THESIS PAPER
ON

MICROWAVE ASSISTED SYNTHESIS AND CHARACTERIZATION OF METHACRYLIC ACID GRAFTED GELLAN GUM, APPLICATION IN DRUG DELIVERY

Submitted By:
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Session: **2014-2016**

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Thesis paper leading to thesis
Submitted in the partial fulfilment of the requirements for the Degree of Master of Pharmacy
in Dept. of Pharmaceutical Technology
JADAVPUR UNIVERSITY
2016

FORWARDING CERTIFICATE

This is to certify that Prasenjit Hudati, B.Pharm.(***Examination Roll No:*** **M4PHA1604,** ***Registration No: 112037 of 2010-2011****) has carried out his research work entitle* **"MICROWAVE ASSISTED SYNTHESIS AND CHARACTERIZATION OF METHACRYLIC ACID GRAFTED GELLAN GUM,APPLICATION IN DRUG DELIVERY"** *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 fulfillment of requirements for the award of the degree of* ***MASTER OF PHARMACY.***

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

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Declaration of Originality and Compliance of Academic Ethics

*I hereby declare that this thesis contains literature survey and original research work by me (**Prasenjit Hudati**), 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.

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Thesis Title ***:*** **MICROWAVE ASSISTED SYNTHESIS AND CHARACTERIZATION OF METHACRYLIC ACID GRAFTED GELLAN GUM, APPLICATION IN DRUG DELIVERY**

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CERTIFICATE OF APPROVAL

This is to certify that ***Prasenjit Hudati (Examination Roll No: M4PHA1604, Registration No: 112037 of 2010-2011)*** has carried out the research work on the subject entitled **"MICROWAVE ASSISTED SYNTHESIS AND CHARACTERIZATION OF ACRYLAMIDE GRAFTED TAMARIND SEED GUM, APPLICATION IN DRUG DELIVERY"** 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.

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Dedicated ***To my beloved***
Teachers, my family
And my friends.

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This is to certify that Prasenjit Hudati, Roll No: M4PHA1604, Reg.No112037 of 2010 – 2011 has carried out his Thesis paper on the subject ***"MICROWAVE ASSISTED SYNTHESIS AND CHARACTERIZATION OF METHACRYLIC ACID GRAFTED GELLAN GUM, APPLICATION IN DRUG DELIVERY"*** *under my supervision in the Dept. of Pharm. Tech. of this University. I am really pleased and satisfied with her term paper in the 2nd semester for Master of Pharmacy. She has carried out her work independently with proper care and attention.*

I appreciate her endeavour to do the term paper and her work has reached my entire satisfaction.

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(**Prasenjit Hudati)**

Date……

CONTENTS:

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. Despite tremendous advancement in drug delivery, oral route remains the preferred route for the administration of therapeutic agents and oral drug delivery is by far the most preferable route of drug delivery because of low cost of therapy. Ease of administration leads to high levels of patient compliance and the gastrointestinal physiology offers more flexibility in dosage form design than most other routes. Consequently much effort has been put into development of strategies that could improve patient compliance through oral route[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. Historical aspect 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. In this regard, scientists are trying to formulate novel drug delivery systems employing microencapsulation technology as one of the methods of formulation development for various dosage forms. The history of controlled-release technology can be divided roughly into three time periods. From 1950-1970 is the period of sustained drug release. A number of system containing hydrophobic polymers and waxes were fabricated with drugs into dosage form with the aim of sustaining drug levels and hence drug action for an extended period of time. However, a lack of understandings of anatomical and physiological barriers imposed impediments on the development of efficient delivery system. The period 1970 to 1990 was involved in the determination of the needs in controlled drug delivery and to understand the barriers for various routes of administration. Post 1990 is the modern era of controlled release technology and represents the period in which an attempt at drug optimization is emphasized. 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
- Better utilization of drugs
- Reduced adverse effects
- Improved efficacy

1.3. Conventional drug therapy[8,9]**:**

To appreciate the value of sustained released drug delivery to therapy it is necessary to review some aspect of conventional dosage forms and drug therapy. In most cases of conventional dosage form the dosing interval is much shorter than the half-life of the drug resulting in a number of limitations

- Unless the dosing interval is relatively short, depending on biological half-life of the drug, large peaks and valleys in the drug level will occur.
- Success by this approach is dependent on patient compliance with the dosing regimen. Numerous studies have documented that lack of compliance is an important reason for drug therapy inefficiency or failure.
- During the early periods of dosing there may be insufficient drug to generate a favorable 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 a situation -

- Development of new, better and safer 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. 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.

1.4.5. Objective, Advantage and disadvantage of controlled/sustained drug delivery system[12-15]**:**

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:

- Patient will get uninterrupted therapeutic response for a prolonged period.
- 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. On the other hand multidose conventional delivery system is wasteful.

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 side effects

- ❖ Minimize or eliminate 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 is 3-4 times and 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. 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[16].
- ❖ **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].

In the 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.

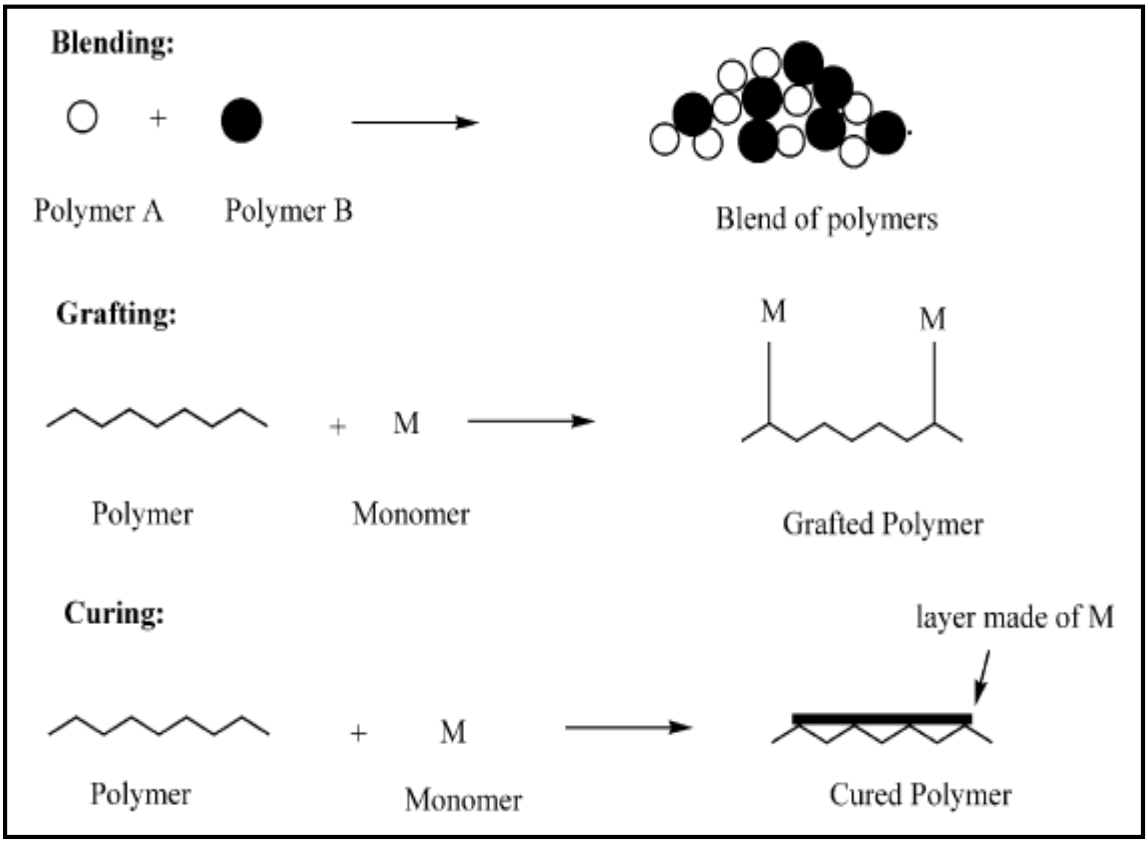


Figure 1.2. Showing the procedures of Blending, Grafting and Curing

1.5.1. 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.

