason for inefficiency or failure of drug therapy.
- During the early periods of dosing there may be insufficient drug to generate a favourable biological response, which may be a significant problem in certain disease states.
- For drugs with short biological half-life, frequent dosing is needed to maintain relatively constant therapeutic levels of drugs

There are two ways to overcome such problems:-

- Development of new safe drugs with long half-lives and large therapeutic indices.
- Effective and safer use of existing drugs through concepts and techniques of controlled and targeted delivery systems.

1.4. The sustained release concept[10]:

Sustained-release dosage forms provide medication over an extended period of time. Controlled release, however, denotes that the system is able to provide some actual therapeutic control, whether of a temporal or spatial nature or both. In other words, the system attempts to control the drug concentration in the target tissue; often, this is blood serum. In general, the goal of a sustained-release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period of time. This is generally accomplished by attempting to obtain zero-order release from the dosage form. Sustained-release systems generally do not attain this type of release; they usually try to mimic zero order release by providing drug in a slow first-order fashion. Controlled release, although resulting in a ‘‘zero-order’’ delivery system, may also incorporate methods to promote localization of the drug at an active site.

1.4.1.Sustained - release dosage forms:

These preparations provide an immediate dose required for the normal therapeutic response,followed

by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time (usually between 8-12hr). The major advantage of this category is that, in addition to the convenience of reduced frequency administration, it provides levels that are devoid of the peak and valley effect, characteristic of the conventional intermittent dosage regimen.

1.4.2.Controlled - release dosage form:

The controlled release systems is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to the eliminated by the body. An ideal controlled drug delivery system is the one, which delivers the drugs at a predetermined rate, locally or systemically, for a specific period of time.

1.4.3.Delayed release preparation:

The drug is released at a later time after administration. The delayed action is achieved by the incorporation of a special coat, such as enteric coating, or other time barriers such as the formaldehyde treatment of soft and hard gelatin capsules. The purposes of such preparations are to prevent side effects related to the drug presence in the stomach, protect the drug from degradation in the highly acidic pH of the gastric fluid.

1.4.4. General principle of controlled release systems[11]:

The concept of controlled release systems is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to that eliminated by the body. The system usually delivers very small amounts of the drug at more frequent intervals.

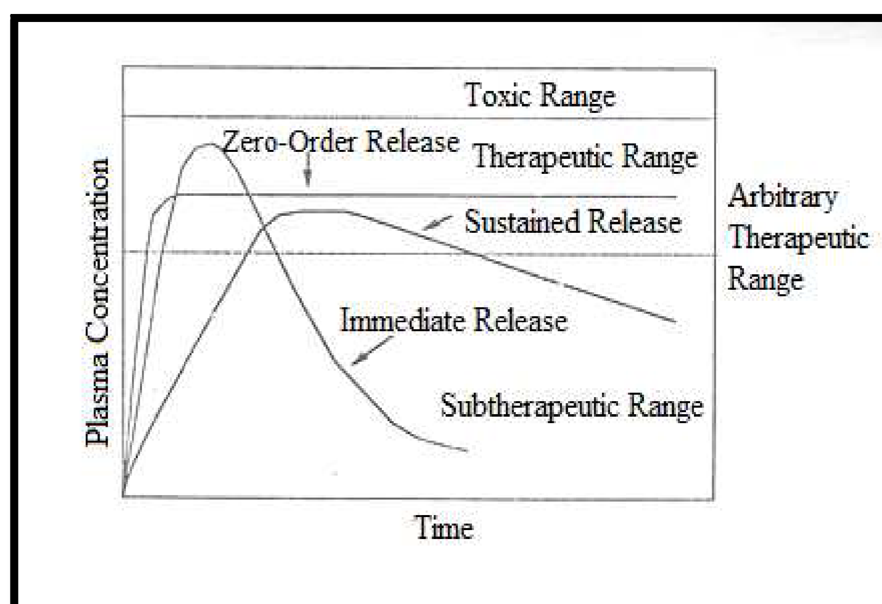


Figure 1.1. Plasma drug concentration versus time profiles of various formulations

1.4.5. Objective, Advantage and disadvantage of controlled/sustained drug delivery system[12-13]:

1.4.5.1. Main objective of sustained release formulation:

The formulation is designed in such a way that the minimum effective plasma concentration (MEC) level of Drug should attain quickly and there after the rate of entry of drug to the body should equal with the rate of total elimination or inactivation of the drug from the body. As a result the plasma drug concentration curve will run parallel to the time axis just above the MEC level. Following are the example of some of the advantage associated with sustained release formulations:

- Uninterrupted therapeutic response for a prolonged period can be achieved.
- Toxicity associated with peak plasma concentrations and the chances of drug resistance associated with the deep ineffective plasma drug concentration would be diminished.
- Frequency of drug administration is reduced, therefore, compliance to the patient as well as Nursing staffs.
- Much lesser amount of drug is essential for the entire course of therapy.

1.4.5.2. Advantages:

All controlled/sustained - release products share the common goal of improving drug therapy over that achieved with their non-controlled counter parts. This improvement in drug delivery is represented by several potential advantages as below.

1. Avoid patient compliance problems
2. Employ less total drug
    - Minimize or eliminate local and systemic side effects
    - Obtain less potentiating or reduction in drug activity with chronic use.
    - Minimize drug accumulation with chronic dosing
3. Improve efficiency in treatment
    - Cure or control condition more promptly
    - Improve control of condition, i.e., reduce fluctuation in drug level
    - Improve bioavailability of some drug

- Make use of special effects, e.g., sustained release aspirin for morning relief of arthritis by dosing before bedtime.

1.4.5.3. Disadvantages:

1. Usually the amount of drug in a sustained release dosage form is 3-4 times more than the conventional one. Hence, if a dosage form is used improperly e.g. by chewing instead of swallowing, the patient would receive an over dose.
2. Improper formulation may result in excessive dosage or the drug release may not be complete.
3. In case of accidental failure of the product effective antidote may be difficult to employ.
4. Sustained release dosage forms are sometimes costlier because of the technology involved in producing the formulation.
5. Sustained release medication should not be used with persons known to have impaired or erratic gastrointestinal absorption or kidney troubles.
6. Drugs having long biological half-life are not suitable for presentation in S.R. forms e.g. digitoxin.
7. There is little control in the hands of the physician so for as dose variation is concerned.
8. It is difficult to formulate an ideal sustained release dosage form.
9. Unpredictable or poor *in vitro-in vivo* correlation.
10. Increase first-pass clearance.

1.5. Interpenetrating polymer network (IPN)[14-16]:

IPN is a polymer comprising two or more networks which are at least partially interlaced on a molecular scale but not covalently bonded to each other and cannot be separated unless chemical bonds are broken. Semi-interpenetrating polymer network (SIPN) is a polymer comprising one or more networks and one or more linear or branched polymer(s) characterized by the penetration on a molecular scale of at least one of the networks by at least some of the linear or branched macromolecules.

An IPN can be distinguished from polymer blend in the way that an IPN swells but does not dissolve in solvents and creep and flow are suppressed. They are also different from graft copolymers and polymer complex that involve either chemical bonds and/or low degree of cross-linking. From this point of view only, IPN can be generally named as “polymer alloys” through which polymer blends can be made chemically compatible to achieve the desired phase morphology.

1.5.1. Classification of IPN[14-15]:

1.5.1.1 Based on Chemical Bonding

a) Covalent Semi-IPN. When two separate polymer systems that are cross-linked form a single polymer network, it is called covalent semi-IPN.

b) Non covalent Semi-IPN. In non-covalent semi-IPNs only one of the polymer systems is cross-linked.

c) Non covalent Full IPN.A non-covalent full IPN is one in which the two separate polymers are cross-linked independently.

1.5.1.2 Based on Method of Synthesis.

IPNs are of different types: sequential IPN, subsequent IPN, latex IPN, gradient IPN, and thermoplastic IPN.

a)Sequential IPN.

In sequential IPN, the first cross linked polymer network is swollen by the monomer of the second polymer that is polymerized and/or cross-linked afterwards. In this class an IPN is formed by polymerizing the first mixture of monomer (I), cross-linker, and initiator to form a network. The network is swollen with the second combination of monomer (II) and cross-linker which is polymerized to form an IPN.

b) Simultaneous IPN.

An IPN is formed by polymerization of two different monomer and cross-linking agent pairs together in one step. The key to the success of this process is that the two components must polymerize simultaneously by non-interfering routes.

c) Latex IPN.

The common problem associated with most IPNs is the difficulty in molding after they are formed since they are thermosets. One way to overcome this problem is to use latex IPN. They are also called interpenetrating In latex type IPN both networks are included in a single latex particle, usually by polymerization of the second monomer together with the cross-linking agent and activator in the original seed latex of the first cross-linked monomer

d)Thermoplastic IPN.

The thermoplastic IPNs are combination of two physically cross-linked polymers. Typical physical cross-links arise from ionic groups, crystallinity, or glassy domains.

e) Gradient IPN.

Gradient IPNs have compositions which vary as a function of position in the sample.They are formed as a result of the swelling of the first monomer network in the network of the second monomer.

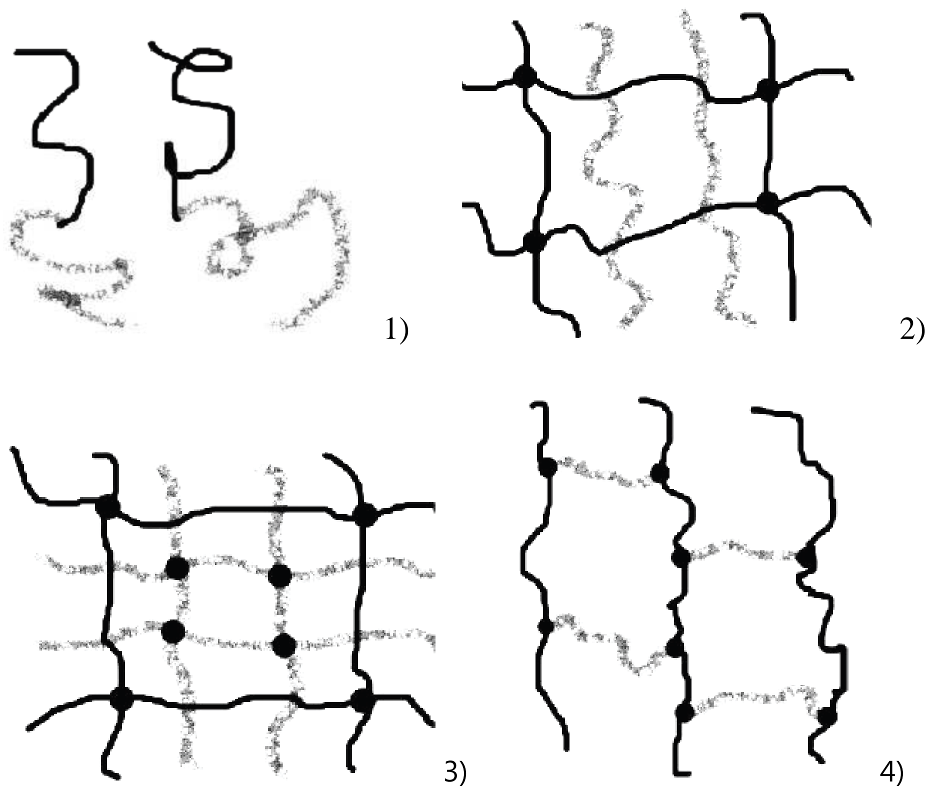


Figure 1.2.1) Graft copolymer, 2) Semi IPN, 3) Full IPN, 4) Crosslinked co-polymer. Bold line indicates polymerI and hazy line indicates polymer II, black circle indicates crosslinker

1.5.2. Preparation of IPN[16]:

a) Casting Evaporation.

This method has been used widely to form cross-linked polymer network. In this method each polymer constituent is heated until it is dissolved and then added to cross-linker solution. In case of sequential process, solution of polymer I is added to the cross-linker solution followed

by addition of polymer II solution. In both cases the solution is heated and mixed and then casted and dried. IPN gels can be prepared by this technique.

b) Emulsification Cross-Linking.

This method is based on phase separation. Generally single emulsion cross-linking technique is based on w/o emulsion but recently w/w emulsion method has also been developed to form IPN. The main advantage of w/w emulsion method is that there is no use of organic solvents which might leave toxic residue that is incompatible with IPN biomaterials. In w/o emulsification method the water soluble materials are dissolved in aqueous phase at specific temperature to form homogenous solution by stirring. This aqueous phase is added to oil phase to prepare w/o emulsion but in w/w emulsion technique an aqueous solution of water soluble polymers is emulsified as a dispersed phase in an aqueous solution of another polymer that acts as continuous phase. Thenthe dispersed polymer phase is cross-linked to form IPN network .

c)Miniemulsion/ Inverse Miniemulsion Technique.

This technique allows one to create small stable droplets in a continuous phase by the application of high shear stress. The idea of miniemulsion polymerization is to initiate the polymer in each of the small stabilized droplets. To prevent the degradation of miniemulsion through coalescence, a surfactant and a co-stablizer are added that are soluble in dispersed phase but insoluble in continuous phase. This process of IPN formation can be divided into three steps. In the first step, constituent polymers are obtained by sonication using specific initiator. In the second step, one of the constituent polymers is polymerized and cross-linked using a cross-linking agent. As a result a semi-IPN is formed till the second stage. In the third step, a full IPN is formed polymerizing and cross-linking the second constituent polymer by the addition of second cross-linker. In case of inverse miniemulsion (water in oil), hydrophilic monomers can be easily polymerized. In this case the monomer solution is miniemulsified in a continuous hydrophobic phase. The polymerization process can be initiated either from the continuous phase or from the droplet.

1.6. Brief introduction of Grafting:

- ✓ **Monomer:**

  Monomers are small molecules which may be joined together in a repeating fashion to form more complex molecules called polymers.

- **Polymer:**

  A polymer may be a natural or synthetic macromolecule comprised of repeating units of a smaller molecule (monomers).While many people use the term 'polymer' and 'plastic' interchangeably, polymers are a much larger class of molecules which includes plastics, plus many other materials, such as cellulose, amber, and natural rubber.

- **Grafted co-polymer:**

  A grafted co-polymer is a macromolecular chain with one or more species of block connected to the main chain as side chain(s). Thus, it can be described as, having the general structure, where the main polymer backbone, commonly referred to as the trunk polymer, has branches of another polymeric chain emanating from different points along its length [17]. Graft copolymerization of synthetic polymers onto polysaccharide backbone offers one of the best ways to use polysaccharides for controlled release delivery. Graft copolymerization is an easy method to modify the structure of natural polymers and thus makes them attractive biomaterials in controlled release applications since native polysaccharides may not be suitable in controlled release drug delivery systems due to their substantial swelling and rapid enzymatic degradation in the biological fluids [18].

Inthe polymeric age, it is essential to modify the properties of a polymer according to tailor-made specifications designed for target applications. There are several means to modify polymers properties, viz. blending, grafting, and curing. ‘Blending’ is the physical mixture of two (or more) polymers to obtain the requisite properties. ‘Grafting’ is a method wherein monomers are covalently bonded (modified) onto the polymer chain, whereas in curing, the polymerization of an oligomer mixture forms a coating which adheres to the substrate by physical forces. Curing gives a smooth finish by filling in the valleys in the surface. This is somewhat different from the curing (or vulcanization) of rubber which produces chemical cross-links between loosely coiled polymeric chains, producing elasticity as the chains stretch under a stress, and retract on release of the stress.

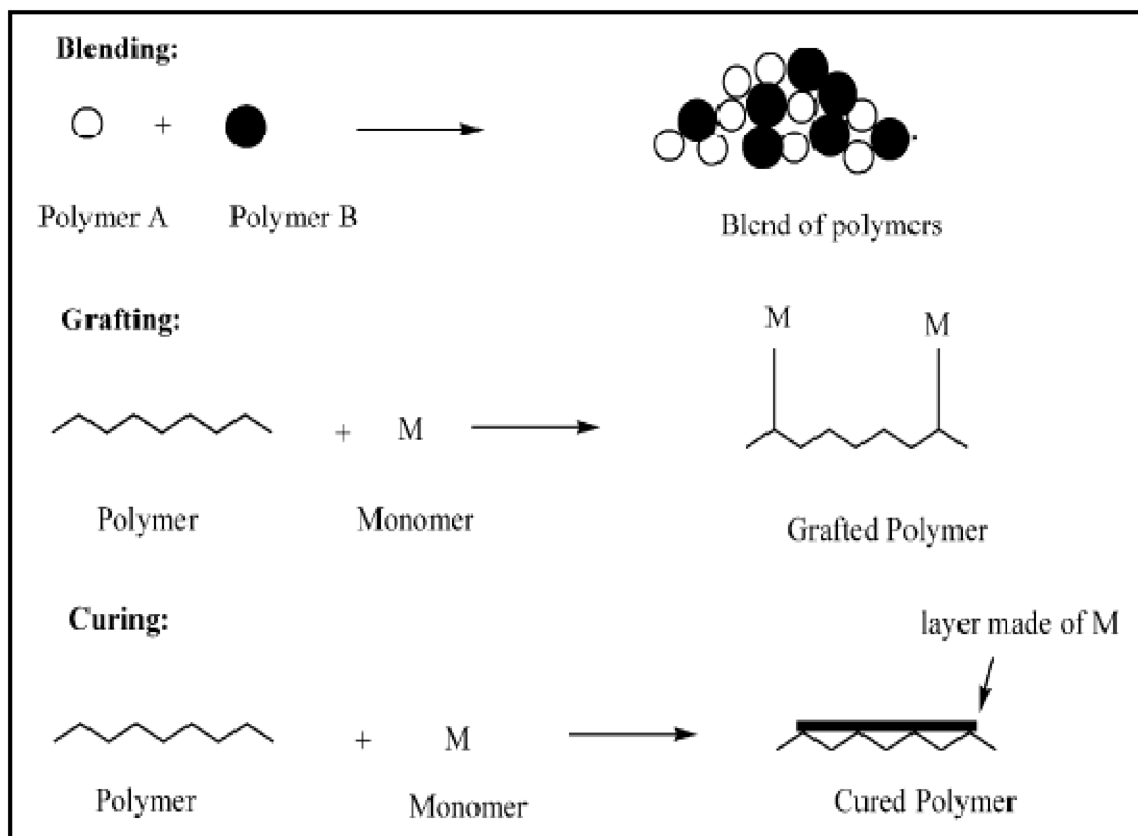


Figure 1.3. Showing the procedures of Blending, Grafting and Curing

1.6.1. Types of grafting:

Two major types of grafting may be considered –

- ✓ Grafting with a single monomer
- ✓ Grafting with a mixture of two (or more) monomers

The first type usually occurs in a single step, but the second may occur with either the simultaneous or sequential use of the two monomers. Mosaic grafting has attracted much attention for binary monomer grafting. Two different monomers are grafted side-by-side to obtain the requisite property. This is the origin of bipolar membranes. The first part of the review discusses different techniques of grafting, and the primary factors, which control the grafting. Following that, two applications are discussed, viz. membrane separation science and conducting polymers. Different grafting techniques include chemical, radiation, photochemical, plasma induced techniques and enzymatic grafting.

1.6.2. Techniques of grafting:

Considerable work has been done on techniques of graft co-polymerization of different monomers on polymeric backbones. These techniques include chemical, radiation, photochemical, plasma-induced techniques and enzymatic grafting.

1.6.2.1.Grafting initiated by chemical means:

Chemical means the grafting can proceed along two major paths, viz. free radical and ionic. In the chemical process, the role of initiator is very important as it determines the path of the grafting process. Apart from the general free-radical mechanism, grafting in the melt and atom transfer radical polymerization (ATRP) are also interesting techniques to carry out grafting.

1.6.2.2. Free-radical grafting:

In the chemical process, free radicals are produced from the initiators and transferred to the substrate to react with monomer to form the graft co-polymers. In general, one can consider the generation of free radicals by indirect or direct methods. An example of free radicals produced by an indirect method is the production through redox reaction, viz. Mn^{n+}/H_2O_2, per-sulphates[19–23].

Equation 1.1. Free-radical grafting:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^\cdot$$

$$Fe^{2+} + {}^-O_3S\text{-}OO\text{-}SO_3^- \rightarrow Fe^{3+}SO_4^{2-} + SO_4^{-\cdot}$$

1.6.2.3. Grafting through living polymerization:

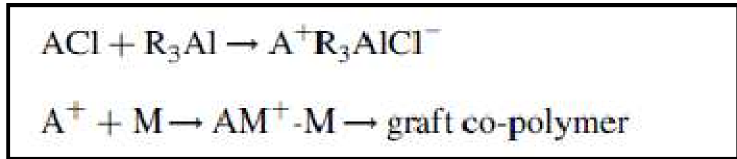
In recent years, methods of 'Living Polymerization' have developed to provide a potential forgrafting reactions. In the view of Szwarc*et al.* [24], the most plausible definition of a 'living polymer' is 'that retains their ability to propagate for a long time and grow to a desired maximum size while their degree of termination or chain transfer is still negligible'. Controlled free-radical polymerizations combine features of conventional free-radical and ionic polymerizations. Conventional free-radical polymerization requires continuous initiation, with termination of the growing chain radicals in coupling or disproportionate reactions, and as a result leads to unreactive ('dead') polymers and essentially time invariant degrees of polymerization and broad molecular weight distribution. In case of a living polymerization, it provides living polymers with regulated molecular weights and low poly-dispersities[25–32].

1.6.2.4. Ionic grafting:

Grafting can also proceed through an ionic mode. Alkali metal suspensions in a Lewis base liquid, organ metallic compounds and sodium naphthalenide are useful initiators in this purpose. Alkyl aluminium (R3Al) and the backbone polymer in the halide form (ACl) interact to form carbonium ions

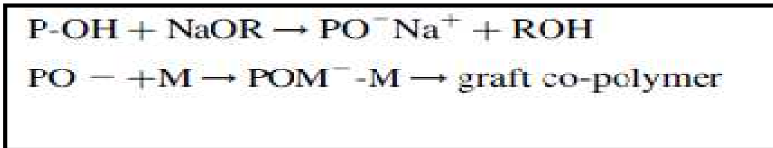
along the polymer chain, which leads to copolymerization. The reaction proceeds through cationic mechanism.

Equation 1.2. Ionic grafting:



Cationic catalyst BF3 can also be used. Grafting can also proceed through an anionic mechanism. Sodiumammonia or the methoxide of alkali metals form the alkoxide of polymer (PO^-, Na^+), which reacts with monomer to form the graft co-polymer.

Equation 1.3. Anionic grafting:



1.6.2.5. Grafting initiated by radiation technique:

1.6.2.5.1. Free-radical grafting:

The irradiation of macromolecules can cause homolytic fission and thus forms free radicals on the polymer. In the radiation technique, the presence of an initiator is not essential. The medium is important in this case, e.g. if irradiation is carried out in air, peroxides may be formed on the polymer. The lifetime of the free radical depends upon the nature of the backbone polymer. Grafting proceeds in three different ways:

- ✓ Pre-irradiation
- ✓ Peroxidation and
- ✓ Mutual irradiation technique.

In the pre-irradiation technique [33–37], the polymer backbone is first irradiated in vacuum or in the presence of an inert gas to form free radicals. The irradiated polymer substrate is then treated with the monomer, in liquid or vapor state or as a solution in a suitable solvent. In the peroxidation grafting method, the trunk polymer is subjected to high-energy radiation in the presence of air or oxygen to form hydro peroxides or diperoxides, depending on the nature of the polymeric backbone and the

irradiation conditions. The stable peroxy products are then treated with the monomer at higher temperature, whence the peroxides undergo decomposition to radicals, which then initiate grafting. The advantage of this technique is that the intermediate peroxy products can be stored for long periods before performing the grafting step. On the other hand, with the mutual irradiation technique, the polymer and the monomers are irradiated simultaneously, to form free radicals and subsequent addition [38–44]. Since the monomers are not exposed to radiation in the pre irradiation technique, the obvious advantage is that the method is relatively free from homopolymer formation, which occurs with the simultaneous technique. However, the decided disadvantage of the pre-irradiation technique is scission of the base polymer due to its direct irradiation, which can result in the formation of block co-polymers.

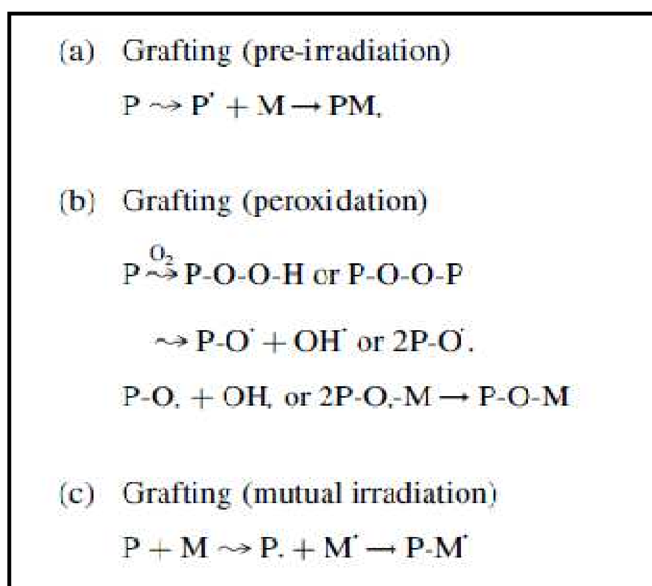


Figure 1.4. Showing mechanism of grafting (pre-irradiation, peroxidation, mutual irradiation)

1.5.2.5.2. Ionic grafting:

Radiation grafting can also proceed through an ionic mode, with the ions formed through high-energy irradiation. Ionic grafting may be of two different types: cationic or anionic. The polymer is irradiated to form the polymeric ion, and then reacted with the monomer to form the grafted co-polymer. The potential advantage of the ionic grafting is high reaction rate. Thus, small radiationdoses are sufficient to bring about the requisite grafting.

1.6.2.6. Photochemical grafting:

When a chromophore on a macromolecule absorbs light, it goes to an excited state, which may dissociate into reactive free-radicals, whence the grafting process is initiated. If the absorption of light does not lead to the formation of free-radical sites through bond rupture, this process can be promoted by the addition of photo sensitizers, e.g. benzoin ethyl ether, dyes, such as Na-2,7

anthraquinonesulphonate or acrylatedazo dye, aromatic ketones (such as benzophenone, xanthone) or metal ions UO_2^{2+}. That means the grafting process by a photochemical technique can proceed in two ways: with or without a sensitizer [45-47]. The mechanism without sensitizer involves the generation of free radicals on the backbone, which react with the monomer free radical to form the grafted co-polymer. On the other hand, in the mechanism 'with sensitizer', the sensitizer forms free radicals, which can undergo diffusion so that they abstract hydrogen atoms from the base polymer, producing the radical sites required for grafting.

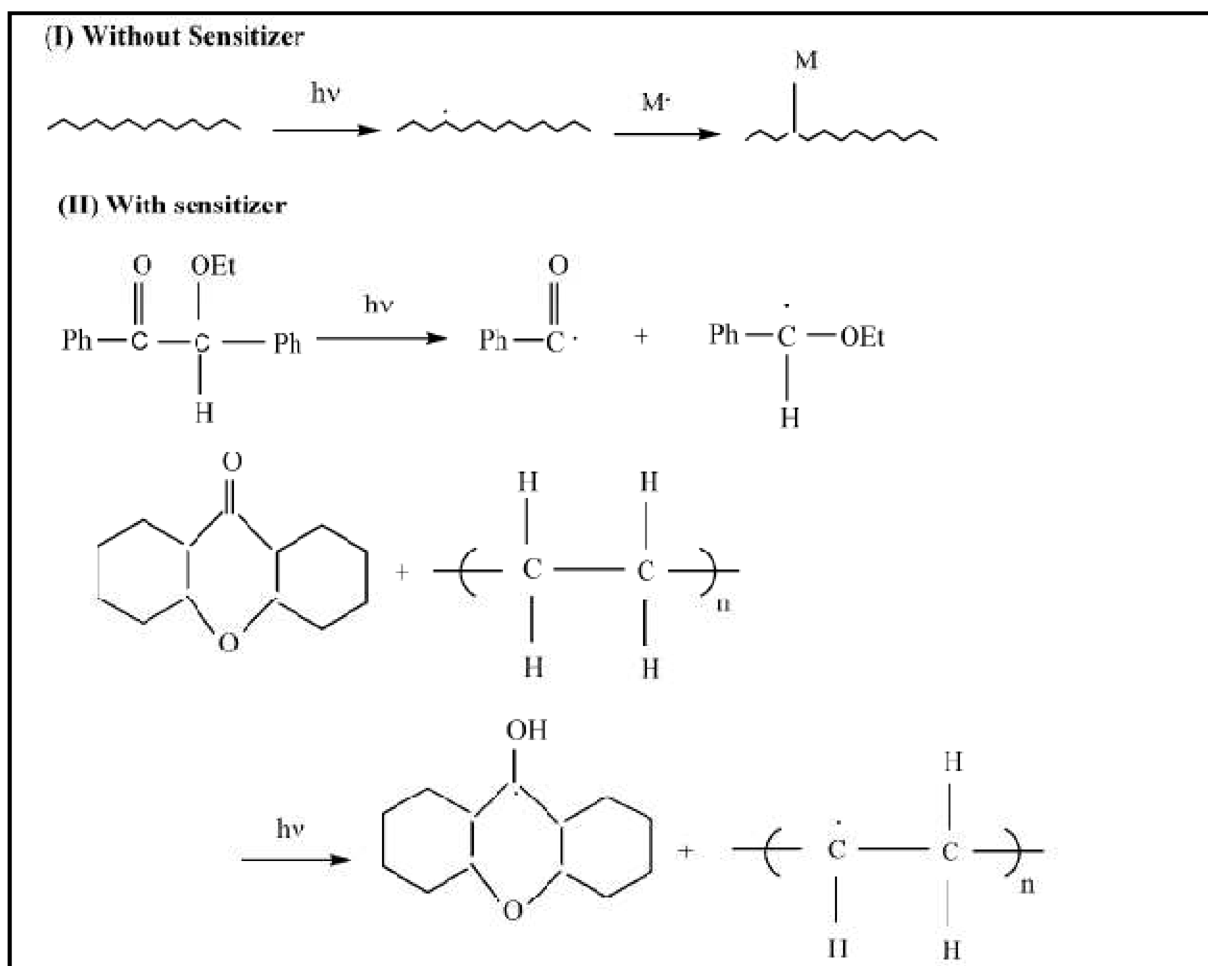


Figure 1.5. Process involved in photochemical grafting

1.5.2.7. Plasma-radiation induced grafting:

In recent years, the plasma polymerization technique has received increasing interest. Plasma conditions attained through slow discharge offer about the same possibilities as with ionizing radiation [48, 49]. The main processes in plasmas are electron-induced excitation, ionization and dissociation. Thus, the accelerated electrons from the plasma have sufficient energy to induce cleavage of the chemical bonds in the polymeric structure, to form macromolecule radicals, which subsequently initiate graft co-polymerization.

1.5.2.8. Enzymatic grafting:

The enzymatic grafting method is quite new. The principle involved is that an enzyme initiates the chemical/electrochemical grafting reaction [50]. For example, tyrosinase is capable of converting phenol into reactive o-quinone, which undergoes subsequent non-enzymatic reaction with chitosan.

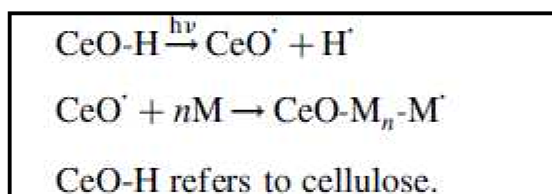
1.5.3. Controlling factors of grafting:

In the following sections, several of the many variables that control grafting will be discussed including the nature of the backbone, monomer, solvent, initiator, additives, temperature, etc.

1.5.3.1. Nature of backbone:

As grafting involves covalent attachment of a monomer to a pre-formed polymeric backbone, the nature of the backbone (viz. physical nature, chemical composition) plays an important role in the process. Ng et al. [51] concluded that whereas cellulose is resistant to grafting reactions in water owing to its insolubility, due to the immense size of the polymeric chain bonding between the amino residues, the cystine linkages and intra-molecular H-bonding in wool are responsible for shaping and setting characteristics. In the presence of UV light, oxidative reactions are initiated and free radicals are formed, leading ultimately to grafting if monomers are present.

Equation 1.4. Grafting in the presence of UV light



$$CeO\text{-}H \xrightarrow{h\nu} CeO^{\cdot} + H^{\cdot}$$

$$CeO^{\cdot} + nM \rightarrow CeO\text{-}M_n\text{-}M^{\cdot}$$

CeO-H refers to cellulose.

1.5.3.2. Effect of monomer:

As with the nature of backbone, the reactivity of the monomer is also important in grafting. The reactivity of monomers depends upon the various factors, viz. polar and steric nature and swellability of backbone in the presence of the monomers and concentration of monomers.

1.5.3.3. Effect of solvent:

In grafting mechanisms, the solvent is the carrier by which monomers are transported to the vicinity of the backbone. The choice of the solvent depends upon several parameters, including the solubility of monomer in solvent, the swelling properties of the backbone; the miscibility of the solvents if more than one is used, the generation of free radical in the presence of the solventetc.

The solubility of the monomer depends on the nature of the solvent and the polymer, e.g. alcohols are useful solvents for grafting styrene [52- 54]. This is because alcohols can swell the backbone effectively and can dissolve the styrene so that the monomer can easily diffuse in the cellulosic structure. The extent of grafting, however, decreases progressively when the alcohol is changed from methanol to ethanol to isopropanol and to t-butanol, this decrease in grafting is due to the gradually decreased swelling properties of the alcohol, known to be corroborated by the bulkiness of the alcohol molecules.

1.5.3.4. Effect of initiator:

Apart from the radiation technique, all chemical grafting reactions require an initiator, and its nature, concentration, solubility as well as function need to be considered. There are various kinds of initiators: (Fe^{2+}–H_2O_2), AIBN, K2S2O8, etc. The nature of the initiator has a profound effect on grafting. For example, as described above, AIBN exhibits resonance stabilization. No such resonance stabilization exists with conventional peroxide initiators, and higher grafting yield should be obtained with peroxide initiators than with AIBN [55]. In another example, in the grafting of HEMA on cellulose, AIBN gives poor grafting and K2S2O8 is unsuitable as an initiator, since it degrades the cellulose chain.

1.5.3.5. Roles of additives on grafting:

Grafting yield or the extent of graft co-polymerization depends on the presence of additives such as metal ions, acids, and inorganic salts. Thus, the reaction between the monomer and the backbone must compete with any reactions between the monomer and additives. Although some additives may enhance the monomer/backbone reaction to augment the grafting efficiency, the reverse will be true if the reaction between the monomer and the additive is dominant [56-58].

1.5.3.6.Effect of temperature:

The temperature is one of the important factors that control the kinetics of graft co-polymerization. In general, grafting yield increases with increasing temperature, until a limit is attained. One factor in this can be faster monomeric diffusion processes in the backbone increases with increasing temperature, facilitating grafting[59]. In the case of grafting MMA on silk, the graft yield increases significantly with increasing temperature due to greater swelling of silk, and a corresponding enhanced rate of diffusion of the monomers in the vicinity of silk [60]. However, Sun et al. [59] explained this behavior as increased thermal decomposition rate of initiator and the initiator efficiency in producing free radicals on base polymer with increasing temperature, resulting in increased polymer macro radicals concentration, and thus enhanced the graft polymerization. Increasing temperature, initially enhancing the grafting yield,

facilitates the decomposition of peroxide. However, as reported by Maldas[61], the grafting yield subsequently decreases with an increase in temperature in case of acrylamide grafting on cellulose acetate. The initial increase in grafting is due to the decomposition of peroxides formed as a result of irradiation of the base polymer in air, making the requisite radicals available for grafting, and the subsequent decrease is due to the increased molecular motion with increased temperature, resulting in increased radical decay.

REFERENCES:

1. Robinson JR., LeeVHL. Controlled drug delivery: fundamentals and applications. 2ndEdn.,Marcel Dekker, Inc., NY, 352-384, 1987.
2. ChienYW. Novel drug delivery systems. 2ndEdn., Marcel Dekker, Inc., NY, 396- 431, 1992
3. Lachman L., Lieberman HA., KalingJL. The theory and practice of industrial pharmacy. 3rdEdn.,Varghese Publishing House, Bombay, 430-439, 1998.
4. AhmadA.,MurtazaG.,WaheedA.,NaeemAM. Salbutamol sulphate-ethylcellulosemicroparticles: formulation and in-vitro evaluation with emphasis on mathematical approaches. *DARU*, **17**: 209-216, 2009.
5. GwenJM., Sustained and controlled release drug delivery systems. In: Robinson JR, editor. Modern pharmaceutics. 2ndEdn., Marcel Dekker, Inc., NY, 253-267, 1996.
6. Thomas YR., Controlled release drug delivery system. In: Robinson JR, editor. The science and Practice of Pharmacy. 3rdEdn., Marcel Dekker, Inc., NY, 304-325, 2001.
7. Li VHK.,Robinson JR.,Lee VHL. Controlled drug delivery systems. 2ndEdn.,Marcel Dekker, Inc., NY, 325-334, 1987.
8. RobinsonJR.,EriksenSP. ECD-Based film coatings for controlled drug delivery. *J. Pharm. Sci*, **55**: 1254-1264, 1966.
9. Welling PG., Dobrinska MR., Robinson JR. Controlled drug delivery systems. 2ndEdn.,Marcel Dekker, Inc., NY, 365-384, 1987.
10. Jose GR., Kinam P. Oral Drug Delivery: Prospects and Challenges. *Drug Delivery Technology,***34**: 325-336, 2004.
11. Jantzen GM., Sustained and controlled release drug delivery systems. In: Robinson JR, editor. Modern pharmaceutics. 2ndEdn., Marcel Dekker, Inc., NY, 335-374, 1996.
12. Fick A., Poggendroffs K. Controlled porosity osmotic pump. *J.PharmSci Tech,***32**: 59-74, 1985.

13. Ghosh LK. Hand book of pharmaceutical technology. 1[st]Edn., CBS Publishers & Distributors, New Delhi, 59-67, 2002.
14. IgnatL. and Stanciu A., Handbook of Polymer Blends and Composites, Rapra Technology, 275-280, 2003.
15. Murugesh S. and Mandal B.K. A review on interpenetrating polymer network, International Journal Of Pharmacy And Pharmaceutical Sciences, vol.4, 1-7, 2012.
16. Kosmala J.D., Henthorn D.B. and Bernnon-Peppas, Biomaterials, vol. 21, 2019-2023, 2000.
17. Zohuriaan MJ. Advances in chitin and chitosan modification through graft copolymerization: A comprehensive review. *Iranian Polymer Journal*, **14**: 235–265, 2005.
18. SoppimathKS.,Aminabhavi TM., Dave AM., Kumbar SG., Rudzinski WE. Stimulus responsive smart hydrogels as novel drug delivery systems. *Int.J.Pharm*,**34**: 212-225, 2002.
19. Pepenzhik MA., Virnik AD., Rogovin ZA. Synthesis of graft cellulose copolymers and calcium salt of poly (acrylic acid). *VysokomolSoedinSer B*,**11**: 245–250, 1969.
20. Misra BN., Dogra R., Mehta IK. Grafting onto cellulose V Effect of complexing agents on Fenton's Reagent (Fe^{+2}–H_2O_2) initiated grafting of poly (ethyl acrylate). *J PolymSciPolymChem*, **18**: 749–752, 1980.
21. Mishra BN., MehtaIK.,Khetrapal RC. Grafting onto cellulose. VIII. Graft copolymerization of poly (ethylacrylate) onto cellulose by use of redox initiators. Comparison of initiator reactivities. *J PolymSciPolymChem*, **22**: 2767–2775, 1984.
22. PrasanthKVH.,Tharanathan RN. Studies on graft copolymerization of chitosan with synthetic monomers. *Carbohydrate Polymer*, **54(3)**: 43–51, 2003.
23. Xie W., Xu P., Liu WW. Preparation and antibacterial activity of a water-soluble chitosan derivative. *Carbohydrate Polymer*, **50**: 35–40, 2002.
24. Szwarc M. Living polymers. Their discovery, characterization and properties Part A. *J PolymSciPolymChem*, **36**: IX–XV, 1998.
25. Russell KE. Free radical graft polymerization and copolymerization at high temperatures. *ProgPolymSci*, **27**: 1007–1038, 2002.
26. Stehling UM., Malmstrom EE., Waymouth RM., Hawker CJ. Synthesis of poly (olefin) graft copolymers by a combination of metallocene and living free radical polymerization techniques. *Macromolecules*, **31**: 4396–4398, 1998.
27. Percec V., Barboiu B. 'Living' radical polymerization of styrene initiated by arenesulfonyl chlorides and CuI (bpy) n Cl. *Macromolecules*, **28**: 7970–7972, 1995.

28. Wang JS., Matyjaszewski K. Controlled ‘Living’ radical polymerization. Atom transfer radical polymerization in the presence of transition-metal complexes. *J Am ChemSoc*, **117**: 5614–5615, 1995.
29. Matyjaszewski K., Xia J. Atom transfer radical polymerization. *Chem Rev*, **101**: 2921–2990, 2001.
30. Matyjaszewski K. Transition metal catalysis in controlled radical polymerization: atom transfer radical polymerization. *ChemEurJ*, **5**: 3095–3102, 1999.
31. Coessens V., Pintauer T., Matyjaszewski K. Functional polymers by atom transfer radical polymerization. *ProgPolymSci*, **26**: 337–377, 2001.
32. Kato M., Kamigaito M., Sawamoto M., Higashimura T. Polymerization of methylmethacrylate with the carbon tetrachloride/dichlorotris (triphenylphosphine) ruthenium(II)/methylaluminumbis(2,6-di-tert-butylphenoxide) initiating system: possibility of living radical polymerization. *Macromolecules*,**28**: 1721–1723, 1995.
33. UflyandIE.,Ilchenko IA., Sheinker VN., Savostyanov VS. Polymers containing metal chelate units. VI. Post-graft polymerization of metal chelate monomers based on1-phenyl-4-methyl pent-4-ene-1, 3 dione. *ReactFunctPolym*, **17**: 289–296, 1992.
34. Bhattacharya A., Das A., De A. Structural influence on grafting of acrylamide based monomers on cellulose acetate. *Ind J Chem Tech*, **5**: 135–138, 1998.
35. Chen J., Iwata H., Maekawa Y., Yoshida M., Tsubokawa N. Grafting of polyethylene by g-radiation grafting onto conductive carbon black and application as novel gas and solute sensors. *Radiat Phys Chem*, **67(3–4)**: 397–401, 2003.
36. Marmey P., Porte MC., Baquey C. PVDF multifilament yarns grafted with polystyrene induced by g-irradiation: influence of the grafting parameters on the mechanical properties. *NuclInstrum Methods B*, **208**: 429–433, 2003.
37. Yamaki T., Asano M., Maekawa Y., Morita Y.,Suwa T., Chen J. Radiation grafting of styrene into cross-linked PTFE films and subsequent sulfonation for fuel cell applications. *Radiat Phys Chem*,**67**: 403–407, 2003.
38. Kaur I., Barsola R., Gupta A., Misra BN. Graft copolymerization of acrylonitrile and methacrylonitrile onto gelatin by mutual irradiation method. *J ApplPolymSci*, **54**: 1131–1139, 1994.
39. Kaur I., Misra BN., Chauhan MS., Chauhan S., Gupta A. Viscometric, conductometric and ultrasonic studies of gelatin-g-polyacrylamide composite. *J ApplPolymSci*, **59**: 389–397, 1996.

40. Kaur I., Misra BN., Barsola R., Singla K. Viscometric studies of starch-g-polyacrylamide composites. *J ApplPolymSci*, **47**: 1165–1174, 1993.
41. Basu S., Bhattacharya A., MondalPC.,Bhattacharyya SN. Spectroscopic evidence for grafting of N-vinyl carbazole on cellulose acetate film. *J PolymSci, PolymChem*, **32**: 2251–2255, 1994.
42. Aich S., Bhattacharya A., Basu S. Fluroscence polarization of N-vinyl carbazole on cellulose acetate film and electron transfer with 1,4 dicyanobenzene. *Radiat Phys Chem*, **50(4)**: 347–354, 1997.
43. Aich S., Sengupta T., Bhattacharya A, Basu S. Magnetic field effect on an exciplex between N-vinyl carbazole grafted on cellulose acetate film and 1,4 dicyanobenzene. *J PolymSciPolymChem*, **37**: 3910–3915, 1999.
44. BhattacharyyaSN.,Maldas D., Pandey VK. Radiation induced graft copolymerization of N-vinyl carbazole and methylmethacrylate onto cellulose acetate film. *J PolymSci*, **A24**: 2507–2515, 1986.
45. Bellobono IR., Calgari S., Leonari MC., Selli E., Paglia ED. Photochemical grafting of acrylated azo dyes onto polymeric surfaces. IV. Grafting of 4-(N-ethyl N-2-acryloxyethyl amino-40 nitroazobenzene onto cellulose. *Die AngewandteMakromolekurareChemie*, **100**: 135–146, 1981.
46. Kubota H., Suka IG., Kuroda S., Kondo T. Introduction of stimuli-responsive polymers into regenerated cellulose film by means of photo grafting. *EurPolym J*, **37**: 1367-1372, 2001.
47. Peng T.,Cheng YL.PNIPAAm and PMAA cografted porous PE membranes: living radical co-grafting mechanism and multi-stimuli responsive permeability. *Polymer*, **42(5)**: 2091–2100, 2001.
48. Uchida E., Uyama Y., Ikada YA. Novel method for graft polymerization onto poly (ethylene erephthalate) film surface by UV-irradiation without degassing. *J ApplPolymSci*, **41**: 677–687, 1990.
49. Wenzel A., Yamgishita H., Kitamoto D., Endo A., Haraya K., T. Nakane T. Effect of preparation condition of photo induced graft filling polymerized membranes on pervaporation performance. *J MembrSci*, **179**: 69–77, 2000.
50. Chen T., Kumar G., Harries MT., SmithPJ.,Payne GF. Enzymatic grafting of hexyloxyphenol onto chitosan to alter surface and rheological properties. *BiotechnolBioeng*, **70(5)**: 564–573, 2000.

51. Ng L-T,Garnett JL., Zilic E., Nguyen D. Effect of monomer structure on radiation grafting of charge transfer complexes to synthetic and naturally occurring polymers. *Radiat Phys Chem*, **62**: 89–98, 2001.
52. Dilli S., Garnett JL. Radiation induced reactions with cellulose. III. Kinetics of styrene copolymerization in methanol. *J ApplPolymSci*, **11(6)**: 859–870, 1967.
53. Yasukawa T., Sasaki Y., Murukami K. Kinetics of radiation induced grafting reactions. II. Cellulose acetate-styrene systems. *J PolymSciPolymChem*, **11(10)**: 2547–2556, 1973.
54. Bhattacharyya SN., Maldas D. Radiation induced graft copolymerization of mixtures of styrene and acrylamide onto cellulose acetate. I. Effect of solvents. *J PolymSciPolymChem*, **20**: 939–950, 1982.
55. Nishioka N., Matsumoto N., Kosai K. Homogeneous graft copolymerization of vinyl monomers onto cellulose in a dimethyl sufoxide-paraformaldehyde solvent system. II. Characterization of graft copolymers. *Polymer*, **15(2)**: 153–158, 1983.
56. ChappasWJ.,Silverman J. The effect of acid on the radiation induced grafting of styrene to polyethylene. *Radiat Phys Chem*, **14**: 847–852, 1979.
57. AssyNBEl. Effect of mineral and organic acids on radiation grafting of styrene onto polyethylene. *J ApplPolymSci*, **42**: 885–889, 1991.
58. Hoffman AS., Ratner BD. The radiation grafting of acrylamide to polymer substrate in the presence of cupric ion. I. A preliminary study. *Radiat Phys Chem*, **14**: 831–840, 1979.
59. Sun T., Xu P., Liu Q., Xue J., Xie W. Graft copolymerization of methacrylic acid onto carboxymethyl chitosan. *EurPolym J*, **39**: 189–192, 2003.
60. Samal S., Sahu G., Lenka S., Nayak PL. Photo induced graft copolymerization. XI. Graft copolymerization of methylmethacrylate onto silk using isoquinoline-sulphur dioxidecharge transfer complex as the initiator. *J ApplPolymSci*, **33(5)**:1853–1858, 1987.
61. Maldas D. Radiation induced grafting of styrene and acrylamide on cellulose acetate from a binary mixture. *Thesis*, University of Calcutta, p. 47, 1983.

CHAPTER: 2

NATURAL GUMSAND MUCILAGES

2. NATURAL GUMS AND MUCILAGES:

2.1. Introduction:

Nature has provided us with a wide variety of materials to help improve and sustain the health of all living beings either directly or indirectly. Gums and mucilages are widely used natural materials for conventional and novel drug delivery systems with the increasing interest in the use of polymers and excipients of natural origin; the pharmaceutical world has compliance to use most of them in their formulations. In the recent years the plant derived polymers have evoked tremendous interest due to their diverse pharmaceutical applications such as diluents, binder, disintegrants in tablets, thickeners in oral liquids, protective colloids in suspension, gelling agent in gels and bases in suppositories; they are also used in cosmetics, textiles, paints and paper making. These naturally available gums can be modified to obtain tailor-made materials for drug delivery systems allowing them to compete with the synthetic products that are commercially available. Demand for these substances is increasing constantly and new sources are being developed regularly. India due to its geographical and environmental variation has traditionally been a good source for such products amongst the Asian countries. Still large quantities of such products are being imported from Europe to meet the increasing demand.

Generally gums are considered to be pathological products formed following a mechanical injury to the plant part or an unfavourable condition, such as drought or by break down of cell walls whereas mucilages are metabolic products of the plants produced within the cell and/or produced without injuring the plants. Gums dissolve in water and are pathological products whereas mucilages are physiological products and form slimy masses with water [1].Acacia, tragacanth and guar gum are example of gum. Mucilages are found in different parts of the plant body for e.g. in the epidermal cells of leaves(senna), in seed coats(linseed and psyllium),roots(marshmellow),in barks(slippery elm) and middle lamellae(aloe)[2].Gums and mucilages are both plant hydrocolloides. They contain hydrophilic molecules which form viscous solutions and gel in contact with water.

2.2. Advantages of natural gum in pharmaceutical uses:

The followings are the advantages of the natural plant based polymers:-

1. They are biodegradable. Natural, biodegradable polymers are produced almost by all living organisms. They are truly renewable sources and have adverse effects neither on human health nor on environmental aspects.
2. They are highly biocompatible and non-toxic in nature. They are usually carbohydrate compounds composed of sugar monomers (monosaccharide).
3. They are cheaper than any other synthetic polymer as their production cost is low.
4. They are locally available.
5. Better patient tolerance and public acceptance. There is less chance of side-effects and adverse effects with the natural materials as compared to the synthetic ones.eg.PMMA, Povidone.
6. Most gums and mucilages are obtained from edible sources.

2.3. Disadvantages of natural polymers in pharmaceutical uses:

The disadvantages of natural gums are stated as follows:-

1. The main problem with the natural gums is that they are easily susceptible to microbial contamination. The equilibrium moisture content of natural gums and mucilages is generally 10% or more .Chemically they are carbohydrates and during their production they are subjected to different environmental condition; so there is a high chance for microbial contamination but this can be prevented by proper handling and proper use of preservatives.

2. Production of synthetic gums and mucilages are dependent on regional, seasonal and environmental factors whereas the synthetic gums are produced in a controlled manner using fixed amount of ingredients.

3. Uncontrolled rate of hydration. Due to differences in collection of natural gums at different times as well as from different regions, species and climatic condition there is a variation in the percentage composition of chemical constituents.

4. It has been noticed that with storage there is a decrease in viscosity. Generally the viscosity of natural gums and mucilages increase in contact with water because of their complex nature but the reverse happens on storage.

2.4. Disadvantages of synthetic polymers in pharmaceutical use:

The synthetic polymers have certain disadvantages such as high cost, toxicity, environmental pollution during synthesis, non-renewable sources, side effects, and poor patient compliance. Acute and chronic adverse effects (skin and eye-irritation) have been observed in workers handling the related substances methyl methacrylate and poly-(methyl methacrylate) (PMMA) [3].Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site produced by povidone. There is also evidence that povidone may accumulate in organs following intramuscular injections [4]. Acute oral toxicity studies in animals have indicated that carbomer-934P has a low oral toxicity at a dose of up to 8 g/kg. Carbomer dust is irritating to the eyes, mucous membranes and respiratory tract. So, gloves, eye protection and dust respirator are recommended during handling [5].Studies in rats have shown that 5% polyvinyl alcohol aqueous solution injected subcutaneously can cause anemia and can infiltrate various organs and tissues [6].Some disadvantages of biodegradable polymers used in tissue engineering applications are their poor biocompatibility, release of acidic degradation products, poor processing ability and rapid loss of mechanical properties during degradation. It has been shown that poly-glycolides, polylactides and their co-polymers have an acceptable biocompatibility but exhibit systemic or local reactions due to acidic degradation products. An initial mild inflammatory response has been reported when using poly-(propylene fumarate) in rat implant studies [7].

2.5. Classification of natural gums and mucilages: [8-13]

Gums and mucilages are present in high quantities in a variety of plants, animals, seaweeds, fungi and other microbial sources, where they perform a number of structural and metabolic functions; plant sources provide the largest amount. The different available gums and mucilages can be classified as follows:

2.5.1. According to charge:

- **Non-ionic seed gums**: guar, locust bean, tamarind, xanthan, amylose, arabinans, cellulose, and galactomannans.
- **Anionic gums**: Arabic, karaya, tragacanth, gellan, agar, algin, carrageenans, pectic acid.