1.5.2. 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.

1.5.2.1. 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.

1.5.2.2. 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:

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

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

1.5.2.3. Grafting through living polymerization:

In recent years, methods of 'Living Polymerization' have developed to provide a potential for grafting 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].

1.5.2.4. 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:

$$ACl + R_3Al \rightarrow A^+R_3AlCl^-$$

$$A^+ + M \rightarrow AM^+\text{-}M \rightarrow \text{graft co-polymer}$$

Cationic catalyst BF3 can also be used. Grafting can also proceed through an anionic mechanism. Sodium ammonia 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:

$$P\text{-}OH + NaOR \rightarrow PO^-Na^+ + ROH$$

$$PO^- + M \rightarrow POM^-\text{-}M \rightarrow \text{graft co-polymer}$$

1.5.2.5. Grafting initiated by radiation technique:

1.5.2.5.1. 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.

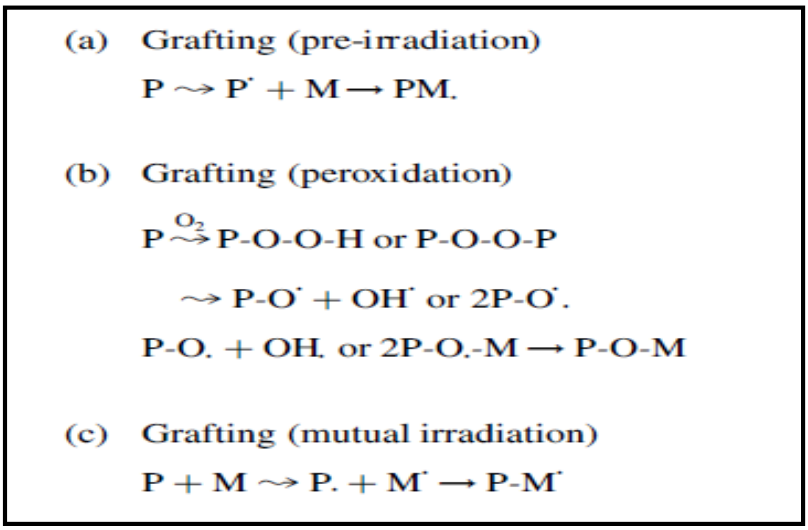


Figure 1.3. Showing mechanism of grafting (pre-irradiation, peroxidation, mutual irradiation)

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 radiation doses are sufficient to bring about the requisite grafting.

1.5.2.6. 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.

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.

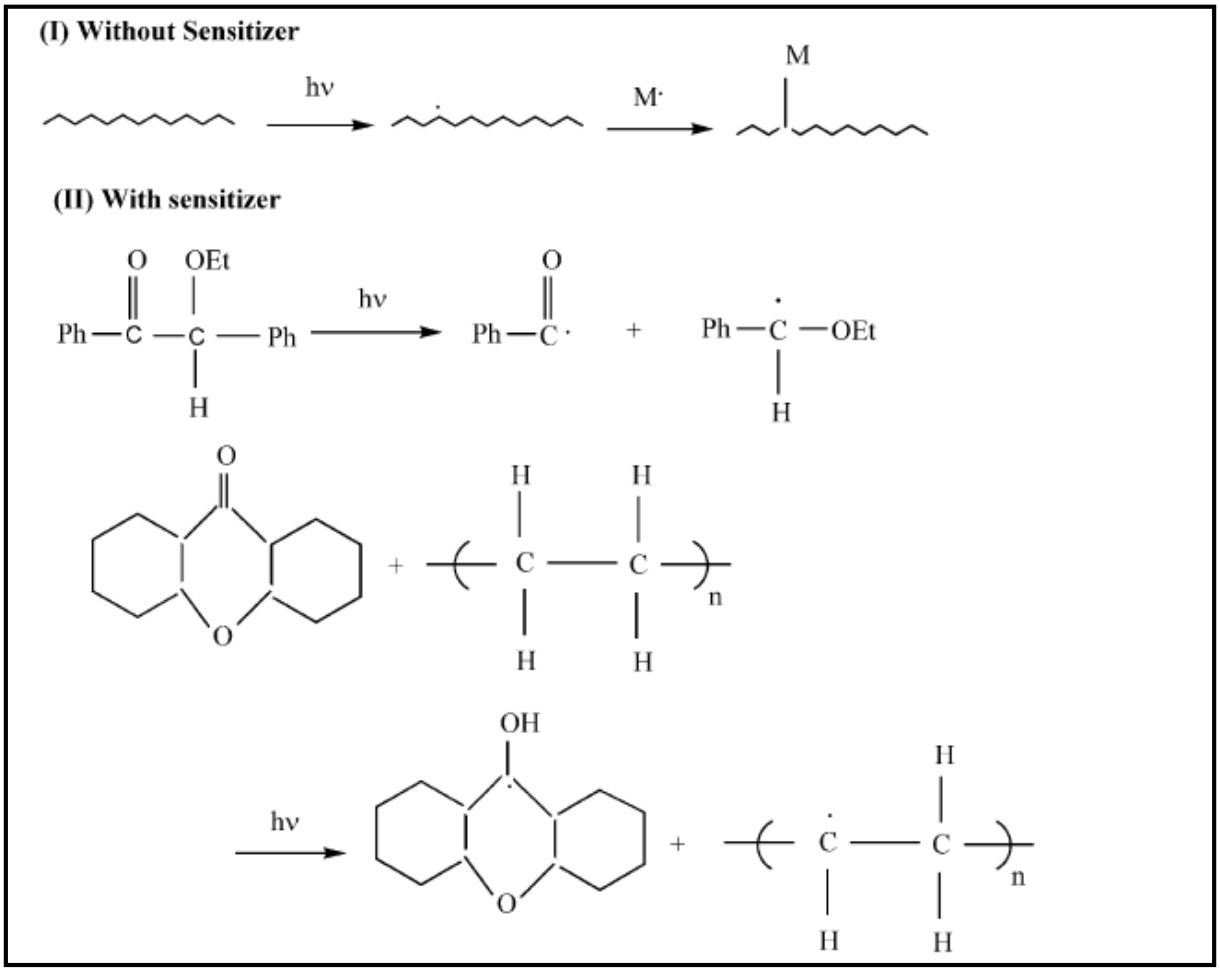


Figure 1.4. Process involved in photochemical grafting

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

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

$$\text{CeO}^{\cdot} + n\text{M} \rightarrow \text{CeO-M}_n\text{-M}^{\cdot}$$

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 solvent etc.

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.

2.3.Introduction of Rheology:

Material scientists have investigated the flow and strain properties of materials since the 17^{th} century. The term rheology was first used in physics and chemistry by E.c. binghamand M. reiner on 29 April 1929 when the American Society of rheology was founded in Columbus, Ohio. Rheological parameters are mechanical properties. They include physical properties of liquids and solids which describe strain and flow behaviour (temporal variation of strain).Strain is observed in all materials and substances when exerting external forces. Rheometry describes measuring methods and devices used to determine rheological properties.

If an external force is exerted on a body, its particles will be displaced relative to each other. This displacement of particles is known as strain. Type and extent of strain are characteristic properties of a body. Ideally elastic bodies undergo elastic strain if external anisotropic forces are exerted on them. The energy needed for this strain is stored and effects spontaneous full recovery of the original form if the external force ceases to act.

Ideally viscous bodies undergo an irreversible strain if external anisotropic forces (e.g. gravitational force) are exerted on them. The input energy is transformed. This increasing viscous strain is known as flowing. There are only few fluids with practical importance which show (almost) ideally viscous behaviour. Most materials are neither ideally viscous nor ideally plastic. They rather exhibit different behaviour and are thus called visco-elastic materials. The most simple model to illustrate rheological properties is the parallel plate model. The topplate, which has a surface area A [m^2], is moved by a force F [$N = kgm/s^2$] at a speed v [m/s].The bottom plate remains at rest. The distance between the plates, to which the material adheres, is described by h [m].Now thinnest elements of the liquid will be displaced between the plates. This laminar flowis of fundamental importance for rheological investigations. Turbulent flows increase the flow resistance thus showing false rheological properties.

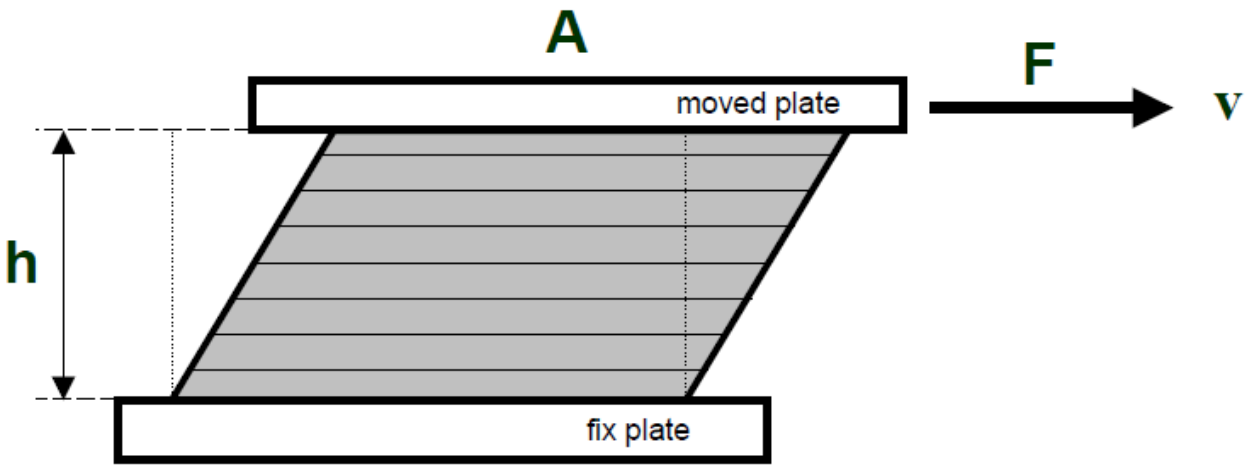


Fig. 2.1: Parallel plate model

Shear rate	$\dot{\gamma} = v / h$	**in s^{-1}**
Shear stress	$\tau = F / A$	**in Pa**
Viscosity	$\eta = \tau / \dot{\gamma}$	**in Pas**
Strain	$\gamma = dx / h$	**dimensionless**

In addition to the expression γ& , the symbol D is also used for the shear rate. Shear tests are usually conducted using rotation viscometers. In contrast to the parallel plate model, the moved surface performs a rotary movement.

2.3.6.1.Flow and viscosity curves:

The flow behaviour of a material is characterised by the relation between shear stress and shearrate γ& . A γ& diagram is often used for graphic representation. Usually, the shear stress is shown on the ordinate and the abscissa the shear rate, irrespective of whether γ were given for the measurement. These diagrams are referred to as flow functions or flow curves.

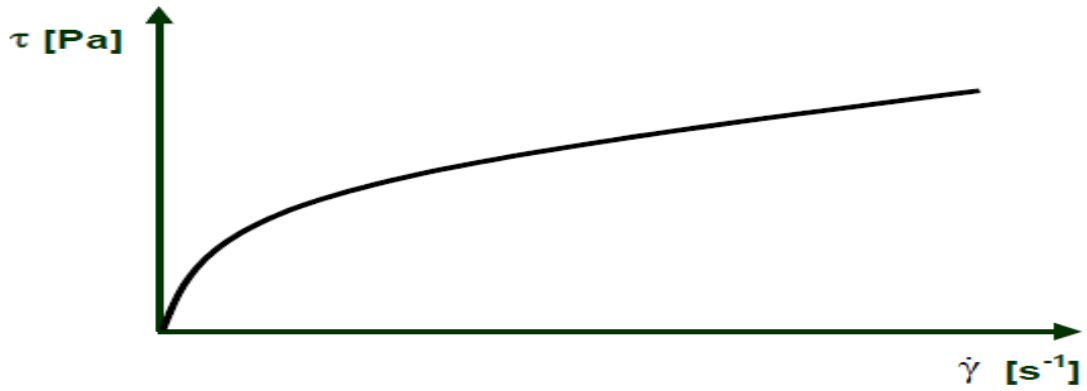


Fig. 2.2.: Flow curve

Plotting the viscosity over the shear rate γ& or shear stress produces the viscosity function or viscosity curve.