2.5.2. According to source:

- **Marine origin/ Algal (seaweed) gums:** agar, carrageenans, alginic acid, laminarin.
- **Plant origin:**
  (1) **Shrubs/Tree exudates**—Gum arabica, Gum ghatti, Gum karaya, Gum tragacanth, Khaya and Albizia gums.
  (2) **Seed gums**—Guar gum, Locust bean gum, Starch, Amylose, Cellulose**.**
  (3) **Extracts**—Pectin, Larch gum.
  (4) **Tuber and roots**—Potato starch.
- **Animal origin:** Chitin and Chitosan, Chondroitin sulphate, Hyaluronic acid.
- **Microbial origin (bacterial and fungal):** Xanthan, Dextran, Curdian, Pullulan, Zanflo, Emulsan, Baker'syeast, Glycan, Schizophyllan, Lentinan, Krestin, Scleroglucan.

2.5.3. Semi-synthetic:

- **Starch derivatives**—Hetastarch, Starch acetate, Starch phosphates.
- **Cellulose derivatives**—Carboxy methyl cellulose (CMC), Hydroxyethylcellulose, Hydroxypropyl methylcellulose (HPMC), Methylcellulose (MC), Microcrystalline cellulose (MCC).

2.5.4. According to shape:

- **Linear:A**lgins, Amylose, Cellulose, Pectin.
- **Branched:**
  (1) **Short branches**— Xanthan, Xylan,Galactomanan.
  (2) **Branch-on-branch**— Amylopectin, Gumarabic, Tragacanth.

2.5.5. According to manomeric units in chemical structure:

- **Homoglycans**— Amylose, Arabinans, Cellulose
- **Di-heteroglycans**—Algins, Carrageenans, Galactomannans
- **Tri-heteroglycans**—Arabinoxylans, Gellan, Xanthan
- **Tetra-heteroglycans**— Gum arabic, Psyllium seed gum
- **Penta-heteroglycans**—Ghatti gum, Tragacanth

2.6. Modification of natural gums and mucilage:

It should be noted that many ‘‘old’’ materials compete successfully with each other today after almost a century of efforts to replace them. It is the usual balance of economics and performance that determines the commercial realities. Natural gums have been modified to overcome certain drawbacks, like uncontrolled rate of hydration, thickening, drop in viscosity on storage, and microbial contamination [14].Since the implementation of polymeric materials in the field of pharmaceutical technology, numerous attempts have been made to modify their physical and chemical properties, and thus, their potential applicability in various areas of drug formulation. Various methods are available to modify the state of molecular interaction between polymers. Basically, two methods are available as the physical method and chemical method. Physical method—a molecular interaction between polymers can be achieved by exposure to dry heat, saturated steam, microwave technology, UV [15,16], and gamma radiation [17]. Chemical method—polymers are treated with chemicals like aldehydes, epichlorhydrin, borax or glutaraldehyde. Temperature is one of the most favourable methods of cross-linking because it avoids both the application of harsh chemical materials for large-scale production and the diversity of equipment and methods used in their application [18].

2.7.7. Conclusion:

Polysaccharides are the choice of materials among the hydrophilic polymers used because they are nontoxic and acceptable by the regulating authorities. A novel polysaccharide named tamarind seed gumis now being used as an excipient in the hydrophilic drug delivery system because of its properties which include non-carcinogenicity, mucoadhesivity, biocompatibility, high drug holding capacity and high thermal stability. There is a need to carry out further research on the efficacy of TSP as an excipient in pharmaceutical formulations.

2.8. REFERENCES:

1. Kottke KM., Edward MR. Tablet Dosage Forms. In: Banker GS, Rhodes CT, Ed. Modern Pharmaceutics. New York, Marcel Dekker, Inc, 287-333, 2002.
2. Aslam A., Parrott E. Effect of aging on some physical properties of hydrochlorothiazide tablets. *J Pharm. Sci.,***60:** 263-266, 1971.

3. Chang RK., Shukla AJ. Polymethacrylates. In: Raymond CR, Paul JS, Paul JW, Ed. Handbook of Pharmaceutical Excipients. The Pharmaceutical Press and The American Pharmaceutical Association, 462-468, 2003.
4. Hizawa K., Otsuka H., Inaba H.Subcutaneous pseudosarcomatous PVP granuloma. *Am. J. Surg. Path*., **8:** 393-398, 1984.
5. KolenJJ.,McGinity JW., Wilber WR. Carbomer–934P. In: Raymond CR, Paul JS, Paul JW, Ed. Handbook of Pharmaceutical Excipients. The Pharmaceutical Press and The American Pharmaceutical Association, 89-92, 2003.
6. Weller PJ., Owen SC. Polyvinyl alcohol. In: Raymond CR, Paul JS, Paul JW, ed. Handbook of Pharmaceutical Excipients. The Pharmaceutical Press and The American Pharmaceutical Association, 491-492, 2003.
7. Khaled Al-T., Jagdish S. Recent patents on drug delivery and formulation. **1:** 65-67, 2007.
8. Kokate CK., Purohit AP., Gokhale SB. Pharmacognosy. Pune, India, NiraliPrakashan, 50-52, 2006.
9. Rangari VD. Pharmacognosy&Phytochemistry.Nashik, India, Career Publication, 45-49, 2006.
10. Wallis TE. Text Book of Pharmacognosy.New Delhi, India, C B S Publishers and Distributors, 69-70, 2004.
11. Mohammed A. Text Book of Pharmacognosy.New Delhi, India, C B S Publishers and Distributors, 101-103, 2005.
12. Ansari SH. Essential of Pharmacognosy. New Delhi, India, Birla Publications Pvt. Ltd., 20-25, 2006.
13. Venkata RE. Chemical and biological aspects of selected polysaccharides.*Indian J. Pharm. Sci.,***54:** 90-97, 1992.
14. Collet J., MoretonC. Modified-release peroral dosage forms. In: M. E. Aulton, ed. Pharmaceutics: The Science of Dosage Form Design. Churchill Livingstone, U. K. 2002:289-305.
15. Vatanasuchart N., Naivikul O., Charoenrein S. Molecular properties of cassava starch modified with different UV irradiatons to enhance baking expansion. *Carbohy.Polym*, **61**: 80-87, 2005.

16. Khan MA., Bhattacharia SK., Kader MA. Preparation and characterization of ultra violet (UV) radiaton cured bio-degradable films of sago starch/PVA blend. *Carbohy.Polym*, **63**:500-506, 2006.
17. Desai KG., Park HJ. Study of gamma-irradiation: effects on chitosan microparticles. *Drug Delivery*, **13**:39-50, 2006.
18. Micard V., Belamri R., Morel M., Guilbert S. Properties of chemically and physically treated wheat gluten films. *J. Agric. Food Chem*, **48**:2948-2953, 2000.

CHAPTER: 3

LITERATURE REVIEW

3. LITERATURE REVIEW:

3.1. INTRODUCTION:

Attempts to sustaining the release of drug by using naturally obtained polymer has started around two decades ago. Several researchers throughout the world have published their different approaches in this purpose sometimes by using natural gum or sometimes by using natural grafted co-polymers to extend the drug release time. The tremendous orientation of Pharma world towards these naturally derived polymers has become a subject of increasing interest. So here is a brief review of literature in this context.

- Sorour. M*et al*[1]Grafted monomer onto polymer backbone is one of the effective and accessible methods for thechemical modification of polysaccharides. Grafting of acrylamide (AAm) onto polysaccharides blend (PsB)composed of starch, chitosan and alginate has been carried out using potassium persulfate (KPS) as aninitiator. The kinetics of the grafting polymerization also has been studied. The grafting parameters havebeen evaluated by changing the initial concentrations of AAm from 8 to 16 g, PsB from 6 to 14 g andKPS from 0.2 to 1 g. Evidence of grafting has been obtained from FTIR, XRD and TGA. The kinetics of thegrafting polymerization also has been studied. The grafting rate equation of the produced hydrogel (PsB-g-AAm) hydrogel has been expressed by: Rg = k[AAm] [PsB]0.5[KPS]0.5. The grafting rate is a first orderdependence to [AAm] initial concentration and square root to [PsB] and [KPS] initial concentrations inthe used concentrations range.
- Deogade. U.M*et al*[2]published a review paper highlighting the main reasons behind the use of natural gums in sustained release dosage form. They have given detailed information about isolation, purification, characterization and standardization of natural gum. Grafting of natural gums to prepare tailor-made much advanced polymers has been given importance and their application has also been mentioned.
- Kaity. S*et al*[3]synthesized acrylamide grafted gellan gum in microwave assisted free radical polymerization method using Cerric ammonium nitrate as redox-indicator. A series of graft copolymers, varying in amount of acrylamide, CAN and microwave irradiation time was prepared. The modified gum was extracted with 20% (v/v) methanol to remove the homopolymer formed during polymerization reaction. These graft copolymers were characterized by FTIR, 13C NMR, CHN, SEM, rheological studies and DSC studies. Comparison of grafting parameters such as grafting

efficiency, percentage grafting and percentage conversion were carried out among various series of graft copolymers and then correlating it with elemental analysis, DSC, viscosity results. The acute oral toxicity study of grated gum was evaluated as per OECD guideline. Tablets were prepared by incorporating anti-diabetic drug metformin hydrochloride (MTF) in grafted gum along with excipients. In vitro studies were performed on prepared tablet formulations showing release up to 8 h.

- Tsubokawa. N*et al*[4]performed the grafting of polymers onto carbon black surface by the direct condensation of surface carboxyl groups with functional polymers in the presence of condensing agent was investigated. It was found that the grafting reaction of surface carboxyl groups with functional polymers having hydroxyl or amino groups readily proceeded in the presence of N,N'-dicyclohexyylcarbodiimide (DCC) as a condensing agent at 30°C and the corresponding polymers were grafted onto carbon black surface with ester or amide bonds: the percentage of grafting of diol-type poly(propylene oxide) (PPG: Mn = 2.0 x 103) and diamine-type poly(dimethylsiloxane) (SDA: Mn = 1.7 x 103) was determined to be 24.5 and 40.2%, respectively. No grafting reaction onto carbon black surface, however, was observed in the absence of DCC. The percentage of grafting increased with increasing carboxyl group content of carbon black and increasing reaction temperature. The percentage of grafting and the number of grafted polymer chains decreased with increasing molecular weight of functional polymers, because the reaction of surface carboql groups was inhibited by the already grafted polymer chains. Polymer-grafted carbon black gave a stable colloidal dispersion in a good solvent for the grafted polymer.
- Moura. E*et al*[5]performed various studies to find out the influence of physical parameters on mutual polymer grafting by electron beam radiation. In this work, mutual radiation grafting was performed and physical parameters like vacuum, pressure of air or inert gas and temperature were studied to verify their influences on styrene grafting onto hydrocarbon and fluorinated polymers. We observed that vacuum and temperature are determinant parameters to be considered in mutual radiation grafting besides the backbone polymer, monomer molecules and solvent. The optimization of these parameters for a specific polymer/monomer system contributes to a good performance and allows mutual radiation grafting to be an attractive technique even if it is performed in commercial accelerators.

- Wei. G*et al*[6]performed grafting of polymers onto vapor grown carbon fiber surface by ligand-exchange reaction of ferrocene moieties of polymer with aromatic rings of the wall-surface. They worked to improve the dispersibility of vapor grown carbon fiber (VGCF) in solvents, the grafting of copolymer containing vinyl ferrocene (VFE) onto the surface by ligand-exchange reaction between ferrocene moieties of the copolymer and polycondensed aromatic rings of VGCF was investigated. The copolymer containing VFE was prepared by the radical copolymerization of VFE with methyl methacrylate (MMA) using 2, 20-azo-bis-iso-butyro-nitrole as an initiator. It was found that by heating of VGCF with poly (VFE-co-MMA) in the presence of AlCl3 and Al powder, the copolymer was grafted onto the wall-surface: the percentage of grafting reached to 57.5%. It is considered that the copolymer was grafted onto VGCF surface by ligand-exchange reaction between ferrocene moieties of the copolymer and polycondensed aromatic rings of VGCF. In addition, carboxyl groups were successfully introduced onto VGCF wall-surface by the ligand-exchange reaction of 1,10- dicarboxyferrocene with VGCF in the presence of AlCl3 and Al powder. The carboxyl groups on VGCF were reacted with hydroxylterminated polymers to give the corresponding polymer-grafted VGCF. The polymer-grafted VGCF gave a stable colloidal dispersion in solvents for grafted polymer. The electric properties of composite prepared from polymer-grafted VGCF in solvent vapor were investigated.
- Pandey. P.K*et al*[7]performed graft copolymerization of acrylic acid onto guar gum initiated by vanadium (V)–mercaptosuccinic acid redox pair. Guar gum was modified by graft copolymerization with acrylic acid in aqueous medium using vanadium (V)–mercaptosuccinic acid redox system. The optimum reaction conditions affording maximum grafting ratio, efficiency, add on and conversion have been determined. The grafting parameters have been found to increase with increase in vanadium (V) concentration upto 1.0×10^{-2}mol dm^{-3}, but these parameters decrease on further increasing the vanadium (V) concentration. On increasing the mercaptosuccinic acid concentration from 1.0×10^{-2} to 4.0×10^{-2}mol dm^{-3} grafting ratio, efficiency and add on increase up to 2.0×10^{-2}mol dm^{-3} but decrease with further increase in mercaptosuccinic acid concentration. On varying the acrylic acid concentration from 5.0×10^{-2} to 30.0×10^{-2}mol dm^{-3}, maximum grafting ratio, efficiency and add on have been obtained at 20.0×10^{-2}mol dm^{-3}. The grafting ratio, add on and conversion

increase, on increasing the H^+ ion concentration from 1.5×10^{-1} to 6.0×10^{-1}mol dm^{-3}. On increasing the guar gum concentration the grafting parameters increase. The grafting ratio, add on and conversion have been found to increase with time period while efficiency started decreasing after 120 min. It has been observed that %G increases on increasing the temperature up to 35^{-C}. The graft copolymer has been characterized by IR spectroscopy and thermogravimetric analysis.

- Arasawa. H*et al*[8]concentrated on grafting of zwitterion-type polymers onto silica gel surface and their properties. To immobilize zwitterion moiety onto silica gel surface, the grafting of zwitterion-type polymer, poly[3-diethyl(methyl-methacryloylethyl)ammonium propanesulfonate], polyDAEMA$^+$ $(SO3)^-$, onto the surface was investigated. The grafting of the zwitterion-type polymer onto silica gel surface was successfully achieved by the treatment of poly[2-dimethylamino)ethyl methacrylate] (polyDAEMA)-grafted silica gel, which was prepared by the graft polymerization of DAEMA initiated by azo groups introduced onto the surface, with 1,3-propane sultone; the percentage of polyDAEMAþ(SO3)_ grafting was determined to be 144.3%. However, the reaction of dimethyl amino groups of grafted polymer with 1,3-propane sultone incompletely proceeded. The grafting of the zwitterion-type polymer (polyDAEMA$^+$$(SO3)^-$) onto silica gel surface was also successfully achieved by the photopolymerization of DAEMA$^+$$(SO3)^-$ initiated by azo groups introduced onto the surface: the percentage of polyDAEMA$^+$$(SO3)^-$ grafting was determined to be 54.3%. The grafting of the zwitterion-type polymer onto the surface was confirmed by infrared spectra and SEM aspect of the polymer-grafted silica gel. It was found that the zwitterion-type polymer-grafted silica gel was applicable to stationary phase for ion chromatography.
- Osemeahon. S.A*et al*[9]developed sodium alginate and konkoli gum grafted polyacrylamide blend membrane. The effect of graft reaction conditions on the percentage graft yield in the graft copolymerization was investigated. It was observed that grafting parameters such as acrylamide (AM), cerric ammonium nitrate (CAN), “konkoli” gum (KG), temperature and reaction time have remarkable influence on the percentage graft yield of the graft copolymer. The percentage graft yield initially increased and then decreased for all the parameters investigated. Optimum percentage graft yield of 83, 85, 86, 84 and 84 were obtained by varying AM, CAN, temperature,

reaction time and KG, respectively. This result present the optimum grafting conditions required for copolymerization of AM onto KG.

- Varshosaz. J*et al*[11]developed matrix sustained release tablets of highly water-soluble tramadol HCl using natural gums (xanthan [X gum] and guar [G gum]) as cost-effective, nontoxic, easily available, and suitable hydrophilic matrix systems compared with the extensively investigated hydrophilic matrices (i.e., hydroxypropyl methylcellulose [HPMC]/carboxymethyl cellulose [CMC] with respect to in vitro drug release rate) and hydration rate of the polymers. Matrix tablets of tramadol (dose 100 mg) were produced by direct compression method. Different ratios of 100:0, 80:20, 60:40, 20:80, 0:100 of G gum (or X): HPMC, X gum: G gum, and triple mixture of these polymers (G gum, X gum HPMC) were applied. After evaluation of physical characteristics of tablets, the dissolution test was performed in thePhosphate buffer media (pH 7.4) up to 8 hours. Tablets with only X had the highest mean dissolution time (MDT), the least dissolution efficiency (DE8 %), and released the drug following a zero-order model via swelling, diffusion, and erosion mechanisms. Guar gum alone could not efficiently control the drug release, while X and all combinations of natural gums with HPMC could retard tramadol HCl release. However, according to the similarity factor (f2), pureHPMC and H8G2 were the most similar formulations to Topalgic-LP as the reference standard.
- Sa. B. et al [12] developed interpenetrating network matrix tablets of diltiazem-HCl (DTZ) by wet granulation method using polyacrylamide-grafted-sodium alginate (PAam-g-SAL) co-polymer and sodium alginate (SAL) for sustained release of the drug. Formulation of IPN structure was examined using FTIR spectroscopy, and compatibility of the drug with the polymers was evaluated through FTIR, DSC, and XRD analyses. The effect of co-polymer/SAL ratios, drug load, and total polymer/calcium gluconate (CG) ratios on drug release in acidic and phosphate buffer solutions was investigated. The release of drug was controlled by the relative magnitude of swelling capacity of IPN matrix and viscosity of the gel formed following dissolution of the polymers. The swelling capacity of the matrix was governed by the formation of calcium alginate gel structure and the rigidity imparted by the co-polymer. The results indicated that IPN matrix tablets of PAam-g-SAL and SAL could be used for sustained release of DTZ.

3.2. REFERENCES:

1. Sorour M., Sayed ME., MoneemNAEl., Talaat H., Shaalan H., MarsafySEl. Free radical grafting kinetics of acrylamide onto a blend ofstarch/chitosan/alginate.*Carbohydrate Polymers*, **98**: 460-464, 2013.
2. Deogade UM., Deshmukh VN.,Sakarkar DM. Natural gums and mucilage in NDDS: Application and recent approaches. *International Journal of PharmTech Research*,**4**(**2**):799-814, 2012.
3. Vijan V., Kaity S., Biswas S., Isaac J., Ghosh A. Microwave assisted synthesis and characterization of acrylamide grafted gellan, application in drug delivery. *Carbohydrate Polymers*, **90**: 496– 506, 2012.
4. Tsubokawa N., Hosoya M., Kurumada J.Grafting reaction of surface carboxyl groups on carbon black with polymers having terminal hydroxyl or amino groups using N, N-/diclohexylcarbodiimide as a condensing agent. *Reactive & Functional Polymers*, **27**: 75-81, 1995.
5. Moura E., Somessari ESR., Silveira CG., Paes HA., Souza CA., FernandesW., ManzoliJE., Geraldon ABC. Influence of physical parameters on mutual polymer grafting by electron beam irradiation. *Radiation Physics and Chemistry*,**80**: 175–181, 2011.
6. Wei G., Saitoh S.,Saitoh H., Fujiki K., Yamauchi T., Tsubokawa N. Grafting of polymers on to vapor grown carbon fibres surface by ligand exchange reaction of ferrocene moieties of polymer with polycondensed aromatic rings of the wall-surface. *Polymer*, **45**: 8723–8730, 2004.
7. Pandey PK., Srivastava A., Tripathy J., Behari K. Graft copolymerization of acrylic acid on to guar gum initiated by vanadium (V)-mercapto succinic acid redox pair. *Carbohydrate Polymers*,**65**: 414–420, 2006.
8. Arasawa H., Odawara C., Yokoyama R., Saitoh H., Yamauchia T., Tsubokawa N. Grafting of zwitterions-type polymers on to silica gel surface and their properties. *Reactive & Functional Polymers*, **61**: 153–161, 2004.
9. Osemeahon SA., BarminasTJ.,Aliyu BA., Nkafamiya II. Development of sodium alginate and konkoli gum grafted polyacrylamide blend memebrane: optimization of grafting condition.*African Journal of Biotechnology*, **7** (**9**):1309-1313, 2008.

10. Sadeghi M., Ghasemi N., Soleimani F. Optimization of synthetic condition of a novel graft copolymer based on alginate. *European Journal of Scientific Research*,**4**: 587-597, 2011.
11. Varshosaz J., Tavakoli N., Kheirolahi F. Use of Hydrophilic Natural Gums in Formulation of Sustained-release Matrix Tablets of Tramadol Hydrochloride. *AAPS PharmSciTech*,**7** (**1**): E168-E174, 2006.
12. Sa B., Mandal S., Basu S. K. Ca^{2+} Ion Cross-linked Interpenetrating Network Matrix Tablets of Polyacrylamide-Grafted-Sodium Alginate and Sodium Alginate for Sustained Release of Diltiazem Hydrochloride. *Carbohydrate Polymers, 82***.**867-873, 2010.

CHAPTER: 4

DRUG ANDEXCIPIENTS PROFILE

4.1. DRUG PROFILE[1-3]:

4.1.1. Monograph of Diclofenac sodium:

Chemical name: Sodium 2[(2,6-dichlorophenyl)-amino] phenyl acetate.

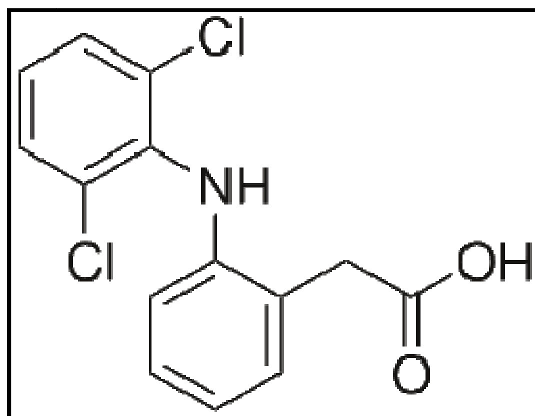


Figure 4.1:Structure of Diclofenac sodium

Molecular weight: 318.13.

Category: Analgesic, anti-inflammatory.

Dose: Orally or by intramuscular injection, 25 to 75 mg.

Description: White to slightly yellowish crystalline powder; slightly hygroscopic.

Solubility: Free soluble in methanol; soluble in ethanol (95%); sparingly soluble in water and in water and in glacial acetic acid; practically insoluble in ether, in chloroform and in toluene.

Storage: Store in well-closed, light-resistant containers.

Standards:

Diclofenac Sodium contains not less than 98.5 per cent and not more than 101.0 per cent of $C_{14} H_{10} N NaO_2$, calculated with reference to the dried substance.

Identification:

A: The infra-red absorption spectrum, is concordant with the reference spectrum of diclofenac sodium or with the spectrum obtained from diclofenac sodium RS.

B: To 1ml of a 0.4% w/v solution in methanol add 1ml of nitric acid; a dark red Color develops.

C: A 1% w/v solution gives the reaction of sodium salts.

D: Melts at about 280°, with decomposition.

pH: Between 6.5 and 8.5, determined on a 1% w/v solution.

Clarity and Color of solution: A 5% w/v solution in methanol is clear, and more intensely Colored than reference solution.

Light absorption: Absorbance of a 5% w/v solution in methanol at about 440nm, not more than 0.050.

Heavy metals: Not more than 20 ppm, determined on 1g by Method B, and using 2.0ml of lead standard solution (10ppm Pb).

Loss on drying: Not more than 0.5% determined on 1 g by drying in an oven at 105 for 3 hours.

Assay: Weigh accurately about 0.2 g, dissolve in 50 ml of anhydrous glacial acetic acid and carry out the Method A for non-aqueous titration, determining the end-point potentiometrically. Perform a blank determination and make any necessary correction. Each ml of 0.1 M perchloric acid is equivalent to 0.03181 g of $C_{14}H_{10}C_{l2}NNaO_2$.

4.1.2. Mechanism of Action:

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID). In pharmacologic studies, diclofenac has shown anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity. Prostaglandins play a major role in causing inflammation, pain and fever. Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those reached in humans.

4.1.3. Pharmacodynamic Effect:

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac sodium elicit a clinical response characterized by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function. In post-traumatic and post-operative inflammatory conditions, diclofenac sodium relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema. Diclofenac sodium has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin. In primary dysmenorrhoea, diclofenac sodium is capable of relieving the pain and reducing the extent of bleeding

4.1.4. Pharmacokinetics:

Absorption:

Diclofenac is completely absorbed from the gastro-resistant tablets after their passage through the stomach. Although absorption is rapid, its onset may be delayed due to the gastro-resistant coating of the tablet. Mean peak plasma concentrations of 1.5 micrograms/mL (5 micromol/L) are attained on average 2 hours after ingestion of one tablet of 50 mg. The amount absorbed is linearly related to the size of the dose. The passage of a tablet through the stomach is slower when ingested with or after a meal than when it is taken before a meal, but the amount of diclofenac absorbed remains the same. Since about half of diclofenac is metabolized during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) following oral or rectal administration is about half that following an equivalent parenteral dose.

Pharmacokinetic behavior does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed. The plasma concentrations attained in children given equivalent doses (mg/kg body weight) are similar to those obtained in adults.

Distribution:

99.7% of diclofenac is bound to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12 to 0.17 L/kg. Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4hours after peak plasma values have been

attained. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma values, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours.

Biotransformation:

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-,4'-hydroxy-,5-hydroxy-,4',5-dihydroxy-and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much smaller extent than diclofenac.

Elimination:

Total systemic clearance of diclofenac from plasma is 263 ±56 mL/min (mean value ±SD).The terminal half-life in plasma is 1 to 2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac has a much longer plasma half-life. However, this metabolite is virtually inactive. About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

4.1.6. Indication:

It is used to treat –

- ✓ Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism.
- ✓ Acute attacks of gout.
- ✓ Painful post-traumatic and post-operative inflammation and swelling.
- ✓ Primary dysmenorrhoea.