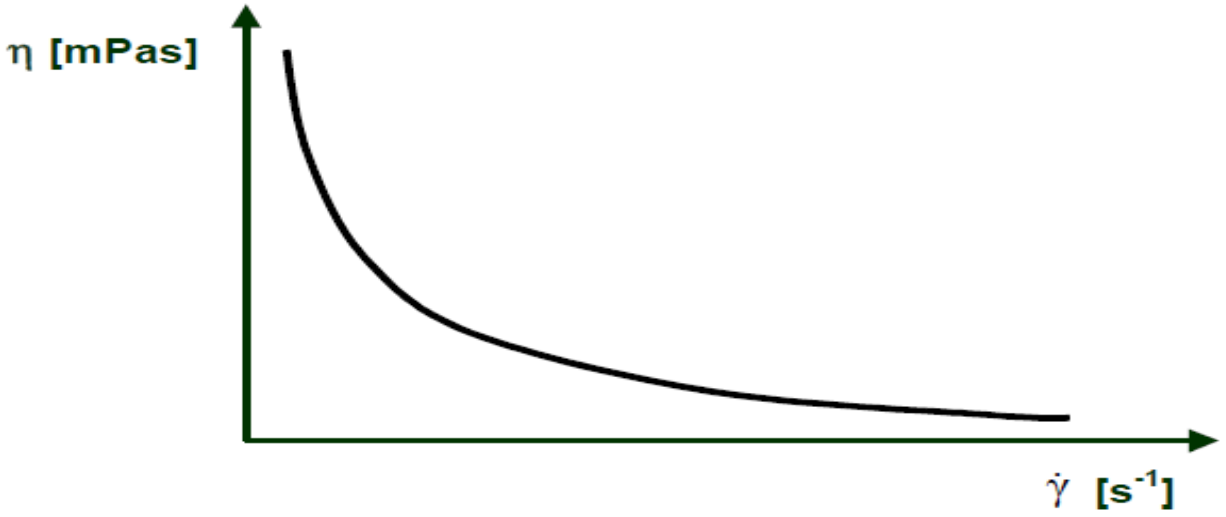


Fig. 2.3: Viscosity curve

The measuring result obtained with a viscometer or rheometer is always a flow curve. However, the viscosity function can be calculated based on the measured values.

2.3.6.2.Newtonian flow behavior:

if a newtonian material is subjected to a shear stress, a shear gradient γ& of viscous flow is generated which is proportional to the applied shear stress. the flow function of a Newtonian material is a straight line which runs through the origin of the coordinate system at an angle. this relation between shear stress and shear gradient is described by newton's law of viscosity.

$$\eta = \frac{\tau}{\dot{\gamma}} = \text{const.}$$

η is the material constant of the dynamic shear viscosity. If the viscosity is plotted over the shear

rate (or shear stress) in a viscosity diagram, a straight line which starts at γ& and runs parallel to the abscissa is obtained for an ideally viscous material.

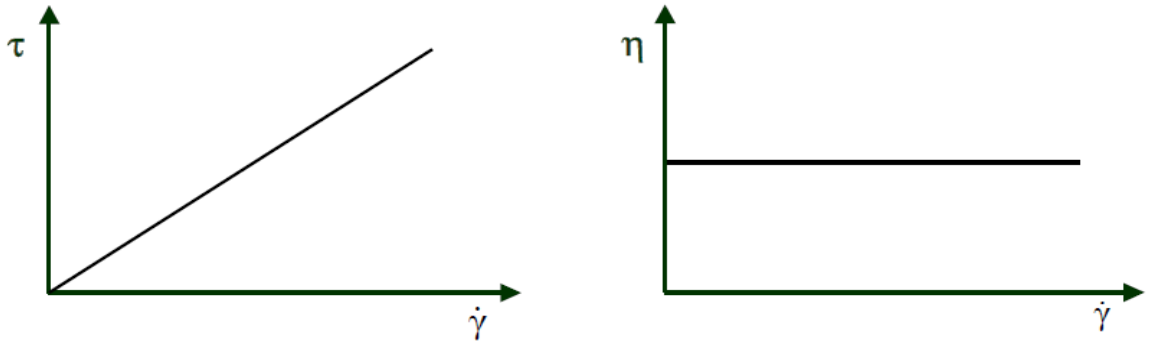


Fig.2.4:Flow curves of Newtonian materials

the viscosity of a newtonian material or ideally viscous material is independent of the shear rate. examples of newtonian materials: water, mineral oil, sugar solution, bitumen according to newton, a viscous body may be represented by the mechanical model of a damper.

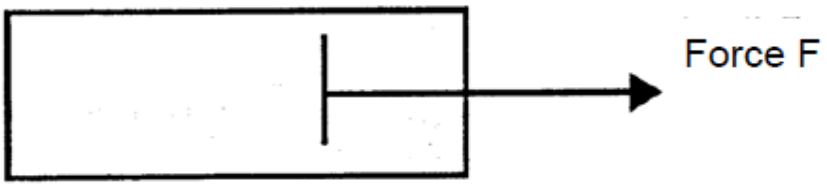


Fig.2.5: Mechanical model of a newtonian body

It can be shown with the help of this model that the material is continuously deformed in the damper as long as a force acts on the piston. If the force ceases to act, the original shape is not restored. A viscous strain is characterised in that the energy input to create a flow is fully transformed into heat in an irreversible process. Materials which show only little interaction between (usually short) molecules exhibit newtonian flow behaviour.

2.3.6.3.Pseudoplasticity:

Many materials exhibit a strong decrease in viscosity if the shear rate grows. This effect is of great technical importance. Compared with an ideally viscous material, a pseudoplastic or structurally viscous material can be pumped through pipelines with a lower energy input at the same flow velocity.

$$\tau / \dot{\gamma} = \eta \neq \text{const.}$$

the proportionality factor γ & in the newtonian constitutive equation is thus referred to as the apparent viscosity and denotes the viscosity at a certain shear rate γ &. mathematical expression for pseudoplastic materials according to ostwald de waele:

$$\tau = K \cdot \dot{\gamma}^{n}$$

REFERENCES:

1. Robinson JR., Lee VHL. Controlled drug delivery: fundamentals and applications. 2nd Edn., Marcel Dekker, Inc., NY, 352-384, 1987.
2. Chien YW. Novel drug delivery systems. 2nd Edn., Marcel Dekker, Inc., NY, 396- 431, 1992
3. Lachman L., Lieberman HA., Kaling JL. The theory and practice of industrial pharmacy. 3rd Edn., Varghese Publishing House, Bombay, 430-439, 1998.
4. Ahmad A., Murtaza G., Waheed A., Naeem AM. Salbutamol sulphate-ethylcellulose microparticles: formulation and in-vitro evaluation with emphasis on mathematical approaches. DARU, 17: 209-216, 2009.
5. Gwen JM., Sustained and controlled release drug delivery systems. In: Robinson JR, editor. Modern pharmaceutics. 2nd Edn., 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. 3rd Edn., Marcel Dekker, Inc., NY, 304-325, 2001.
7. Li VHK., Robinson JR., Lee VHL. Controlled drug delivery systems. 2nd Edn., Marcel Dekker, Inc., NY, 325-334, 1987.
8. Robinson JR., Eriksen SP. 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. 2nd Edn., 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. 2nd Edn., Marcel Dekker, Inc., NY, 335-374, 1996.
12. Fick A., Poggendroffs K. Controlled porosity osmotic pump. J.Pharm Sci Tech, 32: 59-74, 1985.
13. Crank J. The mathematics of Diffusion. 2nd Edn., Oxford, Oxford University Press, 314-337, 1996.
14. Higuchi T. Mechanism of rate of sustained-action medication. J.Pharm sci, 12: 874-897, 1961.
15. Ghosh LK. Hand book of pharmaceutical technology. 1st Edn., CBS Publishers & Distributors, New Delhi, 59-67, 2002.
16. http://grafting/Monomers and Polymers - Introduction to Monomers and Polymers.html.
17. Zohuriaan MJ. Advances in chitin and chitosan modification through graft copolymerization: A comprehensive review. Iranian Polymer Journal, 14: 235–265, 2005.
18. Soppimath KS., 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). Vysokomol Soedin Ser 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 Polym Sci Polym Chem, 18: 749–752, 1980.
21. Mishra BN., Mehta IK., Khetrapal RC. Grafting onto cellulose. VIII. Graft copolymerization of poly (ethylacrylate) onto cellulose by use of redox initiators. Comparison of initiator reactivities. J Polym Sci Polym Chem, 22: 2767–2775, 1984.

22. Prasanth KVH., 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 Polym Sci Polym Chem, 36: IX–XV, 1998.
25. Russell KE. Free radical graft polymerization and copolymerization at high temperatures. Prog Polym Sci, 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 Chem Soc, 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. Chem Eur J, 5: 3095–3102, 1999.
31. Coessens V., Pintauer T., Matyjaszewski K. Functional polymers by atom transfer radical polymerization. Prog Polym Sci, 26: 337–377, 2001.
32. Kato M., Kamigaito M., Sawamoto M., Higashimura T. Polymerization of methylmethacrylate with the carbon tetrachloride/dichlorotris (triphenylphosphine) ruthenium (II)/ methylaluminum bis(2,6-di-tert-butylphenoxide) initiating system: possibility of living radical polymerization. Macromolecules, 28: 1721–1723, 1995.
33. Uflyand IE., Ilchenko IA., Sheinker VN., Savostyanov VS. Polymers containing metal chelate units. VI. Post-graft polymerization of metal chelate monomers based on 1- phenyl-4-methyl pent-4-ene-1, 3 dione. React Funct Polym, 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. Nucl Instrum 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 Appl Polym Sci, 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 Appl Polym Sci, 59: 389–397, 1996.
40. Kaur I., Misra BN., Barsola R., Singla K. Viscometric studies of starch-g-polyacrylamide composites. J Appl Polym Sci, 47: 1165–1174, 1993.
41. Basu S., Bhattacharya A., Mondal PC., Bhattacharyya SN. Spectroscopic evidence for grafting of N-vinyl carbazole on cellulose acetate film. J Polym Sci, Polym Chem, 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 Polym Sci Polym Chem, **37**: 3910–3915, 1999.
44. Bhattacharyya SN., Maldas D., Pandey VK. Radiation induced graft copolymerization of N-vinyl carbazole and methylmethacrylate onto cellulose acetate film. J Polym Sci, 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 Angewandte Makromolekurare Chemie, 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. Eur Polym 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 Appl Polym Sci, 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 Membr Sci, 179: 69–77, 2000.
50. Chen T., Kumar G., Harries MT., Smith PJ., Payne GF. Enzymatic grafting of hexyloxyphenol onto chitosan to alter surface and rheological properties. Biotechnol Bioeng, 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 Appl Polym Sci, 11(6): 859–870, 1967.
53. Yasukawa T., Sasaki Y., Murukami K. Kinetics of radiation induced grafting reactions. II. Cellulose acetate-styrene systems. J Polym Sci Polym Chem, 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 Polym Sci Polym Chem, 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. Chappas WJ., Silverman J. The effect of acid on the radiation induced grafting of styrene to polyethylene. Radiat Phys Chem, 14: 847–852, 1979.
57. Assy NBEl. Effect of mineral and organic acids on radiation grafting of styrene onto polyethylene. J Appl Polym Sci, 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. Eur Polym 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 dioxide charge transfer complex as the initiator. J Appl Polym Sci, 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.

3.1. 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[1].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 molecular interaction between polymers can be achieved by exposure to dry heat, saturated steam, microwave technology UV[2] and gamma radiation Chemical method polymers are treated with chemicals like aldehydes, epichlorhydrin, borax or glutaraldehyde. Temperature is one of the most favorable 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 [3].

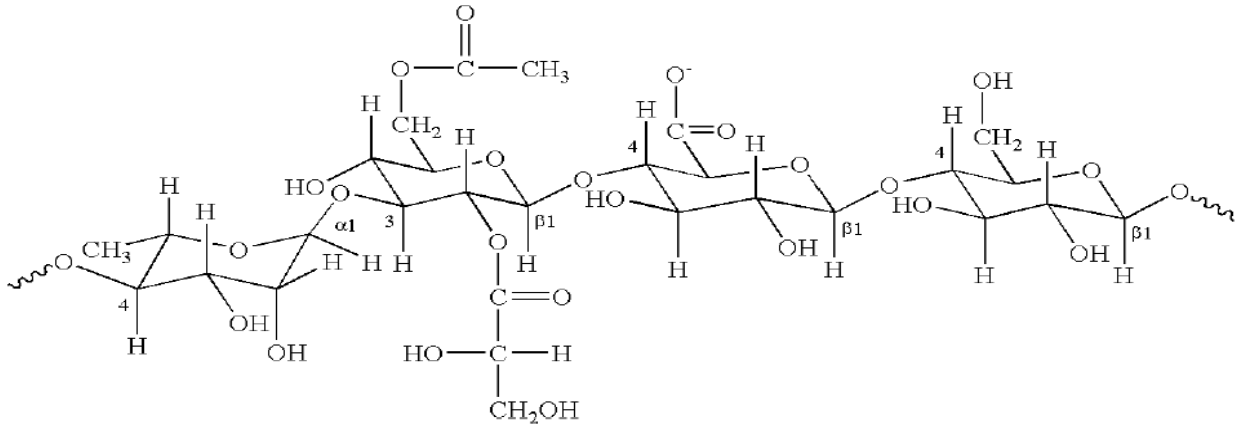
3.2.GELLAN GUM

3.2.1. Origin:

Gellanisa water-soluble anionic polysaccharide produced by the bacterium Sphingomonas elodea (formerly *Pseudomonas elodea*). The gellan-producing bacterium was discovered and isolated by the former Kelco Division of Merck & Company, Inc. in 1978 from the lily plant tissue from a natural pond in Pennsylvania, USA. It was initially identified as a substitute gelling agent at significantly lower use level to replace agar in solid culture media for the growth of various microorganisms. Its initial commercial product with the trademark as "GELRITE" gellan gum, was subsequently identified as a suitable agar substitute as gelling agent in various clinical bacteriological media[4].