4.1.7. Recommended Dosage:

- ✓ **Adults**

The recommended initial daily dose is 100 to 150 mg. In milder cases, as well as for long term therapy, 75 to 100 mg daily is usually sufficient. The total daily dose should generally be divided into 2 to 3 doses. To suppress nocturnal pain and morning stiffness, treatment with tablets during the day can be supplemented by the administration of a suppository at bedtime (up to a total maximum daily dose of 150 mg). In primary dysmenorrhoea, the daily dose should be individually adjusted and is generally 50 to 150 mg. A dose of 50 to 100 mg should be given initially and, if necessary, increased over the course of several menstrual cycles up to a maximum of 200 mg/day. Treatment should be started on appearance of the first symptoms and, depending on the symptoms, continued for a few days.

- ✓ **Children and adolescents**

Children aged 1 year or over and adolescents should be given 0.5 to 2 mg/kg body weight daily in 2 to 3 divided doses, depending on the severity of the disorder. For treatment of juvenile rheumatoid arthritis, the daily dose can be raised up to a maximum of 3 mg/kg daily, given in divided doses. The maximum daily dose of 150 mg should not be exceeded. Because of their dosage strength, Diclofenac sodium Enteric Coated Tablet 50mg are not recommended for use in children and adolescents below 14 years of age; Diclofenac Sodium Enteric Coated Tablet 25mg could be used in these patients.

4.1.8. Mode of administration: Oral

4.1.9. Contraindications:

- ✓ Known hypersensitivity to the active substance or to any of the excipients.
- ✓ Active gastric or intestinal ulcer, bleeding or perforation.
- ✓ Last trimester of pregnancy.
- ✓ Severe hepatic, renal or cardiac failure.

- ✓ Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac sodium is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

4.1.10.Warnings and precautions:

4.1.10.1. Warning:

- ✓ **Risk of gastrointestinal (GI) ulceration, bleeding and perforation with NSAID:**

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms. Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug. Like other NSAIDs,diclofenac sodium may mask the signs and symptoms of infection due to its pharmacodynamics properties.The concomitant use of diclofenac sodium with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

- ✓ **Pre-existing asthma:**

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma

exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke'soedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

- ✓ **Gastrointestinal effects**

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose. Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin or other medicinal products likely to increase gastrointestinal risk. Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors. Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated.

- ✓ **Hepatic effects**

Close medical surveillance is required when prescribing diclofenac sodium to patients with impaired hepatic function, as their condition may be exacerbated. As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac sodium, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), diclofenac sodium should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms. Caution is called for when using diclofenac sodium in patients with hepatic porphyria, since it may trigger an attack.

- ✓ **Renal effects**

As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac particular caution is called for in patients with impaired cardiac or renal

function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery.Monitoring of renal function is recommended as a precautionary measure when using diclofenac sodium in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

- ✓ **Haematological effects**

During prolonged treatment with diclofenac sodium, as with other NSAIDs, monitoring of the blood count is recommended. Like other NSAIDs, diclofenac sodium may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored. Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking diclofenac sodium should refrain from driving or using machines.

4.1.10.2. Precaution:

Severe cutaneous reactions, including Stevens -Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), have been reported with diclofenac sodium. Patients treated with diclofenac sodium should be closely monitored for signs of hypersensitivity reactions. Discontinue diclofenac sodium immediately if rash occurs.

4.1.11. Interactions with Other Medicaments:

The following interactions include those observed with diclofenac sodium enteric-coated tablets and/or other pharmaceutical forms of diclofenac.

- ✓ **Lithium:** If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.
- ✓ **Digoxin:** If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.
- ✓ **Diuretics and antihypertensive agents:** Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive

effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently.

- ✓ **Other NSAIDs and corticosteroids:** Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects.
- ✓ **Anticoagulants and anti-platelet agents:** Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.
- ✓ **Selective serotonin reuptake inhibitors (SSRIs):** Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding.
- ✓ **Antidiabetics:** Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.
- ✓ **Methotrexate:** Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.
- ✓ **Ciclosporin:** Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

- ✓ **Quinolone antibacterials:** There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.
- ✓ **Potent CYP2C9 inhibitors:** Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.
- ✓ **Phenytoin:** When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

4.1.12. Statement on usage during pregnancy and lactation:

- ✓ **Pregnancy:** The use of diclofenac in pregnant women has not been studied. Therefore, diclofenac sodium should not be used during the first two trimesters of pregnancy unless the potential benefit to the mother outweights the risk to the foetus. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductusarteriosus. Animal studies have not shown any directly or indirectly harmful effects on pregnancy, embryonal/foetal development, parturition or postnatal development.
- ✓ **Lactation:** Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac sodium should not be administered during breast feeding in order to avoid undesirable effects in the infant.
- ✓ **Fertility:** As with other NSAIDs, the use of diclofenac sodium may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac sodium should be considered.

4.1.13. Adverse Effects / Undesirable Effects:

- ✓ **Dermatological disorders:**

  Common: Rash.

  Rare: Urticaria.

- **Immune system disorders:**

  Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).

- **Nervous system disorders:**

  Common: Headache, dizziness.

  Rare: Somnolence.

- **Respiratory, thoracic and mediastinal disorders:**

  Rare: Asthma (including dyspnoea).

  .

- **Gastrointestinal disorders:**

  Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.

  Rare: Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoeahaemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation).

- **Hepatobiliary disorders:**

  Common: Transaminases increased.

  Rare: Hepatitis, jaundice, liver disorder.

- **Renal and urinary disorders:**

  Rare: Oedema

  .

4.1.14. Overdose and treatment:

- **Symptoms:**

  There is no typical clinical picture resulting from diclofenacoverdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

- ✓ **Therapeutic measures:**

  Management of acute poisoning with NSAIDs, including diclofenac essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression. Special measures such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism. Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life threatening overdose.

4.2. EXCIPIENTS PROFILE:

4.2.1. GELLAN GUM: [4]

Gellangum is an anionic,high molecular weight, deacetylatedexocellular polysaccharide gum produced by a pure culture of Pseudomonus elodea as a fermentation product, It has a tetrasaccharide repeating unit of one α-rhamnose, β- D-glucuronic acid and two β-D-glucose residues. The production organism is an aerobic, gram negative bacteria which has been very well characterized and demonstrated to be non-pathogenic

Gellangum has the characteristic property of temperature dependent and cation- induced gelation. The gelation involves the formation of double helical junction zones followed by a gellangumregation of the double helical segments to form a three dimensional network by complexation with cations and hydrogen bonding with water.

The native polysaccharide is partially esterified with L-glycerate and acetate but the commercial product Gelrite has been completely de-esterified by alkali treatment. The exact molecular formula of gellan gum may vary slightly depending on the degree to which the glucuronic acid is neutralized by various salts.

The glucuronic acid is neutralized in presence of potassium, calcium and magnesium ions. The relative concentrations of these ions control the physical properties of the gum matter such as gel strength, melting point and setting point.

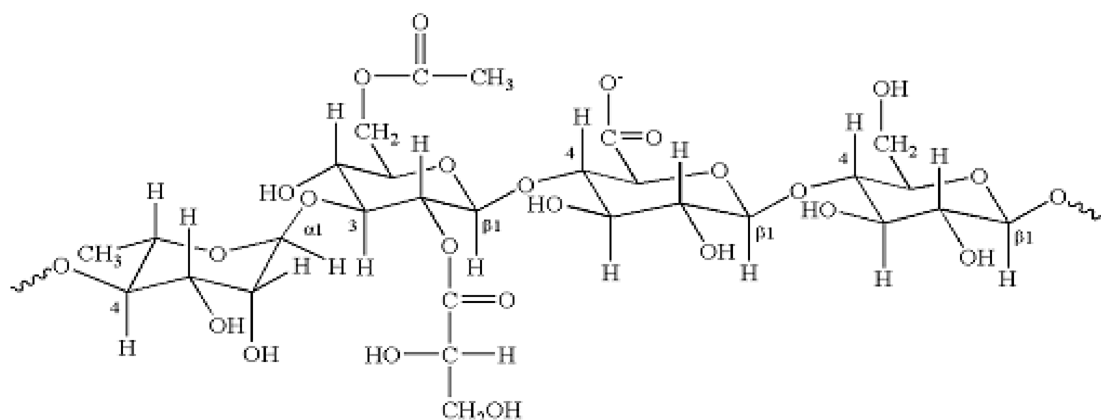


Figure 4.2. The structure of gellan gum

PHYSICAL AND CHEMICAL CHARACTERISTICS

Gellan gum has an outstanding flavor release, high gel strength, excellent stability, process flexibility and tolerance and high clarity. It is an excellent film former, heat and pH stable (pH 3.5-10) thermally reversible gel.

Appearence: Off white powder

Formula weight: 70,000 daltons with 95% 500,000 daltons

Bulk Density: 836kg/m³ (approx.)

Solubility: Soluble in water, forming a viscous solution. insoluble in ethanol

pH (1% solution): Neutral

Moisture content: 98.6%wb or 67.6%db

Loss on drying: Not more than 15% (105^{0}C, 2½h)

Gel strength: 550-850 (gm/cm)

Specific gravity: <1

Stability: Stable at room temperature

Microbiological criteria: Total plate count: Not more than 10,000 colonies per gram

Yeasts and moulds: Not more than 400 colonies per gram

APPLICATIONS OF GELLAN GUM

In food industry:

Gellan gum can furnish textural diversity in water based dessert gels along with outstanding flavor release. It can improve heat stability and raise setting temperature in gelatin based desserts. In fruit based products gellan gum offers robustness,provides good product stability during transportation and storage. In fruit fillings for bakery products, gellan gum can offer additional structure and reduction of starch levels. By using gellan gum in combination with the appropriate starch, it is possible to reduce the set time of starch jellies so they can be removed more quickly from the starch moulds. In decorative icings, frostings and glazes for baked goods, benefits obtained from gellan gum include good shelf stability, moisture retention, spreadability, sheen texture and flavor release.

In personal care:

In cosmetic applicationsgellan gum can be used in lotions and creams, make up, face masks and packs, hair care products, toothpaste and air freshener gels. It can provide stability and suspension to shampoos and conditioners and ideal for products which requires pseudo plastic rheology. In creams and lotions the high yield value of gellun gum fluid gel stabilizes these emulsions and imparts a 'light and silky' feel when rubbed on the skin. In suntans and sunscreens, gellun gum stabilizes the oil phase and delivers ingredients uniformly to the skin. It is beneficial in toothpaste formulations for its binding properties and its reversible non-stringy true-gel structure.

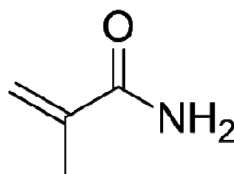
In pharmaceuticals and biotechnology:

Gellan gum can be used to produce easy-to-swallow solid dosage forms, such as gels and coated tablets. It can be used in controlled release dosage forms and in microencapsulated products. Gellan gum can be used as an alternative microbiological culture media, specially suitable for thermophilic microorganisms. It is suitable for plant tissue cultivation as it resists contamination by moulds and allows clear observation of root and tissue development.

4.2.2.METHACRYLAMIDE[5,6]:

IUPAC name: 2-Methyl-2-propenamide

Molecular structure:



Molecular formula: C_4H_7NO

Molecular weight: 85.11

CAS No: 79-39-0

PHYSICAL AND CHEMICAL PROPERTIES:

Physical State: White odorless crystals

Melting Point: 111.3^{0}C

Boiling Point:215 ^{0}C

Water Solubility: 202 g/L at 20^{0}C

Density: 1.10-1.12 g/cm^3

Vapor Pressure: 1.3 x 10^{-4}hPa (at 25°C)

KOC: No significant adsorption

log Pow:-0.15

Reactivity: Polymerizes when heated

Flash Point: 215^{0}C

Auto Ignition Temperature: 510^{0}C

Description:

Methacrylamideis a chemical compound with the chemical formula C_4H_7NO. Its IUPAC name is 2-Methyl-2-propenamide. It is a white odorless crystalline solid, soluble in water, ethanol, ether, and chloroform. It is a precursor of methyl methacrylate. Methacrylamidereacts in the atmosphere with photochemically-produced hydroxyl radicals with a half-life of 0.5 day.

Methacrylamide decomposes in the presence of strong acids, bases and oxidizing agents. It decomposes non-thermally to form ammonia, and thermal decomposition producescarbon monoxide, carbon dioxide, and oxides of nitrogen. In acute toxicity studies of methacrylamide in animal models it was found that in mice it's LD50 is 451 mg/kg (Hashimoto K, 1981 RTECS,1997) and in rat it's LD50 is 1789 mg/kg for males and 1774 mg/kg for females (MHW, Japan,1999). It is moderately irritating to eye and slightly irritating to skin. It has some neuro toxicity but it is not genotoxic or carcinogenic.

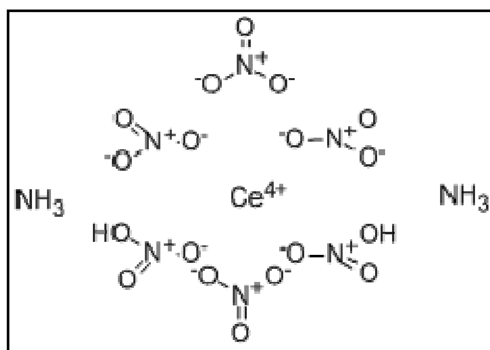
.**Use:**

Methacrylamide is used as a raw material in the production of chemicals for industrial and professional use such as textiles, leather, fur, bulk, large scale chemicals (including petroleum products), fine chemicals, formulation [mixing] of preparations and/or re-packaging, building and construction work, electricity, steam, gas, water supply and sewage treatment. It is mainly used as a raw material for polymerized compounds such as emulsions or latex, whose applications are textile-finishing agent, paper finishing agent, coating agent, condensing agent, etc.

4.2.3. CERRIC AMMONIUM NITRATE[7, 8]:

Common Synonyms: Ammonium cerric nitrate; cerate (2-), hexakis (nitrato-O)-, diammonium (OC-6-11)

Molecular structure:



Molecular formula: $(NH_4)_2Ce\ (NO_3)_6$

Molecular weight: 548.23

CAS No: 16774-21-3

PHYSICAL AND CHEMICAL PROPERTIES:

Appearance: Small, orange-red, monoclinic crystals.

Odor: Slight characteristic odor.

Solubility: 141g/100ml water at 25ºC (77F).

Density: 1.10g/cc at 20°C.

Percent volatiles by volume:0 (at 21°C or 7^0F).

Boiling Point: No information found.

Melting Point: 107-108°C.

Stability and reactivity: Stable under ordinaryconditions of use and storage.

Hazardous Decomposition Products: Oxides of nitrogen..

Conditions to Avoid: Heat, shock, friction, incompatibles.

Incompatibilities: Flammable and organic materials, reducing agents, powdered aluminum, boron phosphide, cyanides, esters, phosphate, phosphorus, sodium cyanide, sodium hypophosphite, stannous chloride, and thiocyanates.

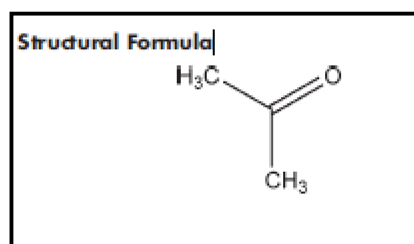
Potential Health Effects:

- ✓ **Inhalation:** Causes irritation to the respiratory tract. Symptoms may include coughing, shortness of breath.
- ✓ **Ingestion:** Large doses of nitrates may cause dizziness, abdominal cramps, vomiting, bloody diarrhoea, weakness, convulsions, and collapse.
- ✓ **Skin Contact:** Causes irritation to skin. Symptoms include redness, itching, and pain.
- ✓ **Eye Contact:** Causes irritation, redness, and pain.
- ✓ **Chronic Exposure:** Under some circumstances methemoglobinemia occurs in individuals when the nitrate is converted by bacteria in the stomach to nitrite. Nausea, vomiting, dizziness, rapid heartbeat, irregular breathing, convulsions, coma, and death can occur should this conversion take place.

4.2.4.ACETONE[9]:

Common Synonyms: 2-Propanone

Molecular structure:



Molecular formula: C_3H_6O

Molecular weight: 58.08

CAS No: 67-64-1

PHYSICAL AND CHEMICAL PROPERTIES:

Functional Category: Solvent.

Boiling point: 56.28^0C
Flash point: 208°C
Melting point: 94.38°C

Solubility Soluble in water: Freely soluble in ethanol (95%)
Vapor pressure: 185mmHg at 208°C
Stability and Storage Conditions: Acetone should be stored in a cool, dry, well-ventilated place out of direct sunlight.
Incompatibilities: Acetone reacts violently with oxidizing agents, chlorinated solvents,and alkali mixtures. It reacts vigorously with sulfur dichloride, potassium t-butoxide, and hexachloromelamine. Acetone should not be used as a solvent for iodine, as it forms a volatile compound that is extremely irritating to the eyes.
Applications in Pharmaceutical Formulation or Technology: Acetone is used as a solvent or co solvent in topical preparations, and as an aid in wet granulation. It has also been used when formulating tablets with water-sensitive active ingredients, or to solvate poorly water-soluble binders in a wet granulation process. Acetone has also been used in the formulation of microspheres to enhance drug release. Owing to its low boiling point, acetone has been used to extract thermo labile substances from crude drugs. Description Acetone is a colorless volatile, flammable, transparent liquid, with a sweetish odour and pungent sweetish taste.

4.2.5. METHANOL[10]:

Common Synonyms: Methyl alcohol, methyl hydrate, wood spirit, methyl hydroxide
Molecular structure: H_3 – C - OH
Molecular formula: CH_3OH

Molecular weight: 32

PHYSICAL AND CHEMICAL PROPERTIES:

Appearance: Liquid, Clear,Colorless.
Odor: Mild characteristic alcohol odour.

Vapor Pressure: 12.8 kPa at 20 ^{o}C.

Solubility: Completely soluble in water, soluble in all proportions in other alcohols, esters, ketones, ethers and most other organic solvents.

Vapor Density: 1.105 at 15 ^{o}C.

Freezing Point: -97.8 ^{o}C.

Boiling Point: 64.7 ^{o}C at 101.3 kPa.

Critical Temperature: 239.4 ^{o}C.

Relative Density: 0.791.

Evaporation Rate: 4.1 (n-butyl acetate =1).

Partition Coefficient: log P (Oct) = -0.82.

Effects of short term (Acute) Exposure:

- ✓ **Inhalation**: Inhalation of high airborne concentrations can also irritated mucous membranes, cause headaches, sleepiness, nausea, confusion, loss of consciousness, digestive and visual disturbances and even death. Odour threshold of methanol is several times higher than the TLV-TWA. Depending upon severity of poisoning and the promptness of treatment, survivors may recover completely or may have permanent blindness, vision disturbances and/or nervous system effects. Concentrations in air exceeding 1000 ppm may cause irritation of the mucous membranes.
- ✓ **Skin Contact**: Methanol is moderately irritating to the skin. Methanol can be absorbed through the skin and harmful effects have been reported by this route of entry. Effects are similar to those described in “Inhalation”.
- ✓ **Eye Contact**: Methanol is a mild to moderate eye irritant. High vapor concentration or liquid contact with eyes causes irritation, tearing and burning.
- ✓ **Ingestion**: Swallowing even small amounts of methanol could potentially cause blindness or death. Effects of sub lethal doses may be nausea, headache, abdominal pain, vomiting and visual disturbances ranging from blurred vision to light sensitivity.

Effects of long term (Chronic) Exposure: Repeated exposure by inhalation or absorption may cause systemic poisoning, brain disorders, impaired vision and blindness. Inhalation may

worsen conditions such as emphysema or bronchitis. Repeated skin contact may cause dermal irritation, dryness and cracking.

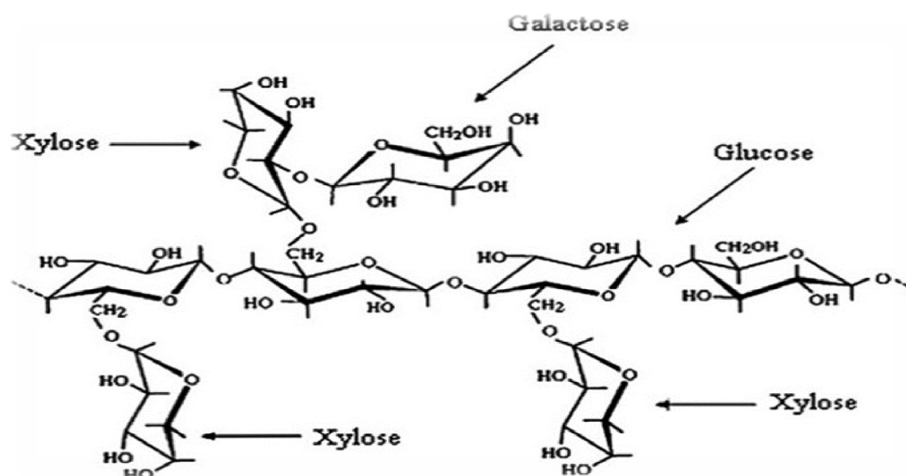
Medical Conditions Aggravated by Exposure: Emphysema or bronchitis.

Handling Procedures: No smoking or open flame in storage, use or handling areas. Use explosion proof electrical equipment. Ensure proper electrical grounding procedures are in place.

Storage: Store in totally enclosed equipment, designed to avoid ignition and human contact. Tanks must be grounded, vented, and should have vapor emission controls. Tanks must be diked. Avoid storage with incompatible materials. Anhydrous methanol is non-corrosive to most metals at ambient temperatures except for lead, nickel, monel, cast iron and high silicon iron. Coatings of copper (or copper alloys), zinc (including galvanized steel), or aluminum are unsuitable for storage. These materials may be attacked slowly by the methanol. Storage tanks of welded construction are normally satisfactory. They should be designed and built in conformance with good engineering practice for the material being stored. While plastics can be used for short term storage, they are generally not recommended for long-term storage due to deterioration effects and the subsequent risk of contamination.

4.2.6. TAMARIND SEED GUM:[11]

Tamarind seed gum is a galactoxyloglucan isolated from seed kernel of *Tamarindusindica*. It possesses properties like high viscosity, broad pH tolerance and adhesivity[11]. These properties led to its application as stabilizer, thickener, gelling agent, and binder in food and pharmaceutical industries. In addition to these, other important properties of TSP have been identified recently which include non-carcinogenicity [12], mucoadhesivity, biocompatibility [13], high drug holding capacity [14] and high thermal stability [15]. These led to its application as excipient in the hydrophilic drug delivery system.



PROPERTIES OF TAMARIND SEED GUM

- ✓ D-mannose and D-galactose
- ✓ This Powder is odorless and is creamish white in color
- ✓ **Moisture Content :** 06 to 12 %
- ✓ **Crude Fibre :** 01 to 02 %
- ✓ **Protein :** 10 to 20 %
- ✓ **Viscosity :** 2800 CPS in 3% solution
- ✓ **Color :** light creamy
- ✓ **pH of 5% slurry :** 6.0 to 7.0
- ✓ **Sieve Value :** 100 mesh 100% w/w passing
- ✓ **Sieve Value :** 200 mesh 99% w/w passing
- ✓ **Sieve Value :** 300 mesh 99% w/w passing
- ✓ **Ash content :** 01 to 03 %
- ✓ Tamarind Kernel Powder has a high water absorption capacity and high viscosity over a broad range of pH

CHEMICAL COMPOSITION

The composition of tamarind seed gum, the source of gum resembles cereals with 12.7-15.4% of protein, 3-7.5% of oil, 7-8.4% of crude fiber, 61-72.2% carbohydrates, and 2.45-3.3% of ash. All of this was measured on dry weight basis. Chemically, tamarind seed gum is a highly branched carbohydrate polymer. TSG is a polymer with an average molecular weight of

52350 daltons and a monomer of mainly three sugars- glucose, galactose and xylose in a molar ratio of 3:2:1. A polymer consists of cellulose-type spine which carries xylose and galactoxylose substituents. About 80% of glucose residues are substituted by xylose residues (1-6 linked), which themselves are partially substituted by p-1-2 galactose residues. The exact sequential distribution of branches is not known. TSG is a branched polysaccharide with a main chain of Â-D-1-glucopyrynosyl units, with a side chain consisting of single D-xylopyranosyl unit attached to every 2nd, 3rd and 4th D glucopyrynosyl unit through1-6 linkage

2.7.6. Applications in Pharmaceutical Industry:

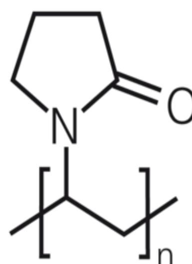
Pharmaceutical applications:

TSG is an interesting candidate for pharmaceutical use. It is used as a carrier for variety of drugs for controlled release applications. Tamarind seed polyose could be used as binder for wet granulation and direct compression tabletting methods [16].TSG is used for production of thickened ophthalmic solutions having a pseudo plastic rheological behaviour and mucoadhesive properties.It is a potential polysaccharide having high drug holding capacity which sustained the release of Verapamil hydrochloride[17].TSG was used as release modifier for the preparation of diclofenac sodium spheroids using the extrusion spheronization technique with microcrystalline cellulose as a spheronization enhancer[18]. It has been tried in bioadhesive tablets and can be used as suspending agent.

4.2.7. POLYVINYLPYRROLIDONE[19-21]:

Common Synonyms: PVP, Polyvinyl pyrrolidone, 1-vinyl-2-pyrrolidinone polymer.

Molecular structure:



Molecular formula: $(C_6H_9NO)_n$

CAS No: 9003-39-8

PHYSICAL AND CHEMICAL PROPERTIES:

Appearance: Free-flowing, white-yellowish, hygroscopic, tasteless powder or flakes having a slight amine odor.

Solubility: Freely soluble in water and most commonly used pharmaceutical solvents including alcohol and polyglycolated vehicles.

Pharmacopoeial listing: USP, EP, JP, FCC, Codex Alimentarius.

Density: 1.2 g/cm³

Melting point: 110 - 180 °C

Description:

A homopolymer of vinyl pyrrolidone, manufactured using different initiator systems depending upon the molecular weight. The low molecular weight polymer, having a K-value of 30 or less (K value represents the average molecular weight of soluble povidone grade and is calculated from the relative viscosity in water), is polymerized in water using a hydrogen peroxide initiator system or in isopropanol using an organic peroxide. Higher K value polymer is made by aqueous homopolymerization using an organic azo or peroxide type initiator. When polymerization is carried out in isopropanol, the alcohol solvent is exchanged with water prior to drying.

Regulatory: Povidone K-30 (MW 40000) is approved in the US, Code of Federal Regulations.

Health & Safety: Reported impurities in povidone are residual monomer, N-vinyl-2-pyrrolidinone, acetaldehyde, and hydrazine. Limit for residual N-vinyl-2-pyrrolidinone is less than 10 ppm, whereas acetaldehyde content is less than 500 ppm and hydrazine below 1 ppm. Peroxide functionalities are also known to be present, with typical conc. well below 400 ppm. No USP organic volatile impurities should be present.The acceptable daily intake is 0 – 50 mg/kg.

Acute oral toxicity: Doses of 300 – 2700 mg/kg were administered with no significant

adverse effects (rabbits).

Sub-chronic oral toxicity: PVP K-90 fed at 2.5 or 5.0% of the diet for 28 days (dogs) demonstrated no toxic, pathological, or histological abnormalities.