3.2.2.Chemical Structure:

The repeating unit of the polymer is a tetrasacharide, which consists of two residues of D-glucose and one of each residues of L-rhamnose and D-glucuronicacid. The tetrasacharide repeat has the following structure:



3.3. Applications in Pharmaceutical Industry:

- **Pharmaceutical applications:** Gellan Gumb(GG) is an interesting candidate for pharmaceutical use. It is used as a carrier for variety of drugs for controlled release applications.
- **Binder in tablet dosage form:** Evaluations of gellan gum polyose as a binder for tablet dosage forms was taken up for the wet granulation as well as direct compression methods. The results indicated that gellan gum polyose could be used as binder for wet granulation and direct compression tabletting methods[5].
- **As a mucoadhesive polymer:** GG is used for production of thickened ophthalmic solutions having a pseudo plastic rheological behaviour and mucoadhesive properties. The solution is used as artificial tear and as a vehicle for sustained release ophthalmic drugs. GG is an adhesive thereby prolongs the retention time of formulation onto the surface of eye unlike other eye preparations. Furthermore, the GG drops did significantly better job of relieving several key subjective symptoms of dry eye syndrome namely trouble blinking, ocular burning, and having sensation of having something in someone's eye[6]. It also increases the resident time of the drug to the cornea, e.g. Â-blockers.
- **In sustained drug delivery:** It is a potential polysaccharide having high drug holding capacity which sustained the release of Verapamil hydrochloride. The release pattern was found to be comparable with matrices of other polysaccharide polymers such as ethyl cellulose, hydroxyethyl cellulose, and hydroxypropylmethyl cellulose, as well as the commercially available sustained release tablets[10]Sustained release behaviours of both water-soluble (acetaminophen, caffeine, theophylline and salicylic acid) and water-insoluble (Indomethacin) drugs on GG was examined. Studies showed that GG could be used for controlled release of both water-soluble and water-insoluble drugs. Zero-order release can be achieved selecting sparingly soluble drugs such as indomethacin along with GG.
- **In ocular drug delivery:** Administration of vicosified preparations produced antibiotic concentrations both in aqueous humor and cornea that were significantly higher than those achieved with the drugs alone. The increased drug absorption and the prolonged drug elimination phase obtained with vicosified formulations indicate the usefulness of the GG as an ophthalmic delivery system for topical administration of antibiotics. Eye drops from GG are used to treat dry eye syndrome.
- **Colon targeting:** The potential use of GG as a carrier for colonic drug delivery was demonstrated. Matrix tablets were prepared by wet granulation methods using ibuprofen as a model drug. In vitro release studies mimicking mouth to colon transit demonstrated the ability of GG to release the drug at pH 6.8. GG was remarkably degraded in rat colon indicating that GG can be used as a carrier for colonic drug delivery[7].
- **Bio-adhesive tablet:** Tablets prepared from the GG and tamarind gum were evaluated as bio-adhesive tablets and was found that the tablets showed longest residence time in oral cavity as compared to that prepared from xanthan gum and carboxycellulose but the unpleasant taste of the former gradually developed.

- **As a suspending agent:**
  The Gellan gum. (GG) possesses properties like high viscosity, broad pH tolerance, no carcinogenicity, mucoadhesive nature, and biocompatibility. Since suspensions are thermodynamically unstable, it requires a suspending agent which reduces the rate of settling and permits easy redispersion of any settled particulate matter. R. Deveswaran et.al. has done an attempt to use this polysaccharide as suspending agent in the formulation of Nimesulide suspension. They found that the TSP powder can be used as an effective suspending agent[8-9].

3.6. 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 Gellangumis 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.

REFERENCES:

1. Collet J., Moreton C. Modified-release peroral dosage forms. In: M. E. Aulton, ed. Pharmaceutics: The Science of Dosage Form Design. Churchill Livingstone, U. K. 2002:289-305.
2. 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.
3. 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.
4. Desai KG., Park HJ. Study of gamma-irradiation: effects on chitosan microparticles. Drug Delivery, 13: 39-50, 2006.
5. 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.
6. Kottke KM., Edward MR. Tablet Dosage Forms. In: Banker GS, Rhodes CT, Ed. Modern Pharmaceutics. New York, Marcel Dekker, Inc, 287-333, 2002.
7. Aslam A., Parrott E. Effect of aging on some physical properties of hydrochlorothiazide tablets. J Pharm. Sci.,60: 263-266, 1971.
8. 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.
9. Mishra MU., Khandare JN. Tamarind seed polysaccharides: biodegradable polymer for colonic drug delivery. Second International Conference and Indo-Canadian Satellite Symposium on Pharmaceutical Science, Technology, Practice and Natural Products, Conference Chronicle. DDS, 35: 206, 2007. .

4. NATURAL GUMS AND MUCILAGES:

4.1. 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.

4.2. 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.

4.3. 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.

4.4. 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].

4.5. 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:

4.5.1. According to charge:

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

5. LITERATURE REVIEW:

5.1. INTRODUCTION:

Attempts of 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.

- **Shailaja. T *et al*[1]** grafted the TS with methyl methacrylate (MMA). Chemical method of grafting by potassium per sulphate and ascorbic acid redox pair was selected for grafting. Taguchi L9 design was applied to optimize the grafting process. The grafted product was subjected to physical, chemical and spectral analysis. The physical characterization reveals no drop of viscosity on storage, controlled rate of hydration of Grafted tamarind seed polysaccharide (GTS). The chemical and spectral characterization confirmed the grafting procedure. Metoprolol succinate a low bioavailable (40-50%) drug was selected for the present study and buccal patches were formulated using TS and GTS as polymers. Central composite design was applied to find out the relationship between percentage of TS/GTS and drug release characteristics and to optimize buccal patches with 12 hour drug release. The 2% of TS and 2.86% of GTS buccal patches were able to show a sustain drug release for 12 hours. Invitro, exvivo drug release studies, release kinetics, physical parameter studies for all optimized patchformulations reflect the ideal characteristics of buccal patch for delivery of metoprolol succinate.
- **Rajaram. S.K *et al*[2]** isolated Tamarind seed polysaccharide (TSP) from tamarind kernel powder was investigated for sustained release manners of salicylic acid drug. Tablet granules of salicylic acid were prepared, with two different grades of TSP and Cross linked TSP and embedded with chemically synthesized ZnS nanocrystals. Five different formulations made and the drug excipient mixtures were subjected to pre-formulation studies such as physicochemical studies, in vitro dissolution test, disintegration test, angle of repose and drug content. The physicochemical properties of tablets were found within the limits. Formulation F1 and F5 containing TSP and Cross linked were found to release the drug in sustained manner up to 24 hour and

were stable under accelerated conditions of temperature for 6 months since there were no significant changes in drug content and physical parameters. This formulation was more comfortable to the user due to less erosion, faster and optimum pH of surrounding medium.