Chronic oral toxicity: No toxic effects were observed in a two-year study at 0, 5.0, or 10.0% PVP K-30 and in a 138-week study at 1, 2, 5, and 5% PVP K-90 (rats).

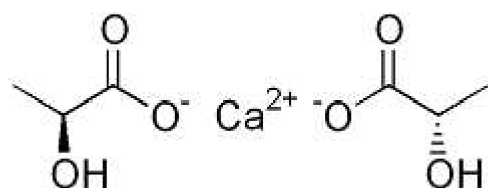
Use: Binder, complexing aid, suspension stabilizer, thickener.

4.2.8. CALCIUM LACTATE[22]:

IUPAC name: calcium 2-hydroxypropanoate
Other names:calcium lactate 5-hydrate, calcium lactate, 2-hydroxypropanoic acid, calcium salt pentahydrate
CAS Number: 814-80-2

Chemical formula: $C_6H_{10}CaO_6$

Molar mass: 218.22 g/mol



Calcium lactate is a black or white crystalline salt made by the action of lactic acid on calcium carbonate. It is used in foods as an ingredient in baking powder and given medicinally.It is synthesized by the reaction of lactic acid with calcium carbonate or calcium hydroxide.

Cheese crystals usually consist of calcium lactate, especially those found on the outside, on younger cheese, and on Cheddar cheese.

PHYSICAL AND CHEMICAL PROPERTIES:

Appearance: white or off-white powder

Odor: slightly efflorescent

Density:1.494 g/cm^3

Melting point: 240 °C (464 °F; 513 K) (anhydrous), 120 °C (pentahydrate)

Solubility: 7.9 g/100 mL (30 °C) in water, very soluble in ethanol

Acidity (pK_a): 6.0-8.5

E number: E327

Refractive index(n_D): 1.470

Applications in Pharmaceutical Formulation or Technology:

In medicine, calcium lactate is most commonly used as an antacid and also to treat calcium deficiencies. Calcium lactate can be absorbed at various pHs and does not need to be taken with food for absorption for these reasons.

Calcium lactate is added to sugar-free foods to prevent tooth decay. When added to chewing gum containing xylitol, it increases theremineralization of tooth enamel.[3] It is also added to fresh-cut fruits, such as cantaloupes, to keep them firm and extend their shelf life, without the bitter taste caused by calcium chloride, which can also be used for this purpose.

.

4.2.9. MAGNESIUM STEARATE[23, 24]:

Common Synonyms: Dibasic magnesium stearate, Magnesium distearate, Magnesiastearas, Magnesium octadecanoate, Octadecanoic acid Magnesium salt, Stearic acid Magnesium salt, Synpro 90.

Molecular weight: 591.24

CAS No: 557-04-0

Functional Category: Tablet and capsule lubricant.

Description:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Related Substances:

Calcium stearate, Magnesium aluminum silicate, Stearic acid, Zinc stearate.

Incompatibilities:

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Stability and Storage Conditions:

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

4.3. REFERENCES:

1. Indian Pharmacopoeia, Volume 1, 242-243, 1996.
2. http://en.wikipedia.org/wiki/File:Diclofenac.svg
3. (http://portal.bpfk.gov.my/aeimages/File/Product_Info/poison/Diclofenac_Sodium_Enteric_Coated_Tablet.pdf)
4. http://www.pharmainfo.net/reviews/gellan-gum-and-its-applications-%E2%80%93-review
5. http://en.wikipedia.org/wiki/Methacrylamide
6. http://corporate.evonik.com/sites/dc/Downloadcenter/Evonik/Corporate/de/Unternehmen/Verantwortung/gps-summary-methacrylamide.pdf
7. http://www.cen.iitb.ac.in/cen/usage-policies/msds/ceric_ammonium_nitrate.pdf
8. http://www.chemicalbook.com/ChemicalProductProperty_EN_CB2302090.htm
9. Rowe RC.,Sheskey PJ., Quinn ME. Handbook of pharmaceutical excipients. 6thEdn., Royal Pharmaceutical Society, United Kingdom, 7-8, 2009.
10. http://www.cen.iitb.ac.in/cen/usage-policies/msds/methanol.pdf.
11. Rao PS., Srivastava HC. Tamarind. In: Whistler RL, editor. Industrial Gums. 2nd Edn., New York, Academic Press,369-411, 1973.
12. Sano M., Miyata E., Tamano S., Hagiwara A., Ito N., Shirai T. Lack of carcinogenicity of tamarind seed polysaccharide in B6C3F mice. *Food and ChemToxicol*, **34**: 463-467, 1996.
13. Burgalassi S., Panichi L., Saettone MF., Jacobsen J., Rassing MR. Development and *in vitro/ in vivo* testing of mucoadhesivebuccal patches releasing benzydamine and lidocaine. *Int J Pharm*, **133**:1-7, 1996.
14. Kulkarni D., Ddwivedi DK., Sarin JPS., Singh S. Tamarind seed polyose: A potential polysaccharide for sustained release of verapamil hydrochloride as a model drug. *Indian J Pharm Sci*, **59**: 1-7, 1997.

15. Datta R., Bandopadhyay AK. A new nasal drug delivery system for Diazepam using Natural Mucoadhesive polysaccharide obtained from Tamarind seeds. *Saudi Pharmaceutical Journal*, **14**: 115- 119, 2006.
16. Kulkarni D., Dwivedi AK., Singh S. Performance evaluation of tamarind seed polyose as a binder and in sustained release formulations of low drug loading. *Indian J PharmaSci*, **1**: 50-53, 1998.
17. Hilkens J., LigtenbergMJ.,Vos HL., Litvinov SV. Cell membrane-associated mucins and their adhesion modulating property. *Trends BiochemSci*, **17**: 359-363, 1992.
18. Giriraj T, Kulkarni K, Gawthamarajan. Development of controlled release spheroids using natural polysaccharides as release modifier. Drug Deliv, 12, 2005, 201-6
19. Lieberman HA., RiegerMM.,Banker GS.Pharmaceutical Dosage Forms: Disperse Systems, volume 3, 2ndEdn.,Marcel Dekker, Inc., 282, 2008.
20. Evaluation of certain food additives and contaminants. WHO technical report series, No. 751 FAO/WHO Rep. 30th report, 30 – 31, Geneva, 1987.
21. Neumann A., Leuschener A., Schwertfeger W., Dontenwill W. Study on the acute oral toxicity of PVP in rabbits, unpublished report to BASF, 1979.
22. http://en.wikipedia.org/wiki/Talc.
23. Rowe RC.,Sheskey PJ., Quinn ME. Handbook of pharmaceutical excipients. 6thEdn., Royal Pharmaceutical Society, United Kingdom, 404-407, 2009.
24. Rowe RC.,Sheskey PJ., Quinn ME. Handbook of pharmaceutical excipients. 6thEdn., Royal Pharmaceutical Society, United Kingdom, 728-730, 2009.

CHAPTER: 5

AIMS ANDOBJECTIVES

5.AIMS AND OBJECTIVES:

In the recent years natural gums has been extensively used in the formulation of extended release dosage forms. Natural gums (gums obtained from plants) are hydrophilic carbohydrate polymers with high molecular weight and generally composed of monosaccharide units joined by glucosidic bonds. Gums are generally soluble in water and swell in contact with water or disperse in cold water producing a viscous jelly like solution. Natural gums generally form three dimensional monomeric network thus trapping water, drug and other excipients in it. Thus the release of drug can be extended to the desired extent.

Natural gums are widely available in our mother nature.Researchers mainly target natural gums for the development of NDDS because of the following reasons:

- ✓ Biodegradable.
- ✓ Easily available.
- ✓ Biocompatible and non-toxic.
- ✓ Low cost.
- ✓ Environment friendly.

But these gums come with certain disadvantages. They are as follows:

- ✓ Susceptible to microbial contamination due to its moisture content.
- ✓ Batch to batch variation due to geographical and environmental effect.
- ✓ Uncontrolled rate of hydration.
- ✓ Reduced viscosity on storage.

In order to overcome these problems, they can be tailored or modified in different ways to not only overcome their drawbacks but also modulate the site of drug release and it's kinetic, and makes them parallel or superior to their synthetic counterparts. Graft copolymerization is an excellent and fruitful technique to make the natural polysaccharides potentially suitable to be used as sustained release matrices (Velasco *et al*, 1996). A graft copolymer can be defined as a macromolecule in which one or more polymeric chains remain covalently bonded as side chains to the main polymeric backbone (Bhattacharya, &Misra, 2004). Modification of the structure of natural polymers by graft copolymerization method makes them intelligent biomaterials in controlled release applications since native polysaccharides may not be suitable in controlled release drug delivery systems due to their substantial swelling and rapid enzymatic degradation in physiological fluids (Soppimath, Aminabhavi, Dave, Kumbar,

&Rudzinski, 2002). Graft copolymerization introduces hydrophobicity and steric bulkiness, which considerably protects the matrix and carbohydrate backbone to retard the drug release (Vijan, Kaity, Biswas, Isaac, & Ghosh, 2012). Concurrent formation of homopolymer during graft copolymerization is the main constraint resulting a low grafting yield (Singh, Tripathy, Tiwari, &Sanghi, 2006). Diclofenac sodium is a water soluble aryl-acetic acid derivative nonselective cyclo-oxigenase inhibitor drug having analgesic, antipyretic and anti-inflammatory actions. It is used in rheumatoid and osteoarthritis, bursitis, ankylosing spondylitis, toothache, dysmenorrhoea, post-traumatic and post-operative inflammatory conditions as pain reliever and edema reducer. Its oral bioavailability is 54% with biological half-life of 1 to 2 hours. Peak plasma concentrations following oral administraton of sustained release and enteric coated tablets are 0.42µg/ml and 2.0µg/ml respectively (Willis, Kendall, Flinn, Thornhill, & Welling, 1979). Extended release tablet of diclofenac sodium is official in USP, 2009 edition.

There are different techniques of grafting viz. grafting initiated by chemical means, grafting initiated by radiation, photochemical grafting, plasma radiation induced grafting, enzymatic grafting. Generation of free-radical sites on a polymeric backbone by direct oxidation of the backbone by certain transition metal ions such as Ce^{4+} is considered as very simple and easier one step method of graft copolymerization (Bhattacharya, &Misra, 2004). Alongwith free-radical initiation by redox initiator, microwave-assisted graft copolymerization has also been employed (Singh, Tripathy, Tiwari, &Sanghi, 2006; Tiwari & Singh, 2008; Singh &Nath, 2013). The microwave irradiation provides rapid transfer of fixed energy in the bulk of the reaction mixture resulting very short reaction time with significantly higher yield.

One important limitation of methacrylamide grafted gellan gum is it has low solubility in water. So it is problematic to prepare a sophisticated tablet with it. One fruitful approach to solve the problem is hydrolysis of the molecule by treating it with sodium hydroxide solution so that it possess adequate solubility in water.

Therefore the main objectives of the study are:

1. **To perform grafting of gellangum with methacrylamide**.
2. **Increase the solubility of methacrylamide grafted gellan gum in water by hydrolysis with sodium hydroxide solution**.
3. **Characterization of the hydrolysedpolymethacrylamide grafted gellangum**

- ✓ Rheological study
- ✓ FT-IR study.
- ✓ DSC and TGA study..

4. **To develop matrix tablet of Diclofenac sodium as model drug using hydrolysedpolymethacrylamide graftedgellan gum (hPmaa-g-GG) and tamarind seed gum (TSG) as excipients and analyse various parameters.**
5. **Characterization of tablet powder and comparing with hydrolysedpolymethacrylamide grafted gellan gum.**
6. **To perform in vitro dissolution studies of the tablets and correlate release characteristics with tablet contents.**

CHAPTER: 6

MATERIALS AND METHODS

6.1: Drug used: Diclofenac sodium, gifted from La ChemicoPvt. Ltd., Kolkata, India.

6.2:Chemicals used: Following chemicals are used during this project work:

Table6.1:List of various chemical used in project work

Sl. No	Chemical Used	Manufacturer
1.	Gellan Gum (Clerigel)	Himedia Laboratories Pvt. Ltd.
2.	Methacrylamide	LobaChemiePvt.Ltd,Mumbai
3.	Cerric Ammonium Nitrate	Qualigens Fine Chemicals,Mumbai
4.	Sodium hydroxide	Merck India limited, Mumbai
5.	Methanol	Merck India limited, Mumbai
6.	Acetone	Sd FineChem Limited Mumbai
7.	Polyvinyl pyrrolidone K-30	Central Drug House(P)Ltd.,New Delhi
8.	Tamarind seed Gum	Isolated from commercially available tamarind seed, purchased from local market in Kolkata.
9.	Calcium Lactate I.P.	Bengal Chemicals Ltd.
10.	Magnesium stearate	LobaChemiePvt. Ltd. Mumbai
11.	Hydrochloric acid	Merck India limited, Mumbai
12.	Potassium dihydrogen phosphate	Merck India limited, Mumbai
13.	Ethanol	Merck India limited, Mumbai

6.3: Instrument handled: Following instruments are handled during my project:

Table6.2:List of various instruments used in experimental work

Sl. No	Instrument	Model no	Manufacturer
1.	Electronic Balance	ML204/A01	Mettler Toledo, Switzerland
2.	Digital pH meter	MK-V1	Systronics, Ahmadabad, India
3.	Sieves	18 and 100 mesh size	Excel Enterprises, Kolkata
4.	Digital Slide Caliper	CD-6CS	DigimaticCaliperMitutoyo Products, Japan
5.	Electrical drier	181824	Lab Inst &Chem Works, Siliguri, India
6.	Magnetic Stirrer	M-Lass 1166	Tarsons Products Pvt. Ltd. Kolkata, India
7.	UV-Visible Spectroscopy	UV 3200	Lab India Analytical Instrument Pvt. Ltd.
8.	Scanning Electron Microscope	JSM 6360	Jeol Make, United Kingdom
9.	FTIR spectroscopy	IR- Prestige-21	Shimatzu make, Japan
10.	X-Ray Diffractometer Cu target slit 10 mm	ULTIMA-III	RigakuMake, Japan
11.	Hardness Tester	Monsanto	Swastic Scientific Company,Mumbai
12.	Differencial Scanning Calorimetry	Pyris Diamond TG/DTA	Perkin Elmer, Singapore
13.	Tablet Compression Machine	Labpress,10 station	Rimek,KarnavatiAhmadabad,India
14.	USP dissolution apparatus II	DS 8000 (6+2)	Lab India Analytical Instrument Pvt. Ltd.
15.	Microwave Oven	C23K101.BB	Electrolux, India
16.	Compact rheometer	Rheoplus, MCR 102	Anton Paar, USA

6.4.METHODS:

6.4.1.Preparation of Standard Calibration Curve of Diclofenac sodium in 0.05 (M) phosphate buffer pH 7.5:

6.4.1.1.Preparationof 0.05 (M) phosphate buffer pH 7.5[1]**:**

6.4.1.1.1. Preparation of 0.2 (M) Potassium dihydrogen phosphate solutions:

About 27.218 gm of potassium dihydrogen phosphate was accurately weighed out and taken into a 1000ml volumetric flask. Finally volume was made upto the mark with distilled water with continuous stirring.

6.4.1.1.2. Preparation of 0.2 (M) Sodium hydroxide solutions:

About 8 gm of sodium hydroxide was accurately weighed out and taken in a 1000ml volumetric flask. Finally volume was made upto the mark with distilled water with continuous stirring.

6.4.1.1.3. Procedure:

500 ml 0.2 (M) potassium dihydrogen phosphate was mixed with 407.5 ml 0.2 (M)sodium hydroxide solution and the volume was made upto 2000ml with distilled water. The pH was adjusted by adding NaOH solution carefully.

6.4.1.2.Preparation of Standard Curve of diclofenac sodium in 0.05 (M) phosphate buffer[2]**:**

100 mg diclofenac sodium was accurately weighed and dissolved in 0.05 (M) phosphate bufferpH 7.5and volume made up to 100 ml (**Solution1**). 10 ml of **solution 1** was diluted with0.05 (M) phosphate bufferpH 7.5to make 100ml (**Solution 2**). The concentration of **solution 2** was 100µg/ml. Suitable volume of **solution 2** was taken in different 25 ml volumetric flasks to produce different standard solutions with concentrations of 2,4,6,8,10 µg/ml. Finally, volume wasadjusted to 25ml with same buffer solution. One of the standard solutions was then scanned from 190 nm to 1100 nm and 500 nm to 1100 nm using UV - Visible Spectrophotometer. Then absorbance of all standard solutions was measured at observed λ_{max}. This was repeated for three times.Then the average concentration versus absorbance curve was plotted and the equation and R^2value of the curve were obtained.

6.4.2. Preparation of Standard Calibration Curve of Diclofenac sodium in 0.1 (N) HCl buffer pH 1.2:

6.4.2.1. Preparationof 0.1 (N)HCl buffer pH 1.2[1]:

About 8.5 ml of HClwas accurately measured in a measuring cylinder and taken in a 1000ml volumetric flask. Finally volume was made upto the mark with distilled water with continuous stirring.

6.4.2.2. Preparation of Standard Curve of diclofenac sodium in 0.1(N) HClbuffer[2]:

100 mg diclofenac sodium was accurately weighed and dissolved in 0.1(N) HCl bufferand volume made up to 100 ml (**Solution 1**). 10 ml of **solution 1** was diluted with0.1(N) HCl bufferto make 100ml (**Solution 2**). The concentration of **solution 2** was 100µg/ml. Suitable volume of **solution 2** was taken in different 25 ml volumetric flasks to produce different standard solutions with concentrations of 2, 4, 6, 8, 10 µg/ml. Finally, volume was adjusted to 25ml with same buffer solution. One of the standard solutions was then scanned from 190 nm to 1100 nm and 500 nm to 1100 nm using UV - Visible Spectrophotometer. Then absorbance of all standard solutions was measured at observed λ_{max}. This was repeated for three times. Then the average concentration versus absorbance curve was plotted and the equation and R^2 value of the curve were obtained.

6.4.3.Isolation and Purification of tamarind seed gum[3]:

Tamarind seed gum powder, isolated from commercially available tamarind seed gum,purchased from local market in Kolkata, India. From these powder 20 g of tamarind seed gum was weight and added in 200 ml of distilled water, and slurry was prepared. The slurry was poured into 800 ml of distilled water. The solution was boiled for 20 min under stirring condition in a water bath. The resulting clear solution was kept overnight so that most of the proteins and fibres settled out. The solution was then centrifuged at 5000 rpm for 20 min. The supernatant was separated and poured into twice the volume of absolute ethanol with continuous stirring. The precipitate was dried at 40^0C to get constant weight. The dried film obtained was crushed to fine powder using domestic mixer and grinder and then it was passed through #100 mesh. The fine powder was taken for the experiments and kept in airtight desiccators.

6.4.4. Synthesis of polymethacrylamide-grafted-gellan gum[4-5]:

Microwave-promoted free radical initiation method was employed for the synthesis of polymethacrylamide-grafted-gellangum (Pmaa-g-GG) .1g of gellan gum (GG) wasweighed accurately and then it was dissolved in 100ml of water (solution A). 10g of methacrylamide(Maa) was weighed accurately and dissolved in 25ml of water (solution B). Solution B was then added to solution A and stirred for 1 h. About 400mg of cerric (IV)ammonium nitrate (CAN) was dissolved in 25ml of water and mixed with the previous mixture. The mixture was then exposed to microwave in a domestic microwave oven of 500 W for 1 min.heating and then cooled for1 min. in an ice bath. Then it was left for overnight. Acetone was added to it in 1:2 ratios (reaction mixture:acetone) for precipitation of the grafted gellan gum. The precipitate was then collected and added in 50 ml of 80% (v/v) aqueous methanol to remove the unreacted free monomer and the homopolymerformed during graft reaction. After stirring for 1 min it was allowed to stand for further precipitation. The precipitate was collected and finally washed with distilled water and dried at 40◦C to a constant weight. The dried grafted gellan gum was then powdered using pestle and mortar and passed through #100 mesh. Different grafting parameters such as % grafting (%G), grafting efficiency (%GE) and% conversion (%C) were calculated using following formula (Eqs. (1)–(3)) to assess the efficiency of the synthesis :

$$\%\text{grafting } (\%G) = (W1 - W0)/W0 \times 100 \quad (1)$$

$$\%\text{grafting efficiency } (\%GE) = (W1 - W0)/W2 \times 100 \quad (2)$$

$$\%\text{conversion } (\%C) = W1/W2 \times 100 \quad (3)$$

where W0, W1and W2are the weight of native gellan gum, grafted gellan gum and methacrylamide respectively.

This method was repeated to obtain 4 different batches of grafted gellan gum (S1, S2, S3 and S4) required to prepare sufficient no. of teblets.

6.4.4.1.Mechanisms Involved in Synthesis of polymethacrylamide grafted gellangum[4]:

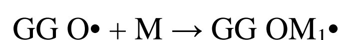
Graft co-polymerization of methacrylamide onto gellan gum was carried out by free-radicalinitiation technique. In several study, cerric (IV) ammonium nitrate was used as free-

radical initiator. Along with free-radical initiator, microwave promoted graft-copolymerization have also been reported. The amount of CAN had major positive influence on the higher grafting efficiency irrespective of other variables. The anomeric -CHOH on gellan gum-backbone was the reactive vicinal group, where the grafting was initiated. The overall reaction mechanism was that, cerric (IV) ammonium nitrate gets dissociated into Ce^{4+}, ammonium and nitrate ions and then cerric(IV) ion attacked the gellan gum macrochains resulting formation of a GG–cerric complex. The cerric (IV) ions in the complex get then reduced to cerric (III) ions by oxidizing hydrogen atom and thereby creating a free radical onto GG-backbone. So, a threshold amount of redox initiator was required for the formation of the free radical. The grafting of Maa onto GG was then initiated by the free radical reacting with the monomer. In the presence of Maa, the GG free radical was chemically coupled to the monomer unit, thereby resulting in a covalent bond between Maa and GG to create the chain reaction for propagation. Cerric ions also attacked monomer resulting the formation of methacrylamide free radicals which join with another monomer molecule by a covalent bond leading to propagation of homopolymer chains. Finally, termination was achieved through a combination of two propagating chain free radicals initiated from GG-backbone. Termination may occur by coupling between GG-propagating-free-radical and monomer free radicalor between GG-propagating-free-radical and homopolymer-propagating-free radical (composed of only monomers).Homopolymerwas formed due to termination by coupling betweentwo homopolymer-free-radicals. Themicrowave irradiation provides rapid transfer of energy in the bulkof the reaction mixture, which reduces reaction time therefore itacts as a catalyst and gives a synergistic activity. The structures ofnative gellan gum and Pmaa-g-GG have been shown in Figure 6.1. Theproposed mechanism of the reaction is as follows:

Initiation:

$Ce(NH_4)_2(NO_3)_6 \rightarrow Ce^{4+} + 2NH_4^+ + 6NO_3^-$

$Ce^{4+} + GG\ OH \rightarrow complex \rightarrow GG\ O\bullet + Ce^{3+} + H^+$



$GG\ O\bullet + M \rightarrow GG\ OM_1\bullet$

$Ce^{4+} + M \rightarrow M\bullet + Ce^{3+} + H^+$

$M\bullet + M \rightarrow M_2\bullet$

Propagation:

$GG\ OM_1\bullet + M \rightarrow GG\ OM_2\bullet$

$GG\ OM_{n-1}\bullet + M \rightarrow GG\ OM_n\bullet$

$M_2\bullet + M \rightarrow M_3\bullet$

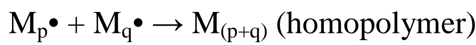
$M_{p-1}\bullet + M \rightarrow M_p\bullet$

Termination:

$GG\ OM_n\bullet + GG\ OM_m\bullet \rightarrow GG\ OM_{(m+n)}$ (graftcopolymer)

$GG\ OM_n\bullet + M\bullet \rightarrow GG\ OM_{(n+1)}$ (graftcopolymer)

$GG\ OM_n\bullet + M_p\bullet \rightarrow GG\ OM_{(n+p)}$ (graftcopolymer)



$M_p\bullet + M_q\bullet \rightarrow M_{(p+q)}$ (homopolymer)

(GG OH = nativegellangum; M = methacrylamide).

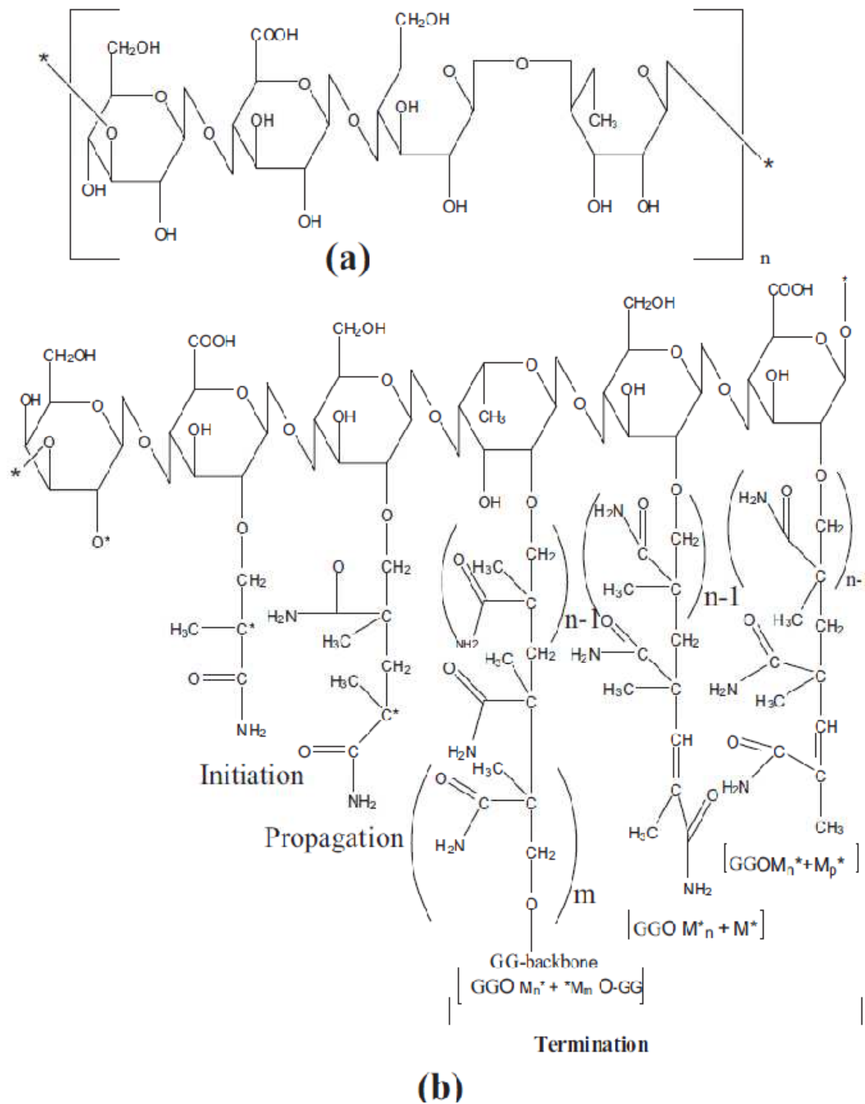


Figure 6.1(a)gellan gum and (b)polymethacrylamide grafted gellan gum (Pmaa-g-GG)

6.4.5. Hydrolysis of Polymethacrylamidegrafted gellangum (Pmaa-g-GG):

The dried powder of polymethacrylamide grafted gellan gum was then added to 250ml of 0.1 (M)NaOHsolution. Excess amount of NaOH solution was added with continuous stirring to dissolve the powder completely and to achieve complete hydrolysis. The mixture was heated mildly when the solution became too much thick. The mixture was kept aside for an hour and then acetone was added of equal volume of the mixture. It was kept overnight in a large beaker and then filtered with a sieve to get the precipitate. The precipitate was then air-dried for few hours so that the adhered acetone get evaporated. After that it was dried at 60◦C to a constant weight.It was then grinded into fine powder and passed through #100 mesh sieve. Hydrolysis converts the –CONH2 group int –COONawhich increases the solubility of grafted gum in water significantly.

6.4.6.Characterization of hydrolysed polymethacrylamidegrafted gellangum:

6.4.6.1.Rheological studies:

Most rheological studies made on in situ gels use the viscosity of the gel as the rheological parameter. When high shear is applied to gel to observe rheological properties , it destroys structure of gel. By using oscillatory measurements, where the oscillating amplitude is small enough, the gel structure remains intact during measurements. From oscillating measurements, shear strain, shear stress, and phase angel is determined. The parameters obtained are complex modulus (G*) and phase angel (δ). The elastic modulus (G’), viscous modulus (G”) and dynamic viscosity (η’) are calculated by the following equations:

$G' = G^* \cos(\delta)$; $G'' = G^* \sin(\delta)$; $\eta' = G^*/\omega$

where ω is the anguler frequency.

Different rheological parameters of gellan gum and hPmaa-g-GG (5%, w/v) was determined by a programmable Anton Paar Compact Rheometer.

6.4.6.3. Infrared spectral analysis[6]:

FTIR spectra ofgellan gum, hPmaa-g-GG were obtained to predict the possible changes of functional groups of grafted gellan gum as compared to its native form. A small amount of each material was mixed with KBr (1%w/w sample) and compressed into tablet. The scanning range selected was 550-4000 cm^{-1}. Diclofenac sodium and its tablet formulation

were also analyzed by FTIR to predict the possible interactions between drug and modified polymer by same process.

6.4.6.4.Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis[7]:

DSC and TGA thermogramsofgellan gum, hPmaa-g-GG, diclofenac sodium and drug formulation were recorded under N_2 flow (50 ml/min). The heating range was from 30^0C to 500^0C at a heating rate of 10^0C/min and sample mass of 3-5 mg.

6.4.7.Preparation of sustained release monolithic matrix tablet of diclofenac sodium:

Monolithic matrix tablets of a water soluble drug diclofenac sodium were prepared with hPmaa-g-GG and TSG of different 8 batches (F1, F2, F3, F4, F5, F6, F7 and F8) employing wet granulation method. Thick gel was prepared from hPmaa-g-GG,PVP K30 and TSG with minimum amount of water and then drug and calcium lactate were mixed intimately with it to form dough. Here amount of hPmaa-g-GG, TSG and calcium lactate were taken as independed variables and effect of them on drug release was compared. Calcium lactate was used as cross linker and PVP K30 was used as binder. The mass was then passed through #18 mesh to obtain granules. These granules were dried at 60ºC for 20 mins and passed through # 18 mesh. The granules were lubricated with magnesium stearate. The tablets were compressed in a rotary tablet machine with single punch of 8 mm and 9 mm diameter keeping the hardness within the range of 4-6 kg/m^2. The amounts of drug and excipients mentioned below were for one tablet.

Table 6.3: Composition of matrix tablets of Diclofenac sodium

Batch code	Drug (mg)	hPmaa-g-GG (mg)	TSG (mg)	Calcium Lactate (mg)	PVP K - 30 (mg)	Magnesium stearate (mg)	Tablet Wt (mg)
F1	100	50	50	50	40	5	295
F2	100	50	50	125	40	6.5	371.5
F3	100	50	125	50	40	6.5	371.5
F4	100	50	125	125	40	8	448
F5	100	125	50	50	40	6.5	371.5
F6	100	125	50	125	40	8	448
F7	100	125	125	50	40	8	448
F8	100	125	125	125	40	9.5	524.5

6.4.6.*In-vitro* drug release study:

In vitro dissolution studies were carried out in USP type-I dissolution apparatus using 900ml phosphate buffer pH 7.5 as dissolution media. The paddle was rotated at 50 rpm and the temperature was maintained at 37±0.5°C throughout the study. At predetermined time interval 10 ml of the samples were withdrawn by means of an auto sampler machine with a pre filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug releases by measuring the absorbance at 275 nm using UV-Visible spectrophotometer. *In vitro* dissolution studies were also carried out in USP type-II dissolution apparatus using 0.1(N) HCl buffer keeping the other parameters constant. The results of *in vitro* release data were fitted in to following mathematical models fordescribing the drug release pattern:

- ✓ **Zero order kinetics[8]:**

  Zero order release would be predicted by the following equation:

$$\mathbf{A_t = A_O - K_O\, t}$$

Where, A_t = Drug release at time t

A_O = Initial drug concentration

K_O = Zero-order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release versus time, if the plot islinear then the data obeys zero-order release kinetics, with a slope equal to K_O.

- ✓ **First order kinetics[9]:**

  First order release would be predicted by the following equation:

$$\mathbf{\log C = \log C_O - Kt/2.303}$$

Where,C = Amount of drug remained at time t

C_O = Initial amount of drug

K = First order rate constant (hr^{-1}).

Whenthedataisplottedaslog cumulativepercentdrugremainingversus timeyieldsastraightline,indicatesthat thereleasefollowsFirst-orderkinetics. The constant ‘Kt’ can be obtained by multiplying 2.303 with slope values.

- ✓ **Higuchi’sModel[10]:**

Drugreleasedfromthematrixdevicesbydiffusionhas been described by following Higuchi’s classical diffusion equation:

$$\mathbf{Ft = Q = A \sqrt{D (2C - Cs) Cs\ t}}$$

Where, Q = Amount of drug released at time t

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

C_S= the solubility of the drug in the diffusion medium

ε = Porosity ofthe matrix

τ = Tortuosity

t = Time (hrs) at which ‘Q’ amount of drug is released.

This equationmay be simplified if one assumes that D, C_S and A are constant. Then equation becomes:

$$\mathbf{Q = Kt^{1/2}}$$

Whenthedataisplottedaccording to above equationi.e.,cumulativedrug releasedversussquarerootoftime,yields astraightline,indicatingthatthedrug was released by diffusion mechanism.The slope is equal to ‘K’.

- ✓ **KorsmeyerandPeppasModel[11]:**

Thereleaseratesfromcontrolledrelease polymericmatricescanbedescribed by the equation proposed by Korsmeyer*et al.*

$$\mathbf{Q = K_1 t^n}$$

Where, Q = Percentage of drug released at time t

K_1 = Kinetic constant incorporatingstructuralandgeometriccharacteristics of thetablets

n = Diffusional exponent indicative of the release mechanism.

ForFickianrelease,n=0.45,whileforanomalous(Non-Fickian)transport, n ranges between 0.45 and 0.89 and for zero order release, n = 0.89.

6.5. REFERENCES:

1. Indian Pharmacopoeia, Volume2,1199-1200, 2010.
2. Sharma YR. Elementary organic spectroscopy: Principles and chemical applications. 1stEdn.,S. Chand, New Delhi, 245-264, 1980.
3. Jana S., SahaA.,NayakAK,.SenKK., BasuSK. Aceclofenac-loaded chitosan-tamarind seed polysaccharide interpenetrating polymeric network microparticles. *Colloids and Surfaces B: Biointerfaces*, **105:** 303-309,2013.
4. Nandi G., Patra P., Priyadarshini R., Kaity S. Synthesis, Characterization and Evaluation of Methacrylamide Grafted Gellan as Sustained Release Tablet Matrix, *International Journal of Biological Macromolecules,* **72:**965-974, 2015.
5. Vijan V.,Kaity S.,Biswas S.,Isaac J.,Ghosh A. Microwave assisted synthesis and characterization of acrylamide grafted gellan, application in drug delivery. *Carbohydrate Polymers*, **90:** 496-506, 2012.
6. SilversteinRM., BasslerGC,.Morrill TC. Spectrometric Identification of Organic Compounds. 4thEdn.,Wiley, New York, 166, 1981.
7. Skoog DA.Principles of instrumental analysis. 5thEdn.,Harcourt Publishers, 203-221, 2001.
8. Baveja SK., Rao R.,Devi KPV. Zero-order release hydrophilic matrix tablets of beta-adrenergic blockers. *Int. J Pharm*, **39**: 39-45, 1987.
9. Narashimhan B., MallapragadaSK., PeppasNA.Release kinetics, data interpretation, In: Encyclopedia of controlled drug delivery, Mathiowitz E. 2ndEdn., John Wiley and Sons, Inc, New York, 921-951, 1999.
10. Dash SK., PadalaS., MurthyN., NathLK., ChowdhuryP. Kinetic modeling on drug release from controlled drug delivery systems.*ActaPoloniaePharmaceutica and Drug Research*, **67(3)**: 217-223, 2010.
11. CostaP., Lobo JMS. Modeling and comparison of dissolution profiles. *Eur J Pharm Sci*, **13**: 123-133, 2001.

CHAPTER: 7

RESULTS ANDDISCUSSION

7. RESULTS AND DISCUSSION:

7.1. EVALUATION OF DRUG:

7.1.1. Standard calibration curve of Diclofenac Sodium in 0.05 (M) Phosphate buffer pH 7.5:

Table 7.1. Standard calibration curve of Diclofenac Sodium in 0.05 (M) Phosphate buffer pH 7.5.

Sl. No.	Concentration (µg/ml)	Absorbance	Equation	R^2 Value
Blank	0	0	$y = 0.0294x + 0.0024$	0.9995
1	2	0.061		
2	4	0.123		
3	6	0.181		
4	8	0.235		
5	10	0.295		

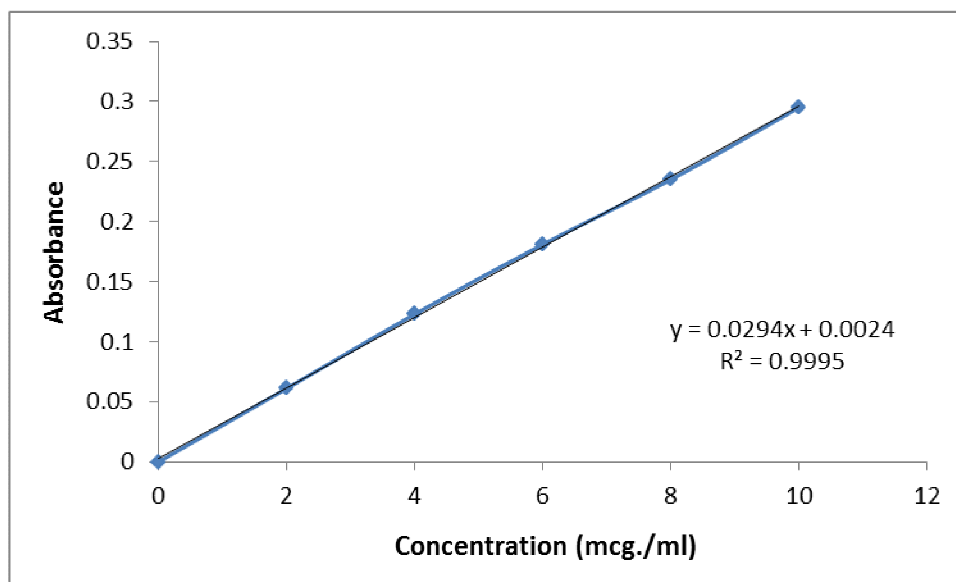


Fig. 7.1. Standard Calibration Curve of Diclofenac sodium in 0.05(M) phosphare buffer

Discussion:

Graph of absorbance versus concentration was plotted and found to be linear over the range of 2 to 10 µg/ml, indicating its compliance with Beer's Lambert's Law. λ_{max} was found at 276 nm which is similar to the official λ_{max} of the drug

7.1.2. Standard calibration curve of Diclofenac sodium in 0.1 (N) HCl buffer pH 1.2:

Table 7.2. Standard calibration curve of Diclofenac Sodium in 0.1 (N) HCl buffer pH 1.2

Sl. No.	Concentration (µg/ml)	Absorbance	Equation	R^2 Value
Blank	0	0	y = 0.006x + 0.0003	0.9979
1	2	0.012		
2	4	0.024		
3	6	0.038		
4	8	0.049		
5	10	0.059		

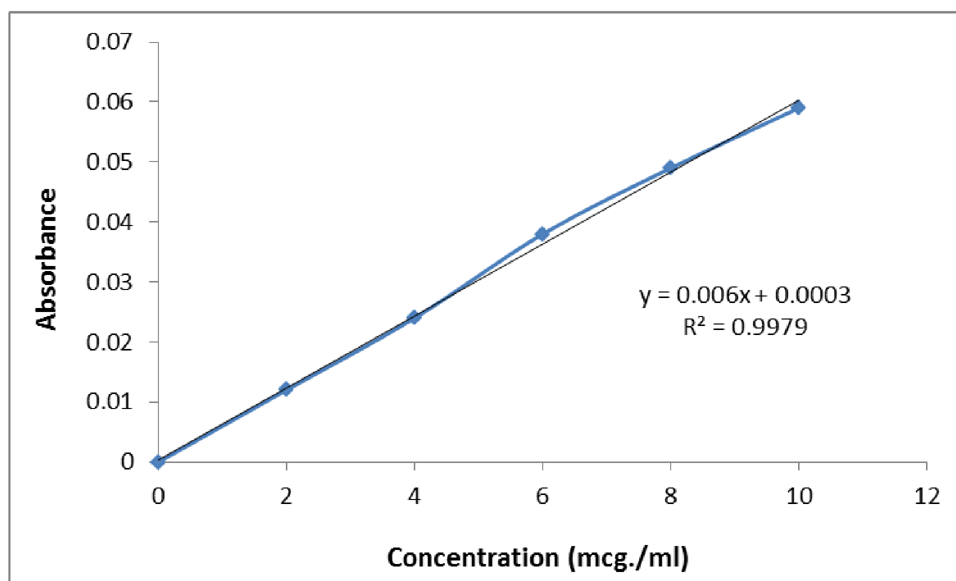


Fig. 7.2. Standard Calibration Curve of Diclofenac sodium in 0.1(N) HCl

Discussion:

Graph of absorbance versus concentration was plotted and found to be linear over the range of 2 to 10 µg/ml, indicating its compliance with Beer's Lambert's Law. λ_{max} was found at 275 nm which is fair enough.

7.2. Synthesis of Polymethacrylamide grafted gellan gum (Pmaa-g-GG):

Table 7.3. Synthetic details of polymethacrylamide-grafted-gellan gum

Batch Code	Amount of GG (gm)	Amount of Maa (gm)	Amount of CAN (mg)	Microwave irradiation time (min.)	Wt. of grafted gum (gm)

S 1	1.0030	10.0094	450	1	8.9605
S 2	1.0080	10.0582	430	1	8.0974
S 3	1.0082	10.0513	432	1	8.3494
S 4	1.0185	10.0015	410	1	8.0615

7.2.1. Grafting parameters of Polymethacrylamide grafted gellan gum (Pmaa-g-GG):

Different grafting parameters such as % grafting (%G), grafting efficiency (%GE) and % conversion (%C) were calculated using following formula (Eqs. (1)–(3)) to assess the efficiency of the synthesis.

%grafting (%G) = $(W_1 - W_0)/W_0 \times 100$ (1)

%grafting efficiency (%GE) = $(W_1 - W_0)/W_2 \times 100$ (2)

%conversion (%C) = $W_1/W_2 \times 100$ (3) ; where W_0, W_1 and W_2 are the weight of native gellan gum, grafted gellan gum and methacrylamide respectively.

Table 7.4. Synthetic details of polymethacrylamide-grafted-gellan gum

Batch Code	% Grafting (%G)	Grafting efficiency (%GE)	% Conversion (%C)
S 1	793.36	79.50	89.52
S 2	703.31	70.48	80.50
S 3	728.15	73.03	83.06
S 4	691.50	70.42	80.60

From these four batches (S 1, S 2. S 3 and S 4) a sum of 33.4688g of grafted gellan gum was obtained. After grinding some product was lost due to adhesion on grinder wall and the wt. of final product became 32.400 g. This product was then hydrolysed using 1 ltr. of 0.1 (N) NaOH which contained about 4.050 g of NaOH. The wt. of hydrolysed product was 35.450 g which means a certain percentage of the grafted gum got hydrolysed. After grinding the final

wt. of hydrolysed Pmaa-g-GG became 34.400 g due to some loss of product inside the grinder machine.

7.3. EVALUATION OF HYDROLYSED POLYMETHACRYLAMIDE GRAFTED GELLAN GUM (hPmaa-g-GG):

7.3.1.Rheological Studies:

Different rheological parameters of gellan hPmaa-g-GG (5%, w/v) was determined by a programmable Anton Paar Compact Rheometer. The parameters obtained are complex modulus (G*) and phase angel (δ). The elastic modulus (G'), viscous modulus (G") and dynamic viscosity (η') are calculated by the following equations:

$G' = G^* \cos(\delta)$; $G'' = G^* \sin(\delta)$; $\eta' = G^*/\omega$

where ω is the anguler frequency.

On the next page, **Figure 7.3** shows the rheological behavior of hPmaa-g-GGat 5% (w/v) concentration and **Figure 7.4** and **Figure 7.4(a)** show the same at 10% (w/v) concentration. From the graphs it can be said that at 10% (w/v) conc. The gum became very stable due to much more network formqtion after hydration

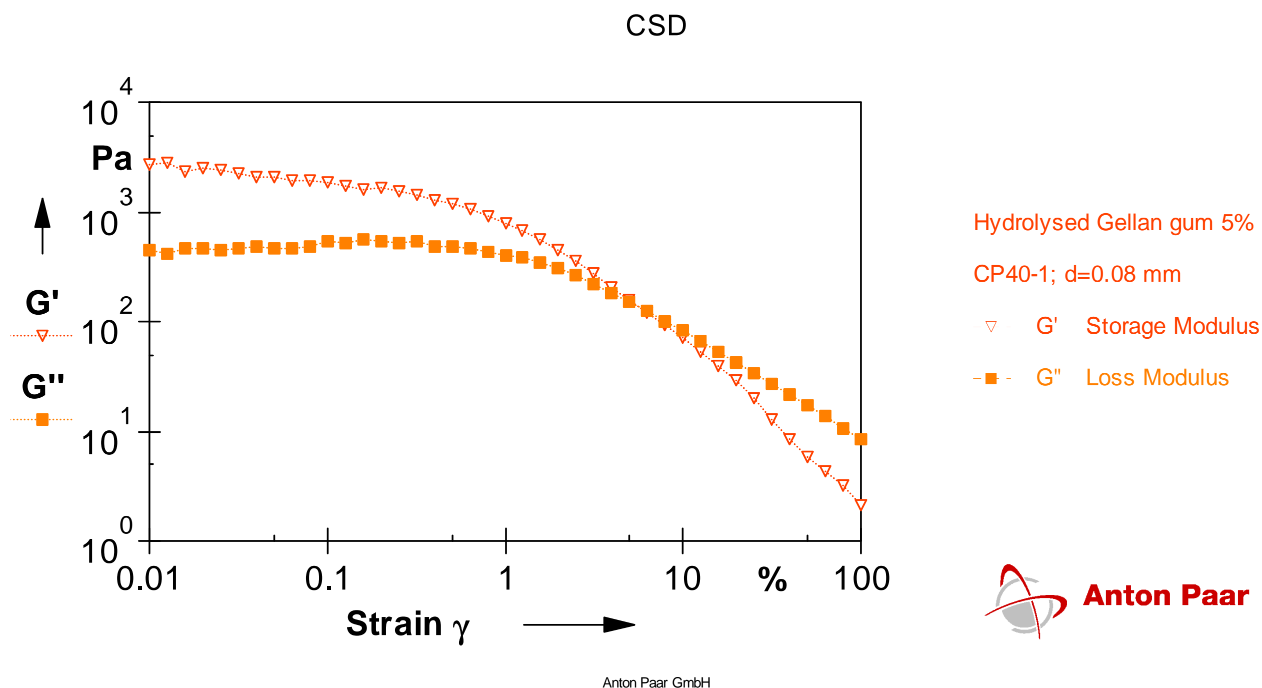


Figure 7.3. Rheological behavior of hPmaa-g-GG at 5% (w/v) concentration

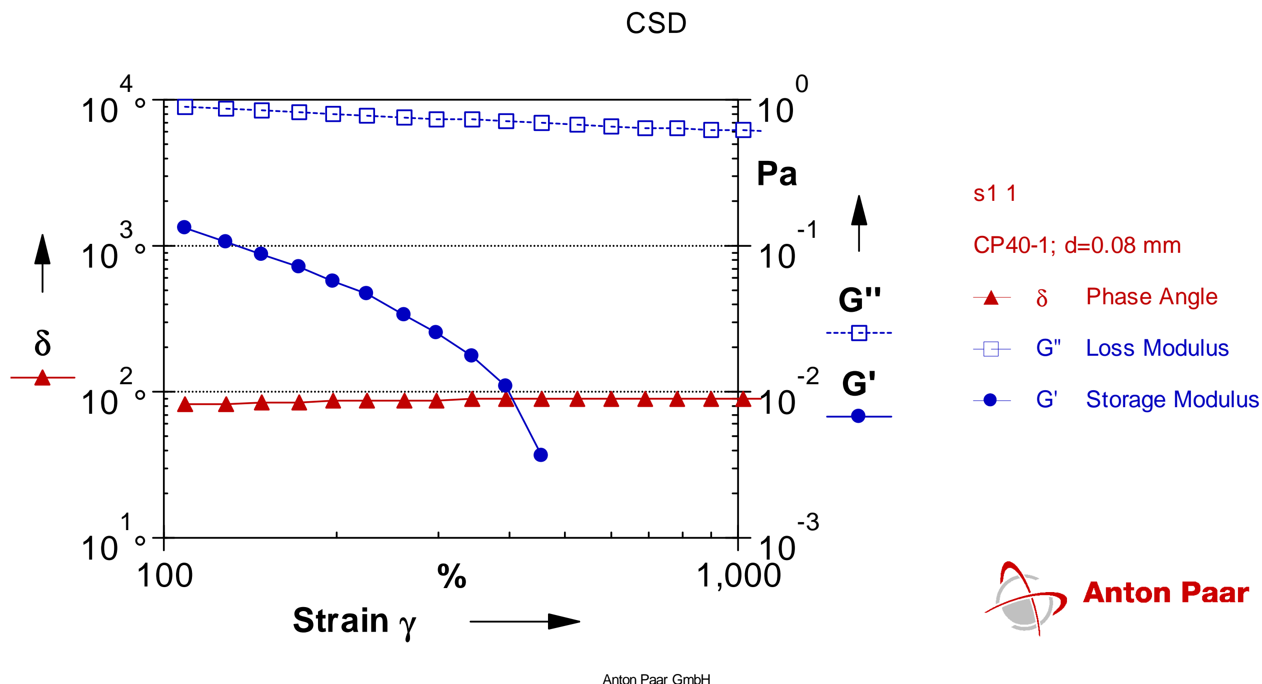


Figure 7.4. Rheological behavior of hPmaa-g-GG at 10% (w/v) concentration

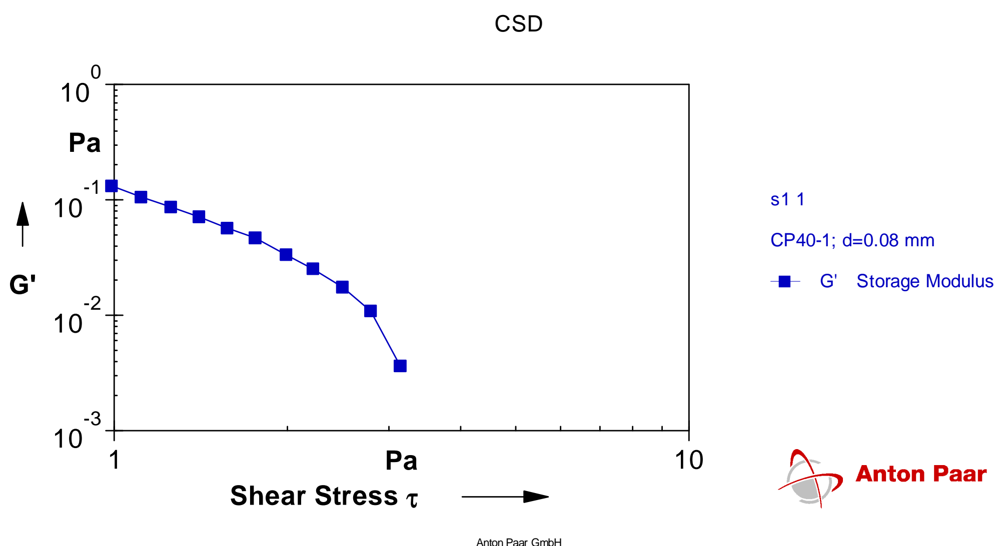


Figure 7.4(a) Shear stress vs. storage modulus of hPmaa-g-GG at 10% (w/v) conc.

7.3.3. Infrared spectral analysis:

Infrared spectra of gellan gum (GG) and hydrolysed grafted gum (hPmaa-g-GG) are shown in **Figure 7.5** and **7.6** respectively. GG showed characteristic peaks at 3292.49 cm^{-1} for –OH group, at 1080.14 cm^{-1} for etheric and alcoholic –C-O group.

Some differences were observed in spectra of hydrolysed grafted GG compared to GG. The infrared spectra of acrylamide hPmaa-g-GG shows characteristic peaks at 3595.60 cm^{-1} for $-NH_2$ group due to addition of methacrylamide which was grafted on to GG. An additional peak at 1685.79 was observed due to carbonyl group and another peak at 1207.44 for acidic –CO group conforms hydrolysis of the grafted gum.

Infrared spectra of diclofenac sodium and tablet formulation are shown in **Figure 7.7.** and **7.8** respectively. Diclofenac sodium shows the characteristic peaks at 1556.55 cm^{-1} and 1502.55 cm^{-1} for N-H bending, at 1454.33 cm^{-1} for C-C in aromatic ring. Peaks at 1284.88 $cm^{-1}$and 1087.85 cm^{-1} indicate C-N stretching and ester C-O group respectively. Peaks at 3080.25 cm^{-1} and at 745.82cm^{-1} indicate C-H bond in aromatic ring and C-Cl stretching respectively. All these peaks have been observed in the infrared spectra obtained from tablet formulation, which demonstrates that there is no significant incompatibility between the drug and the hydrolysed grafted gum.