- **Ahuja. M *et al*[3]** studied thiol-functionalization of tamarind seed polysaccharide was carried out by esterification with thioglycolic acid. Thiol-functionalization was confirmed by SH stretch in Fourier-transformed infra-red spectra at 2586 cm−1. It was found to possess 104.5 mM of thiol groups per gram. The results of differential scanning calorimetry and X-ray diffraction study indicate increase in crystallinity. Polymer compacts of thiolated tamarind seed polysaccharide required 6.85-fold greater force to detach from the mucin coated membrane than that of tamarind seed polysaccharide. Comparative evaluation of Carbopol-based metronidazole gels containing thiolated tamarind seed polysaccharide with gels containing tamarind seed polysaccharide for mucoadhesive strength using chicken ileum by modified balance method revealed higher mucoadhesion of gels containing thiolated tamarind seed polysaccharide. Further, the gels containing tamarind seed polysaccharide and thiolated tamarind seed polysaccharide released the drug by Fickian-diffusion following the first-order and Higuchi's-square root release kinetics, respectively.
- **Deogade. U.M *et al*[4]** 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*[5]** 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*[6]** 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*[7]** 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*[8]** 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*[9]** 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.
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5.2. REFERENCES:

1. Shailaja T., Latha K., Sasibhushan P., Alkabab AM., Uhumwangho UM. A novel bioadhesive polymer: grafting of tamarind seed polysaccharide and evaluation of its use in buccal delivery of metoprolol succinate. Scholars Research Library Der Pharmacia Lettre, 4 (2): 487-508, 2012.
2. Ganesan K., Rajaram SK., Chinnathambi A., Murugesan V., Muruganantham K., Amanullah TR., Barthelomai IS, Chinnasamy S. A sustained release of tablet granules associated with ZnS nanocrystals using Tamarind seed polysaccharide. Journal of Applied Pharmaceutical Science, 3 (4 Suppl 1): S44-S47, 2013.
3. 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.
4. 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.
5. 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.
6. Moura E., Somessari ESR., Silveira CG., Paes HA., Souza CA., Fernandes W., Manzoli JE., Geraldon ABC. Influence of physical parameters on mutual polymer grafting by electron beam irradiation. Radiation Physics and Chemistry, 80: 175–181, 2011.
7. 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 poly condensed aromatic rings of the wall-surface. Polymer, 45: 8723–8730, 2004.
8. 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.
9. 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.

6.1.Description of Vinpocetine:

Vinpocetine (vinpocetine-ethyl apo-vincaminate) was synthesized in the late 1960s from the alkaloid vincamine, extracted from the leaf of the lesser periwinkle plant (Vinca minor).[1]Vinpocetine was made available under the trade name Cavinton in 1978 and has since been used widely in Japan, Hungary, Germany, Poland and Russia for the treatment of cerebrovascular-related pathologies[2]. Several clinical studies have confirmed the neuroprotective effects of this compound. Intelectol is the purest form of Vinpocetine available.Research suggests that Vinpocetine helps to maintain healthy blood circulation in the brain and supports certain neurotransmitters in the memory process. Vinpocetine supports and protects brain blood vessel health and aids mental function.

6.2.Pharmacokinetics:

Vinpocetine when taken on an empty stomach, has an absorption rate of 6.7%[3]. When taken with food absorption increases 60-100%.Vinpocetine reaches the bloodstream approximately one hourafter administration whether taken with food or on an empty stomach[4]. The elimination half-life of the oral form is one to two hours and the majority of vinpocetine is eliminated from the body within eight hours. 3 Recent studies, either following i.v. infusion of vinpocetine in patients with cerebrovascular disorders or using positron emission tomography (PET) scans in animals, have shown that vinpocetine crosses the blood-brain barrier and is taken up by cerebral tissue[5,6]. PET studies have also clearly shown in human subjects vinpocetine is preferentially absorbed in the central nervous system at twice the level that would be expected according to total body distribution[7]. The highest uptake of vinpocetine was seen in the thalamus, putamen, and neocortical regions.

6.3.Mechanisms of Action:

Vinpocetine appears to have several different mechanisms of action that allow for its antioxidant,vasodilating, and neuroprotective activities.

6.3.1.Voltage-Dependent Sodium Channel Inhibition:

It has been hypothesized that vinpocetine’s application in ischemic stroke is secondary to its effecton voltage-dependant sodium channels in the brain[8]. Inhibition of sodium channels in neural tissue is theprimary mechanism of several different drugs reported to have neuroprotective effects in experimental ischemia[9]. This action, effectively blocking accumulation of sodium in neurons, decreases the damage ofreperfusion injury and may be beneficial in lessening the toxic effects of oxidative stress resulting fromanoxia[10].

6.3.2.Phosphodiesterase-1 Inhibition:

Vinpocetine inhibits Ca+2/calmodulin-dependent phosphodiesterase (PDE) type 1[11]. This effect would theoretically lead to an increase of cyclic AMP over cyclic GMP and may be responsible for the benefits in cerebral circulation and decreased platelet aggregation observed after vinpocetineadministration[12].

6.4.1.Antioxidant Effects:

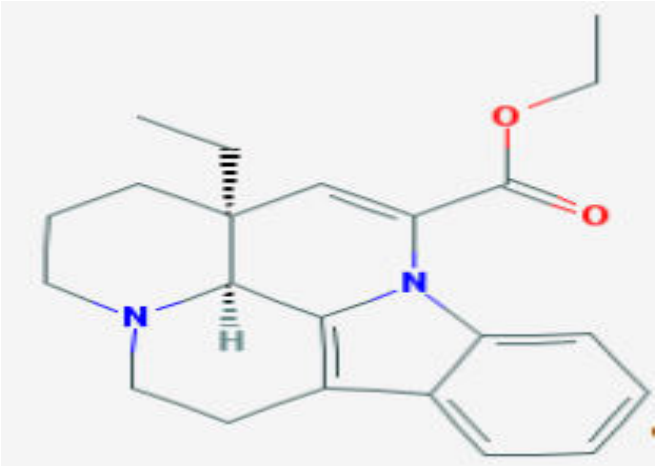
Like vitamin E, vinpocetine is an effective scavenger of hydroxyl radicals[13]. It has also been shown to inhibit lipid peroxidation in synaptosomes of murine brain tissue and to protect against global anoxia and hypoxia in animals. Vinpocetine has decreased areas of neuronal necrosis in animal models up to 60 percent in experimentally- induced ischemia[10].

6.4.2.Other Neuroprotective Effects:

Vinpocetine has been shown to protect neurons from the toxicity of glutamate and Nmethyl-d-aspartate (NMDA)[14].Vinpocetine lowers blood viscosity in patients with cerebrovascular disease,[15] has significant vasodilating properties, [16] decreases platelet aggregation,[17] and increases and maintains erythrocyte flexibility under oxidative stress,[18] all of which are potentially beneficial in cerebrovascular disease. Vinpocetine causes a selective increase in cerebral blood flow and increases cerebral metabolic rate.[19,20]

6.5.Cautions:

Take product with food to avoid stomach upset. Not recommended for use by pregnant women, nursing mothers or anyone under 18 years old. Consult a doctor or health care professional before use if you have any medical condition or if taking any medication. Not recommended for use by anyone with hemophilia, heart problems or low blood pressure. Keep out of reach of children.