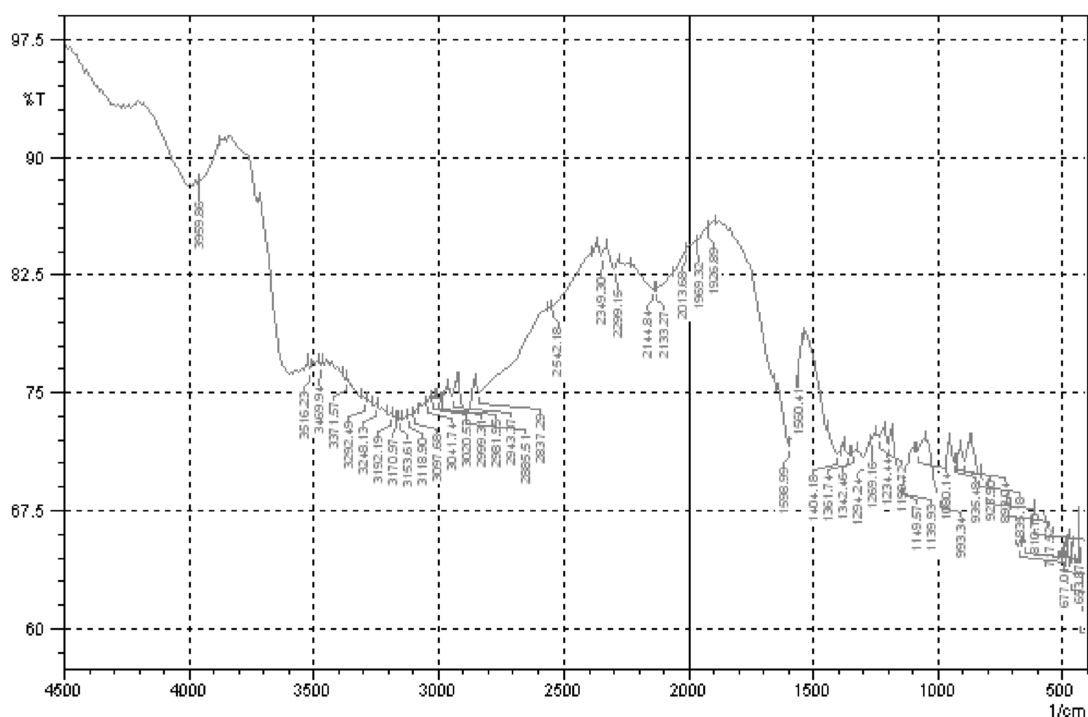


Figure 7.5. FTIR spectrum of Gellan Gum (GG)

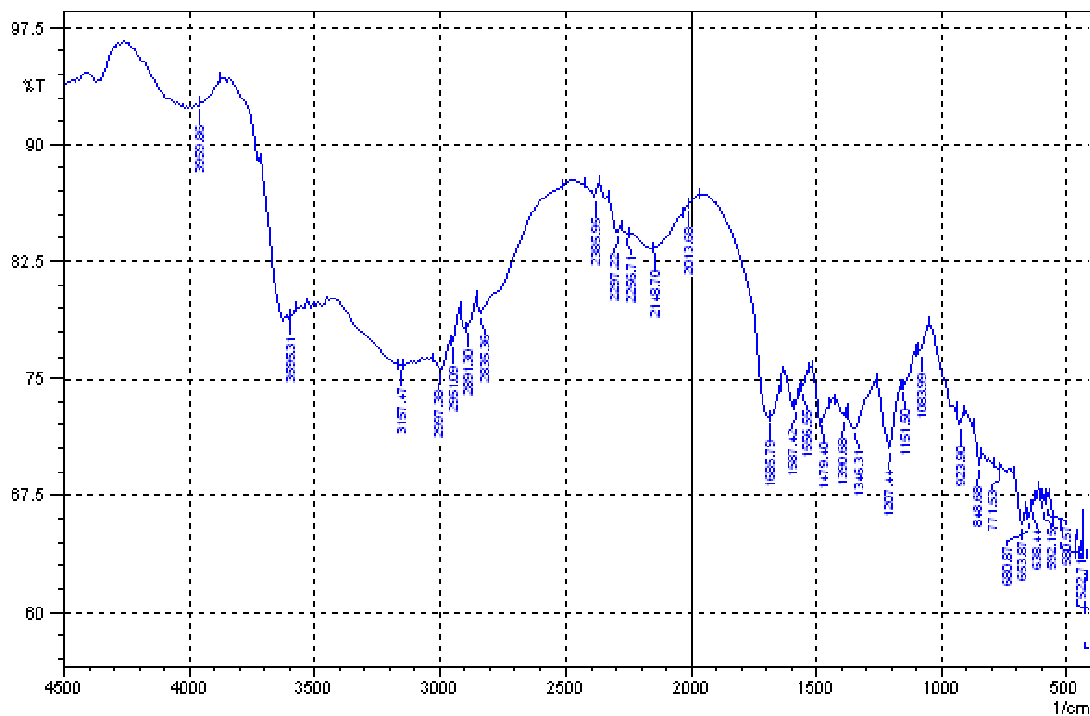


Figure 7.6. FTIR spectrum of Hydrolysed Polymethacrylamide grafted GG (hPmaa-g-GG)

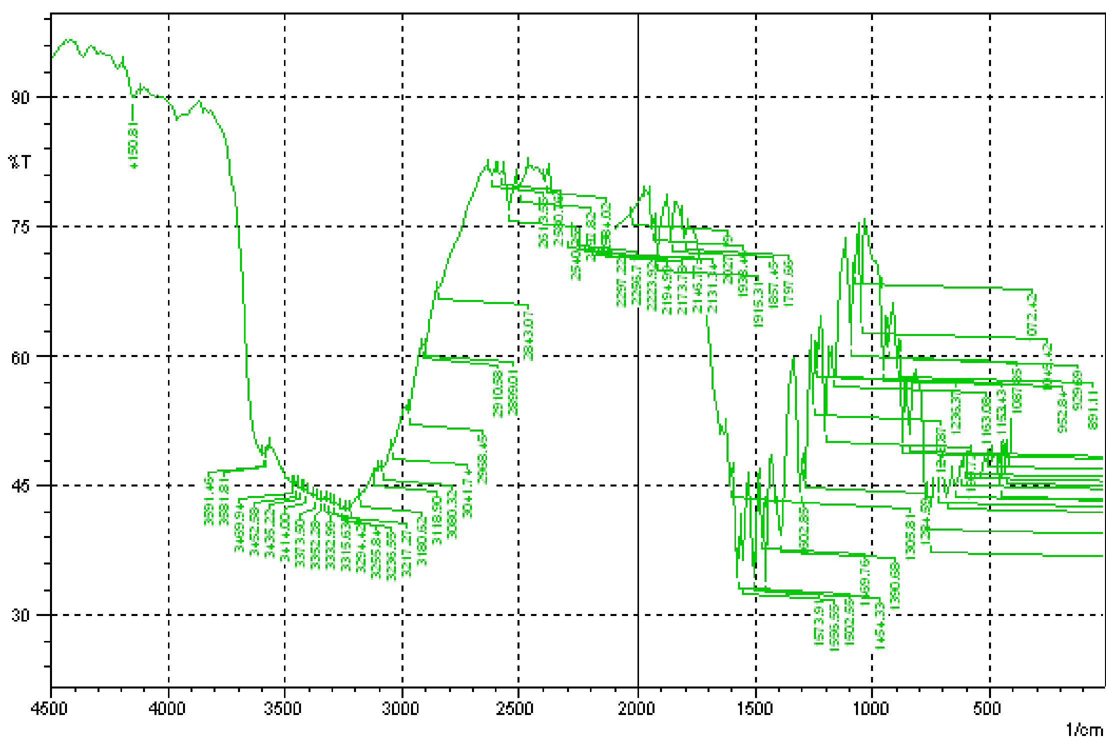


Figure 7.7. FTIR spectrum of Pure Diclofenac sodium

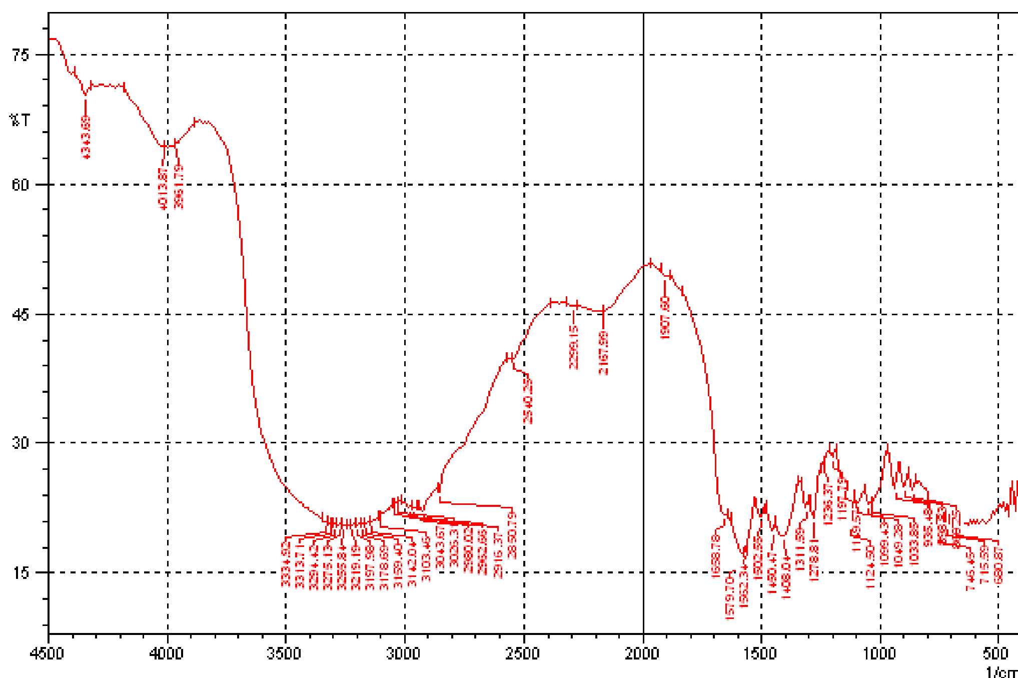


Figure 7.8. FTIR spectrum of prepared tablet formulation

7.3.4. Differential scanning calorimetry and thermogravimetric analysis:

DSC and TGA curves of GG, hPmaa-g-GG, diclofenac sodium and tablet formulations are shown in **Figure 7.9, 7.10, 7.11.** and **7.12.** respectively. An endothermic peak at 76⁰C was recorded in DSC thermogram of GG. TGA thermogram of GG shows a 43% weight loss in the temperature range from 30⁰C to 260⁰C. The correlation between endothermic peak and simultaneous reduction in weight indicates the loss in moisture present in the GG. DSC thermogram of hPmaa-g-GG shows an endothermic peak at 77⁰C similarly with GG indicating loss in moisture content, which is further established by the 30% reduction in weight in the temperature range from 30⁰C to 265⁰C observed in corresponding TGA curve. An endothermic peak at 67⁰C was observed in DSC thermogram of diclofenac sodium for moisture content. Another endothermic peak at 278⁰C and an exothermic peak at 306⁰C have been seen in DSC thermogram of diclofenac sodium, which indicates melting and subsequent thermal degradation respectively. Approximately 32% weight loss in the temperature range from 275⁰C to 340⁰C substantiates the thermal degradation of diclofenac sodium in the aforesaid temperature range. Two endothermic peaks at 78⁰C and 270⁰C observed in DSC

curve for tablet formulation demonstrate moisture loss and melting of diclofenac respectively. The significant change in melting point of drug in the formulation may be due to dilution effect in presence of other excipients.

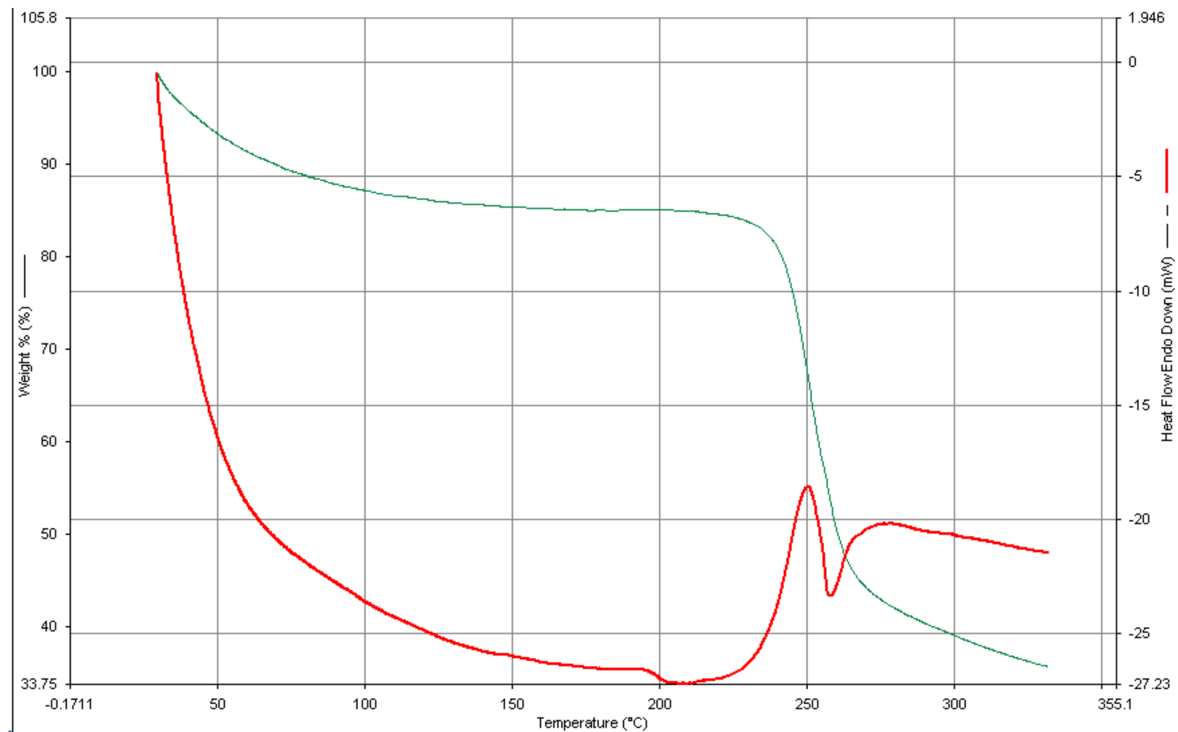


Figure 7.9. DSC thermogram of Gellan Gum (GG)

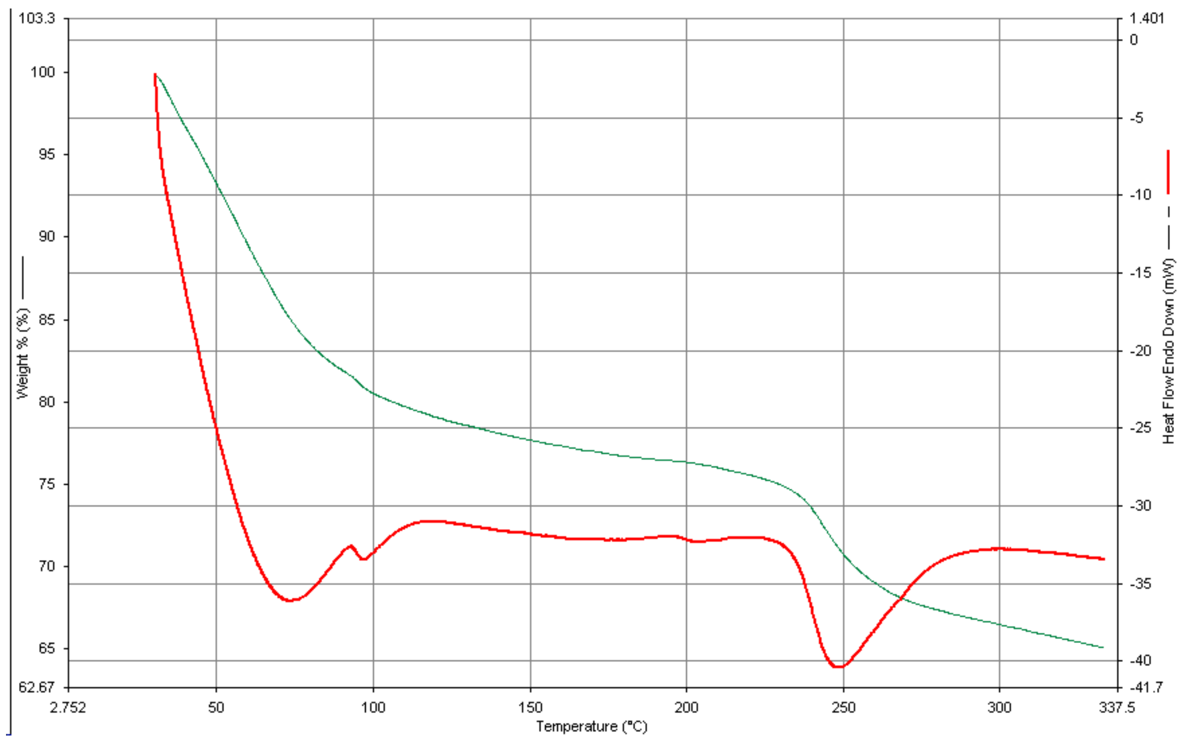


Figure 7.10. DSC thermogram of Hydrolysed Polymethacrylamide grafted Gellan Gum

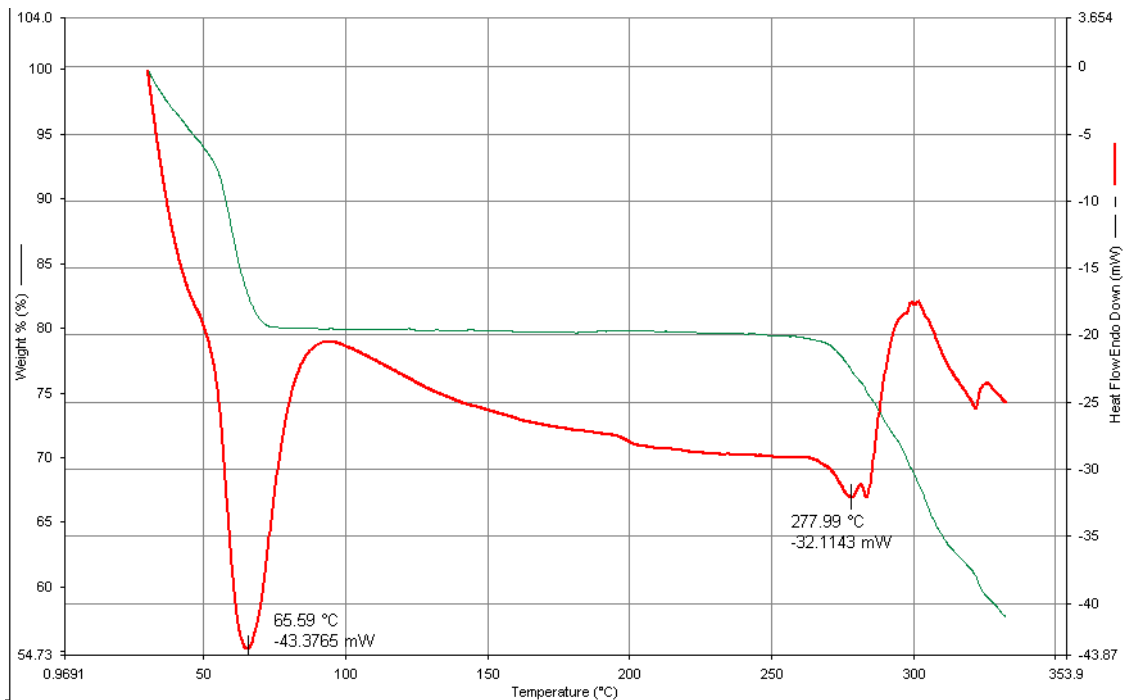


Figure 7.11. DSC thermogram of Pure Diclofenac sodium

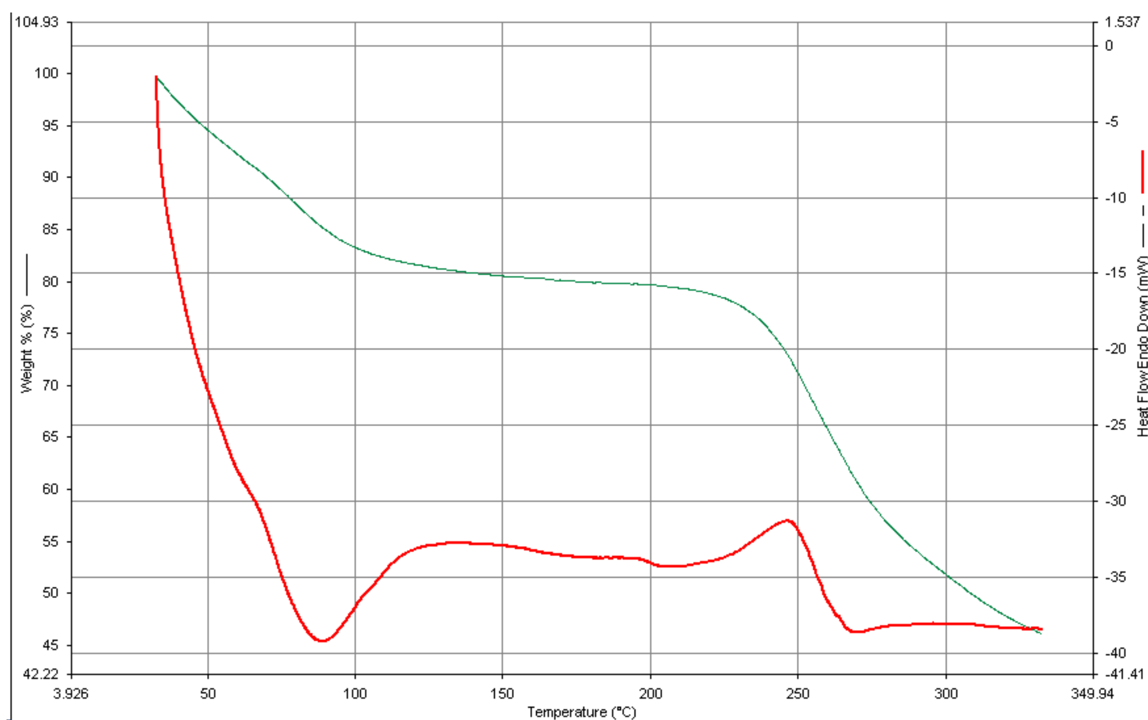


Figure 7.12. DSC thermogram of prepared tablet formulation

7.4 TABLET CHARACTERSTICS OF DIFFERENT FORMULATIONS:

Table 7.5. Physical parameters of tablets of different batches:

Batch No.	Avg. weight (mg)	Avg. diameter (mm)	Avg. thickness (mm)	Avg. hardness (kg)
F 1	292.5	7.9	4.98	4.5
F 2	369	9.0	4.86	4.6
F 3	368	8.9	4.85	4.6
F 4	442.5	9.0	5.81	4.8
F 5	368.5	8.9	4.85	4.7
F 6	443.5	9.0	5.81	5.0
F 7	445	9.0	5.82	5.1
F 8	520.5	9.1	6.44	5.3

7.5. *In vitro* DRUG RELEASE STUDY AND RELEASE MECHANISM IN 0.05 (M) PHOSPHATE BUFFER pH 7.5:

The cumulative percentage of drug release versus time curves obtained from different formulations (F1, F2, F3, F4, F5, F6, F7 and F8) is shown in **Figure 7.13**. The cumulative

percentage release at different time points profile (**Table 7.6**) reflects that the release of drug from the monolithic matrix tablet depends on the amount of hPmaa-g-GG, TSG and calcium lactate. In case of F1 and F2, amount of calcium lactate is higher in F2, so it shows drug release for a longer period than F1. It is probably due to more extent of cross linking by calcium lactate. In case of F3 and F4, calcium lactate plays the same role and due to higher amount of TSG in both formulations, they deliver the drug for a longer period compared to F1 and F2. In case of F5 and F6, calcium lactate controls drug delivery by cross linking, but due the presence of higher amount of hPmaa-g-GG compared to F1, F2, F3 and F4, both of them showed drug release for somewhat longer period than the previous four samples. It indicates that hPmaa-g-GG possess greater drug holding capacity than TSG in tablet matrix. In case of F7 and F8, drug release continues for more than 10 hours which is higher than the rest, F8 showed highest drug holding due to the higher amount of all three modulators. The regression coefficient (R^2) values and diffusion exponent (n) are shown in **Table 7.7**. The results demonstrate that all of the formulations followed Korsemeyer-Peppas release kinetic. The diffusion exponent (n) values for all the formulations are within the range of 1.0-1.5, which means the release mechanism is anomalous diffusion or non-Fickian diffusion.

Table 7.6. *In-vitro* drug release profiles from various tablets in phosphate buffer.

Time (Hrs.)	Cumulative Percent of Drug Release (%CDR)							
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8
0	0	0	0	0	0	0	0	0
0.25	4.8214	4.8214	4.0561	4.0561	2.9081	2.9081	2.9081	2.9081
0.5	10.9974	9.8495	9.0756	7.9277	6.7670	6.0017	6.0017	4.8537
0.75	14.8920	14.1139	12.9574	12.1794	9.8707	9.8622	7.9489	7.9362
1	21.0569	17.9872	17.2091	16.0527	15.2619	14.1139	12.1794	11.0314
2	43.3188	40.2236	36.0059	34.0799	32.1581	29.8495	27.1496	25.9889
3	63.4634	60.3682	53.4336	50.3511	47.2687	45.3299	41.0909	39.1649

4	79.7559	75.5127	68.5484	64.6879	60.4447	59.2755	53.4889	51.1717
5	91.7967	88.6887	80.5765	76.7074	72.4515	71.6734	63.5739	61.6352
6	99.9643	96.8690	91.0399	86.7882	82.9149	80.6105	72.4855	70.5510
7		100.7849	98.0425	94.9345	90.6828	88.7440	80.6190	78.6845
8			100.7976	100.7636	96.8903	94.9557	87.9787	85.6615
9					100.7849	99.9983	93.0340	90.7125
10							96.9158	94.9770

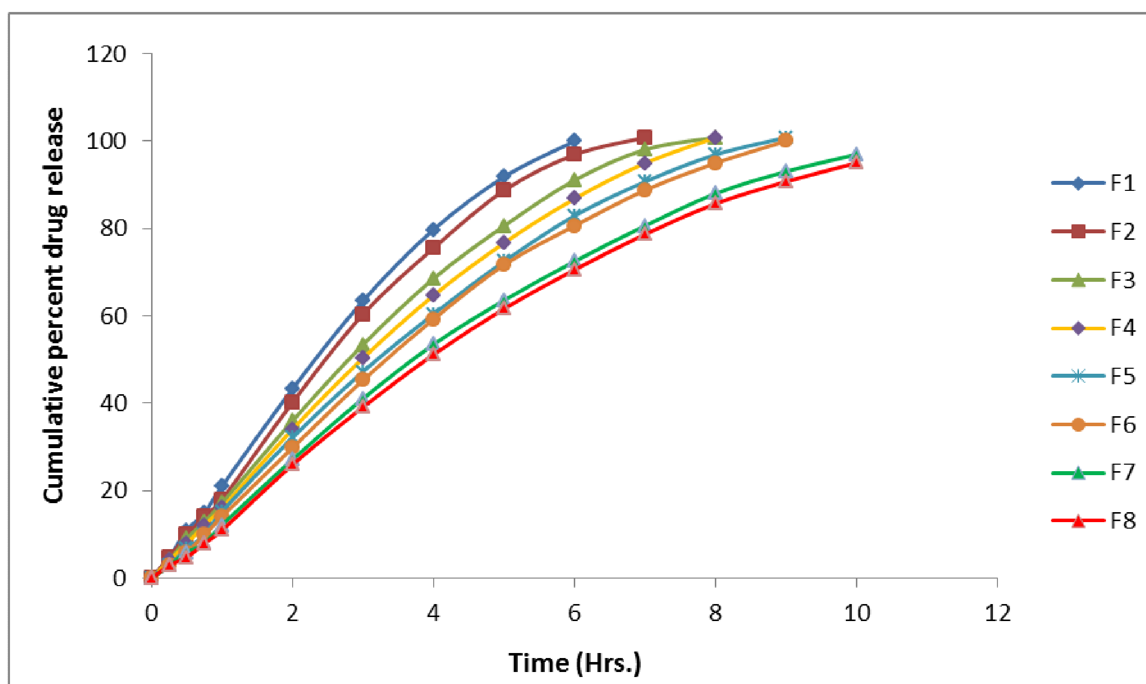


Figure 7.13. ***In-vitro*** **drug release profiles as per zero order kinetic model from various tablets in phosphate buffer**

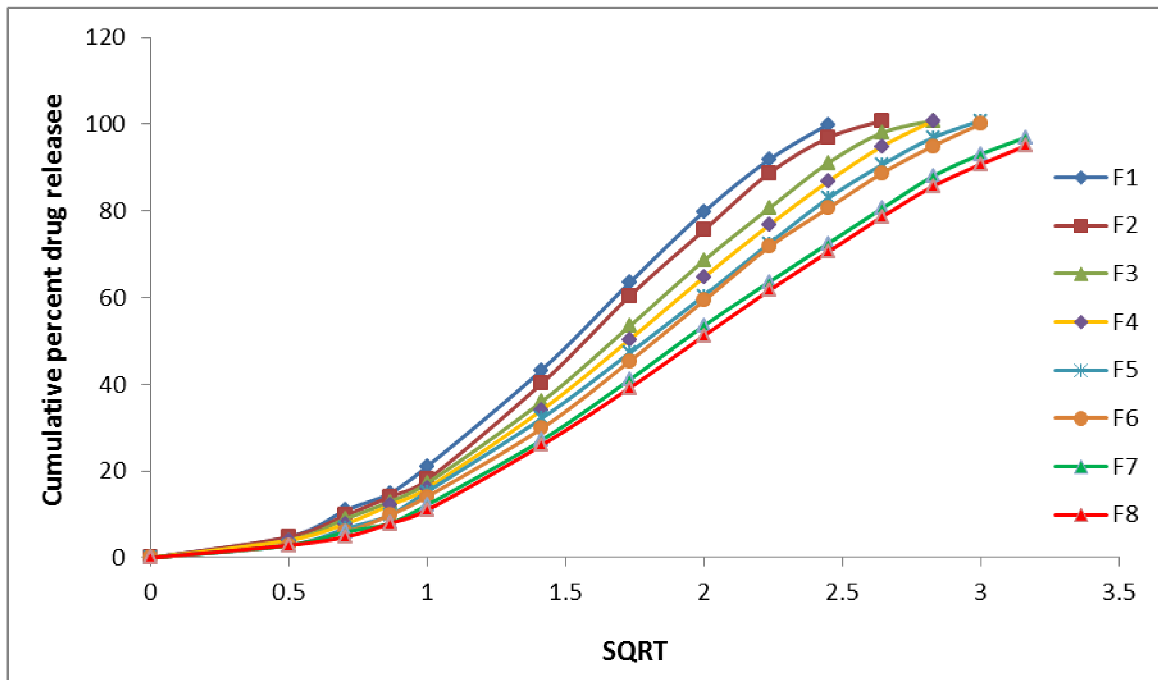


Figure 7.14. Comparison of Higuchi model followed by different tablets in phosphate buffer.

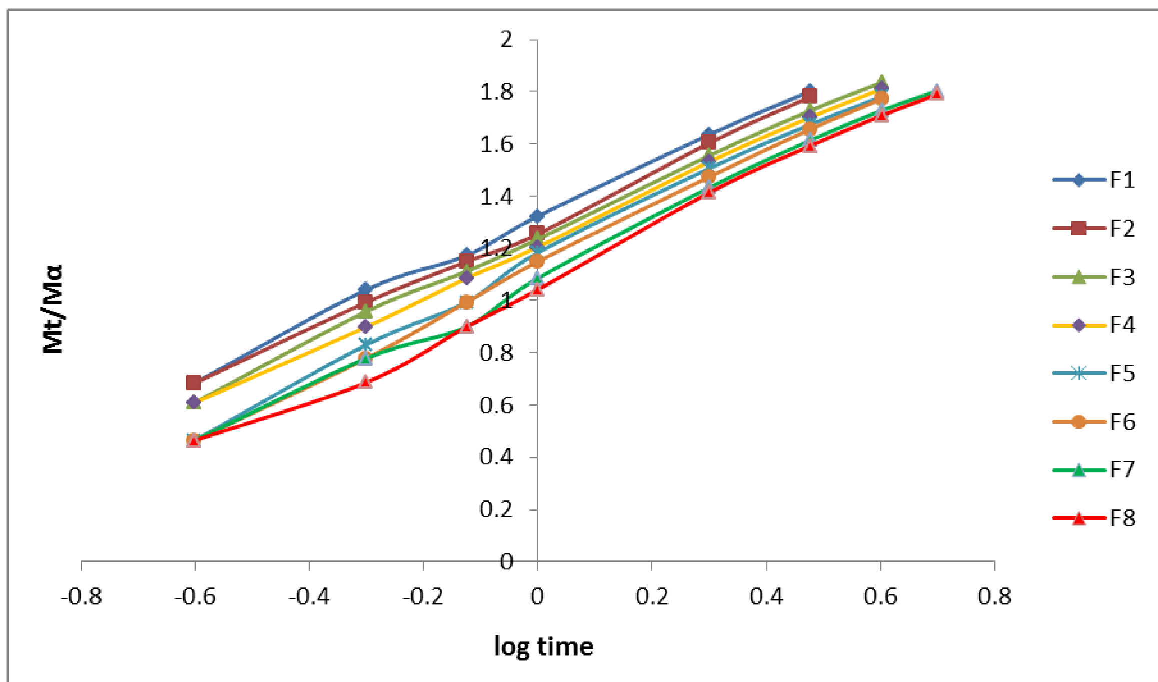


Figure 7.15. Comparison of Korsemeyer-Peppas model from tablets in phosphate buffer.

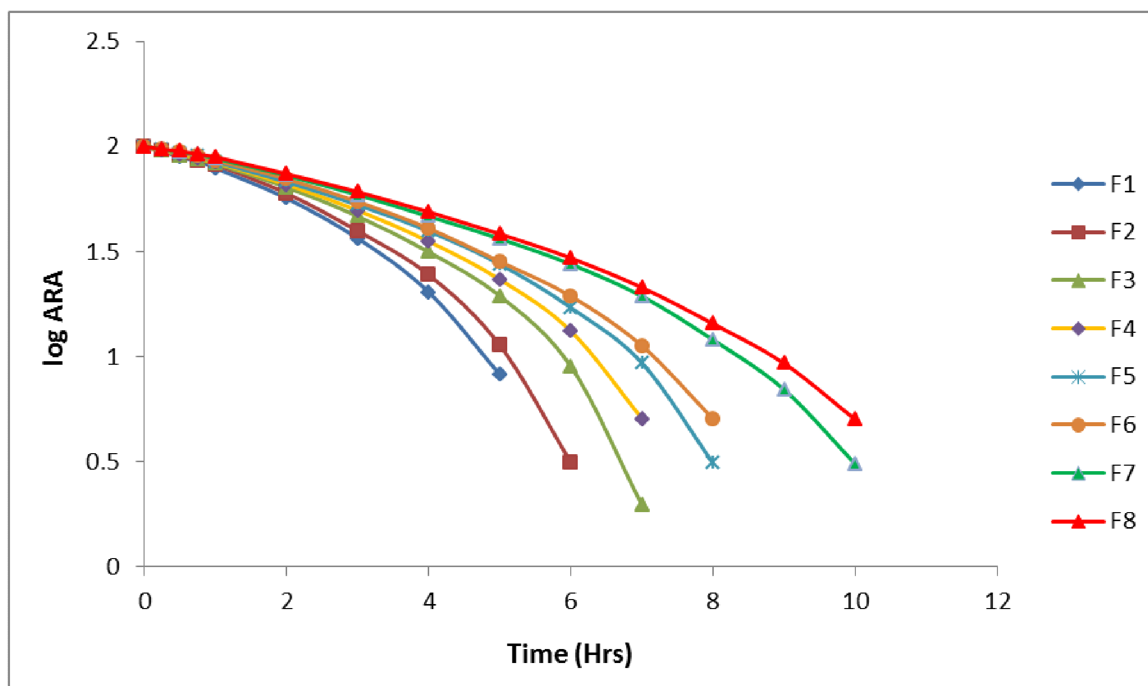


Figure 7.16. Comparison of First order kinetic model followed by different tablets in phosphate buffer.

Table 7.7. Model fitting analysis for phosphate buffer:

Batch No.	R^2 Values					Best fit model
	Zero order	First order	Higuchi	Korsemeyer-Peppas		
				R^2	n	
F 1	0.9833	0.9565	0.9591	0.9979	1.0307	Korsemeyer
F 2	0.9721	0.9253	0.9636	0.9981	1.0168	Korsemeyer
F 3	0.9722	0.8987	0.9697	0.9988	1.0164	Korsemeyer
F 4	0.9815	0.9405	0.9686	0.9995	1.0128	Korsemeyer
F 5	0.9746	0.9272	0.9719	0.9972	1.1023	Korsemeyer
F 6	0.9773	0.9508	0.9697	0.9990	1.1019	Korsemeyer
F 7	0.9761	0.9428	0.9731	0.9970	1.0588	Korsemeyer
F 8	0.9783	0.9612	0.9713	0.9954	1.0712	Korsemeyer

7.6. *In vitro* DRUG RELEASE STUDY AND RELEASE MECHANISM IN 0.1 (M) HCl BUFFER pH 1.2:

The cumulative percentage of drug release versus time curves obtained from different formulations (F1, F2, F3, F4, F5, F6, F7 and F8) is shown in **Figure 7.17**. The cumulative percentage release at different time points profile (**Table 7.8**) reflects that the release of drug from the monolithic matrix tablet depends on the amount of hPmaa-g-GG, TSG and calcium lactate. But here the effect of calcium lactate is not that much prominent as seen in case of phosphate buffer. The extent of drug release is considerably less in all formulations as compared to that in phosphate buffer. This is probably due to less solubility of diclofenac sodium and release modulators (i.e. hPmaa-g-GG, TSG etc.) in HCl. F3 and F4 showed drug release for a bit longer period of time as compared to F1 and F2 due to higher amount of grafted gum in them. F5 and F6 delivered drug for longer time than previous four formulations. It again indicates that hPmaa-g-GG possess greater drug holding capacity than TSG in tablet matrix. In case of F7 and F8, drug release continued for much longer period and also the extent of drug release was very low. The regression coefficient (R^2) values and diffusion exponent (n) are shown in **Table 7.9**. The results demonstrate that most of the formulations followed first order release kinetic. The diffusion exponent (n) values for all the formulations are within the range of 1.0-1.5, which means the release mechanism is anomalous diffusion or non-Fickian diffusion.

Table 7.8. *In-vitro* drug release profiles from various tablets in HCl buffer

Time (Hrs.)	Cumulative Percent of Drug Release (%CDR)							
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8
0	0	0	0	0	0	0	0	0
0.25	0	0	0	0	0	0	0	0
0.5	3.75	3.75	1.875	1.875	1.875	1.875	1.875	1.875
0.75	5.6666	7.5416	5.6458	5.6458	3.7708	5.6458	3.7708	3.7708
1	7.5625	9.4583	9.4375	9.4375	7.5416	11.3125	5.6666	7.5416
2	16.9583	18.8541	15.1041	15.1041	11.3333	13.25	13.1875	11.3333

3	26.4375	24.5833	22.6666	22.6666	17	20.7708	17.0208	17
4	34.0416	34.0208	35.875	37.75	24.5625	24.6041	22.6875	24.5625
5	39.75	41.625	41.6458	45.4166	32.1458	35.8958	30.25	30.2708
6	45.4375	47.3333	47.3333	49.25	37.8541	39.7708	35.9583	37.8333
7	51.125	54.8958	51.1458	53.0416	39.7916	43.5625	41.6458	41.6666
8	60.562	62.4791	56.8125	56.8333	47.3125	47.3541	47.3333	45.4583
9	64.4166	68.1875	62.5	62.5	56.7708	54.8958	49.2708	49.25
10	71.9583	70.125	64.4375	66.3125	60.625	60.6041	51.1666	51.1666

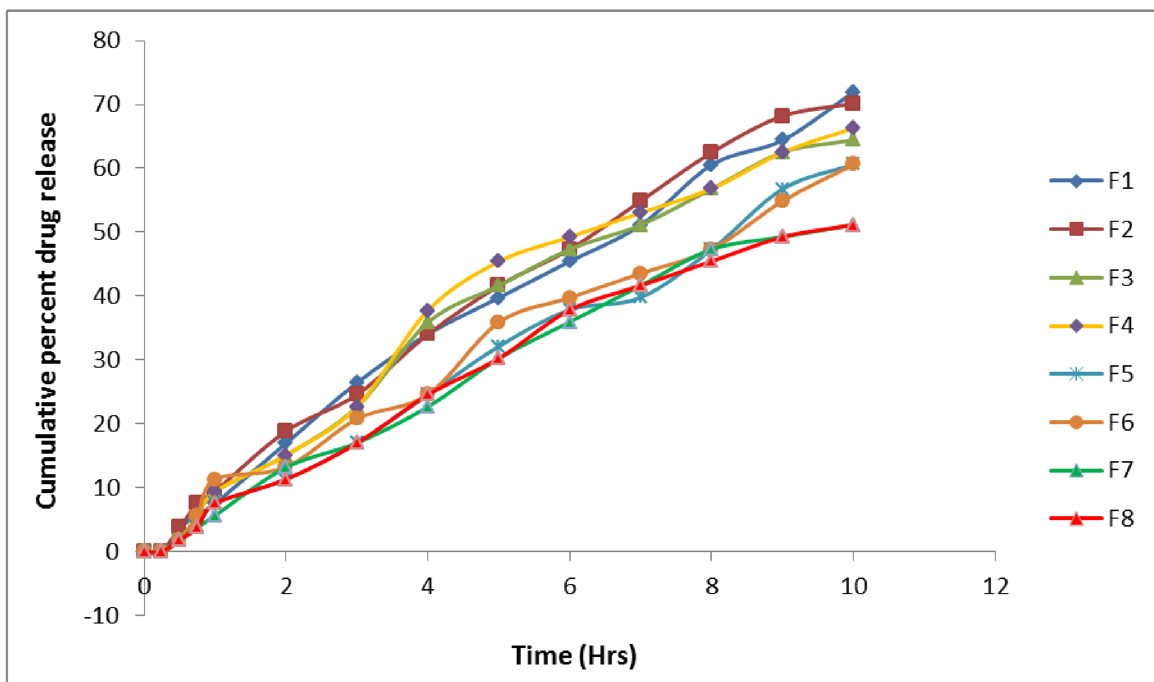


Figure 7.17. ***In-vitro*** **drug release profiles as per zero order kinetic model from various tablets in HCl buffer**

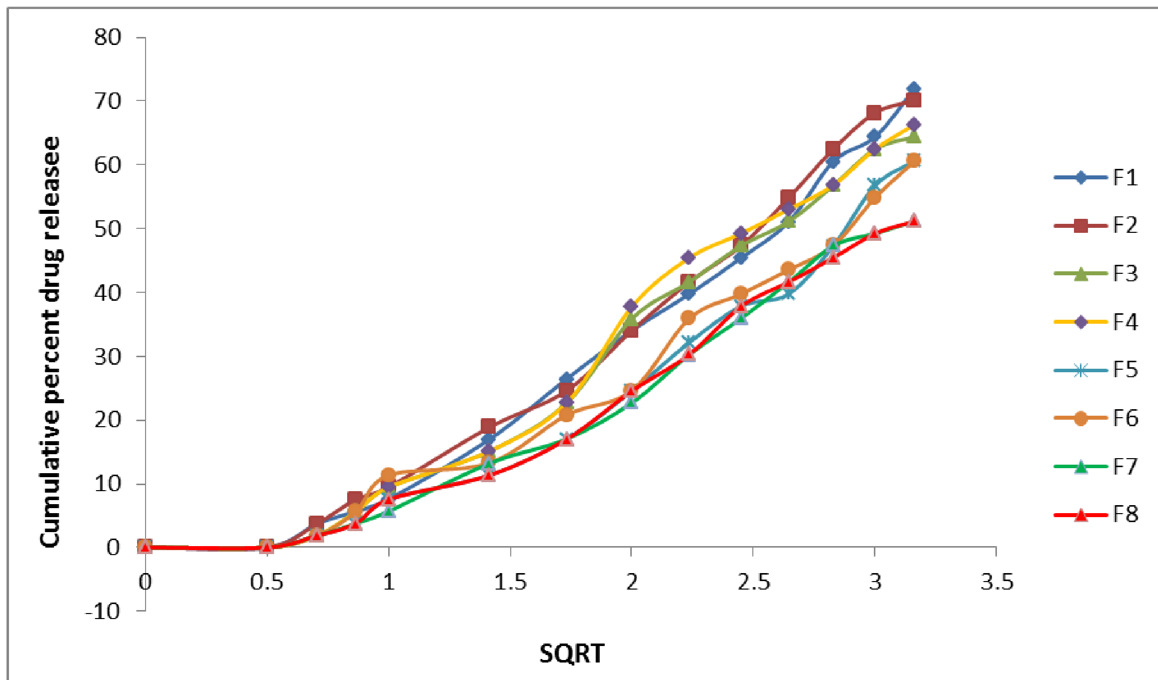


Figure 7.18. Comparison of Higuchi model followed by different tablets in HCl buffer.

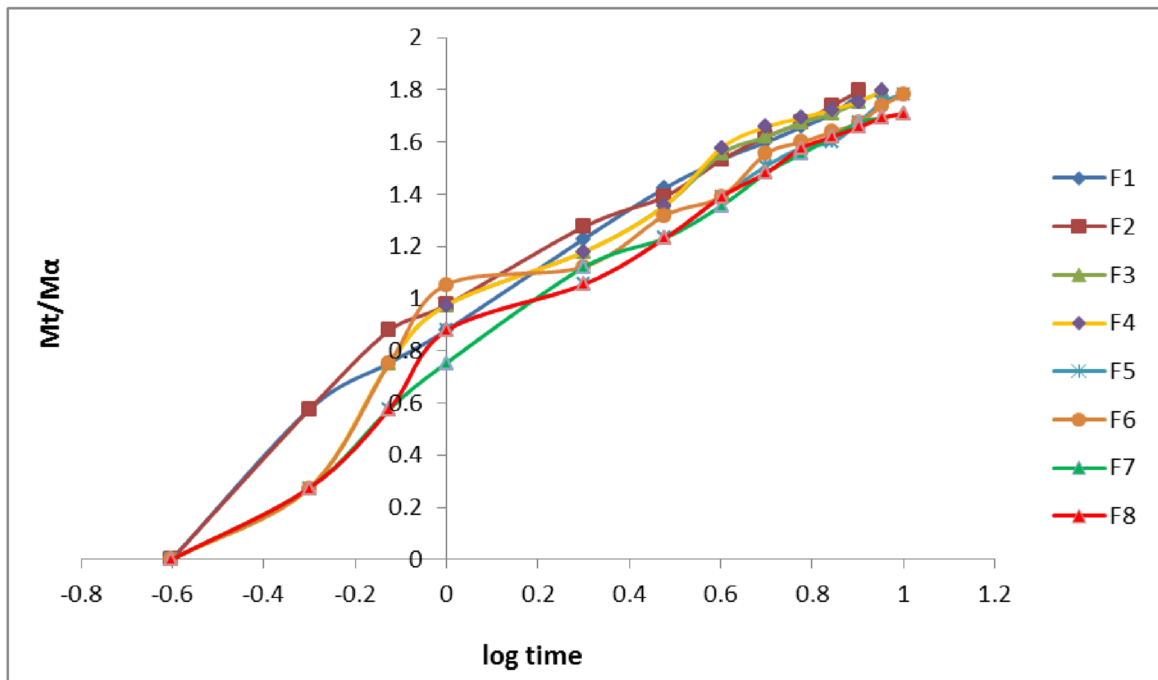


Figure 7.19. Comparison of Korsemeyer-Peppas model from tablets in HCl buffer.

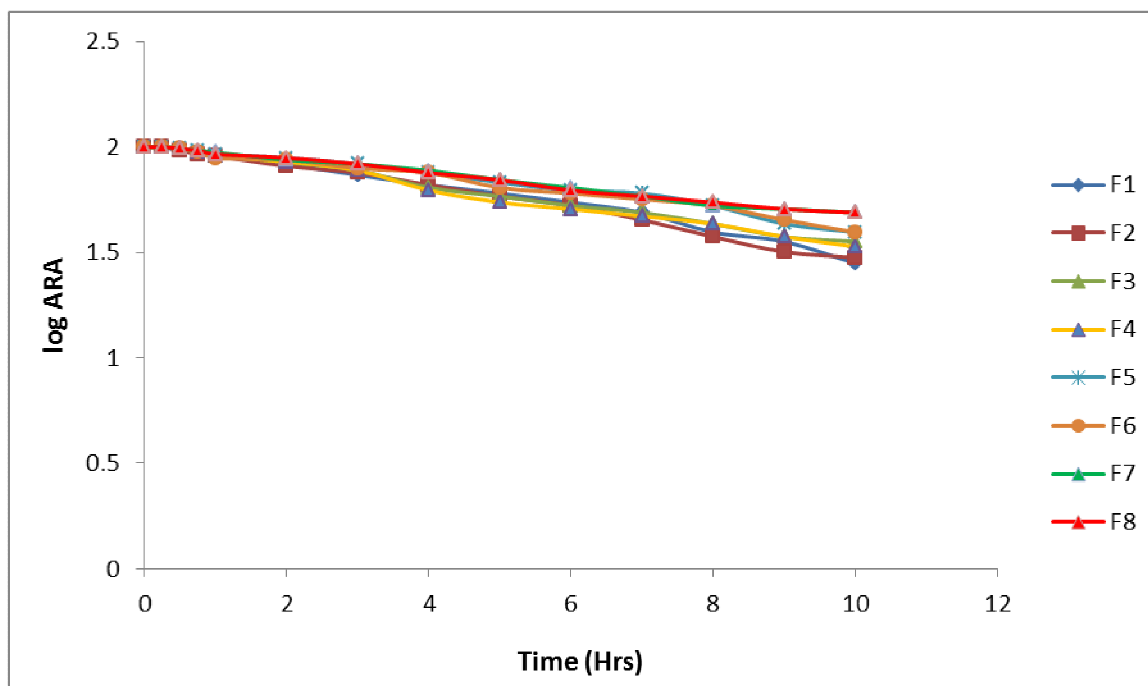


Figure 7.20. Comparison of First order kinetic model followed by different tablets in HCl buffer.

Table 7.9. Model fitting analysis

Batch No.	R^2 Values					Best fit model
	Zero order	First order	Higuchi	Korsemeyer-Peppas		
				R^2	n	
F 1	0.9932	0.9867	0.9623	0.9831	1.1084	Zero Order
F 2	0.9911	0.9921	0.965	0.9709	1.0876	First Order
F 3	0.9793	0.996	0.9656	0.973	1.1471	First Order
F 4	0.9712	0.9927	0.9632	0.9722	1.1577	First Order
F 5	0.9957	0.98	0.9385	0.9888	1.1051	Zero Order
F 6	0.9888	0.9885	0.9567	0.9603	1.0613	Zero Order
F 7	0.9891	0.9941	0.9556	0.992	1.0922	First Order
F 8	0.9871	0.9953	0.9583	0.9859	1.0804	First Order.

CHAPTER: 8

SUMMARY &CONCLUSION

8. SUMMARY &CONCLUSION:

Polymethacrylamide grafted gellan gum (Pmaa-g-GG) was synthesized using microwave-promoted cerric (IV) ion initiated graft copolymerization method. The synthesis was carried out with adequate amount of gellan gum, methacrylamide, CAN and optimum microwave irradiation time to get satisfactory yield. Solubility of grafted gum was considerably increased by hydrolysis. Sustained release tablet of water soluble drug diclofenac sodium was formulated using the hPmaa-g-GG as major rate controlling polymer. Effect of TSG was also observed.The hydrolysed grafted gum showed its capability to deliver the drug for a long period of time; upto 10 hours in many cases. Tablets followed korsemeyer-peppas model in phosphate buffer and first order model in HCl buffer. Drug delivery rate was much low in HCl buffer as compared to phosphate buffer which means this gum can be used in colon targeted drug delivery. The rate of drug release was regular in most cases and the amount of drug released in first 30 min. was low. It means using a coat of drug on the outer part of tablet without grafted gum, we can develop a tablet which will deliver a certain amount of drug initially to achieve therapeutically active plasma level of drug within a short time and then maintain the level for several hours. FTIR studies of drug and hydrolysed polymethacrylamidegrafted GG were carried out to establish compatibility between drug and modified polymer. Thus, microwave-promoted cerric (IV) initiated graft copolymerization is an easy, efficient, less time consuming, reproducible and one-pot synthesis method for the development of graft copolymer which can be fabricated as sustained release polymer in a desired sustained-release drug delivery device.

FUTURE PLAN OF WORK:

- ✓ Long term stability study.
- ✓ *In-vivo*pharmacokinetic study with suitable animal model.
- ✓ Development of colon targeted drug delivery system.
- ✓ Development of bilayer sustained release tablet.