6.6.Chemical and Physical Properties:

Molecular Weight	350.45404 g/mol
Molecular Formula	$C_{22}H_{28}N_2O_2$
XLogP3	4.1
Hydrogen Bond Donor Count	0
Hydrogen Bond Acceptor Count	3
Rotatable Bond Count	4
Exact Mass	350.199428 g/mol
Monoisotopic Mass	350.199428 g/mol
Topological Polar Surface Area	34.5 A^2
Heavy Atom Count	26
Formal Charge	0
Complexity	617
Isotope Atom Count	0
Defined Atom Stereocenter Count	2
Undefined Atom Stereocenter Count	0
Defined Bond Stereocenter Count	0
Undefined Bond Stereocenter Count	0
Covalently-Bonded Unit Count	1

	U.S. Pharmacopeia	British Pharmacopoeia	European Pharmacopoeia
Definition	≥98.5% and ≤101.5% vinpocetine, calculated on dried basis	≥98.5% and ≤101.5% vinpocetine, calculated based on dried substance	≥98.5% and ≤101.5% vinpocetine, calculated based on dried substance
Appearance		White or slightly yellow, crystalline powder	White or slightly yellow, crystalline powder
Organic Impurity	≤0.6% ethyl vincaminate ≤0.5% apovincamine ≤0.3% methoxyvinpocetine ≤0.5% dihydrovinpocetine ≤0.1% unspecified individual impurities ≤1.0% total impurities [as determined on liquid chromatograph]	≤0.6% ethyl vincaminate ≤0.5% apovincamine ≤0.3% methoxyvinpocetine ≤0.5% dihydrovinpocetine ≤0.1% unspecified individual impurities ≤1.0% total impurities [as determined on liquid chromatograph]	≤0.6% ethyl vincaminate ≤0.5% apovincamine ≤0.3% methoxyvinpocetine ≤0.5% dihydrovinpocetine ≤0.1% unspecified individual impurities ≤1.0% total impurities [as determined on liquid chromatograph]

6.7.Drug Interactions:

Because vinpocetine decreases platelet aggregation it should be avoided in patients on blood thinning medications.

6.8.Safety/Toxicity:

Some studies have noted flushing, rashes, or minor gastrointestinal problems in some subjects;however, these side effects did not warrant discontinuation of the medication.[22] In one study no significant side effects were reported, even in larger doses of 20 mg threetimes daily.[21]

REFERENCES:

1.Lorincz.C,Szasz.K,Kisfaludy.L.

The synthesis of ethyl apovincaminate.Arzneimittelforschung1976;26:1907.

2. Bereczki D, Fekete I. A systematic review of vinpocetine therapy in acute ischaemic stroke.Eur J ClinPharmacol1999;55:349-352.

3. Miskolczi P, Korma K, Polgar M, Vereczkey L. Pharmacokinetics of vinpocetine and its main metabolite apovincaminic acid before and after the chronic oral administration of vinpocetine to humans. Eur J Drug MetabPharmacokinet 1990;15:1-5.

4. Lohmann A, Dingler E, Sommer W, et al. Bioavailability of vinpocetine and interference of the time of application with food intake. Arzneimittelforschung1992;42:914-917.

5. Polgar M, Vereczkey l, Nyary I. Pharmacokinetics of vinpocetine and its metabolite, apovincaminic acid, in plasma and cerebrospinal fluid after intravenous infusion. J PharmBiomed Anal 1985;3:131-139.

6. Gulyas B, Halldin M, Karlsson P, et al. Brain uptake and plasma metabolism of [11C]vinpocetine: a preliminary PET study in a cynomolgus monkey. J Neuroimaging 1999;9:217-222.

7. Guylas B, Halldin C, Farde L. PET studies on the uptake and regional distribution of [11C]vinpocetine in human subjects. ArchNeurol.In press.

8. Molnar P, Erdo SL. Vinpocetine is as potent as phenytoin to block voltage-gated Na+ channels in rat cortical neurons. Eur J Pharmacol1995;273:303-306.

9. Urenjak J, Obrenovitch TP. Pharmacological modulation of voltage-gated Na+ channels: a rational and effective strategy against ischemic brain damage. Pharmacol Rev 1996;48:21-67.

10. Bonoczk P, Gulyas B, Adam-Vizi V, et al. Role of sodium channel inhibition in neuroprotection: effect of vinpocetine. BrainRes Bull 2000;53:245-254.

11. Beavo JA. Cyclic nucleotide phosphodiesterases: functional implications of multiple isoforms. Physiol Rev 1995:75:725-748.

12. Chiu PJ, Tetzloff G, Ahn HS, SybertzEJ.Comparative effects of vinpocetine and 8-Brcyclic GMP on the contraction and 45Cafluxes in the rabbit aorta.Am J Hypertens1988;1:262-268.

13. Stolc S. Indole derivatives as neuroprotectants. Life Sci1999;65:1943-1950.

14. Miyamoto M, Murphy TH, Schnaar RL, Coyle JT. Antioxidants protect against glutamateinduced cytotoxicity in a neuronal cell line. JPharmacolExpTher1989;250:1132-1140.

15. Osawa M, Maruyama S. Effects of TCV-3B (vinpocetine) on blood viscosity in ischemiccerebrovascular diseases. Ther Hung1985;33:7-12.

16. Tamaki N, Kusunoki T, Matsumoto S. The effect of vinpocetine on cerebral blood flow inpatients with cerebrovascular disorders.TherHung1985;33:13-21.

17. Kuzuya F. Effects of vinpocetine on platelet aggregability and erythrocyte deformability.Ther Hung 1985;33:22-34.

18. Hayakawa M. Comparative efficacy of vinpocetine, pentoxifylline and nicergoline on red blood cell deformability.Arzneimittelforschung1992;42:108-110.

19. Imamoto T, Tanabe M, Shimamoto N, et al.

Cerebral circulatory and cardiac effects of vinpocetine and its metabolite, apovincaminicacid, in anaesthetized dogs.Arzneimittelforschung1984;34:161-169.

20. Shibota M, Kakihana M, Nagaoka A. The effect of vinpocetine on brain glucose uptake in mice.NipponYakurigaku Zasshi1982;80:221-224. [Article in Japanese]

21. Szakall S, Boros I, Balkay L, et al. Cerebral effects of a single dose of intravenous vinpocetine in chronic stroke patients: a PET study. J Neuroimaging 1998;8:197-204.

7.1.Methacrylic acid:

Methacrylic acid is an organic compound. This colorless, viscous liquid is a carboxylic acid with an acrid unpleasant odor. It is soluble in warm water and miscible with most organic solvents. Methacrylic acid is produced industrially on a large scale as a precursor to its esters especially methyl methacrylate and poly(methyl methacrylate).The methacrylates have nuerous uses most notably in the manufacture of polymers with trade names such as Lucite and Plexiglas.MAA occurs naturally in small amounts in the oil of Roman chamomile.

Acrylic acid is the simplest unsaturated carboxylic acid which has double bond and carboxyl group in C3 onemolecule with the formula CH2=CHCOOH.The vinyl group is attached to the carbonyl carbon directly.Thesystemic name is 2propenoicacid.Acrylic acid has two reaction points or functional groups required for polymerization process.Purified (glacial) acrylic acid is a clear colorless liquid with a characteristic acrid odor. It is miscible with water, alcohols and ethers. Acrylic acid is produced from C 3 refinery.Acrylic acid undergoes thetypical reactions of a carboxylic acid and forms acrylic esters basicalkyl esters are methyl,butyl,ethyl acrylate and 2ethylhexylacrylate.Acrylic acid and its esters undergo the reactions of the double bond which readilycombine with themselves or other monomers (e.g amides, methacrylates, acrylonitrile, vinyl, styrene and butadiene) to form homopolymers or copolymers which are used in the production of coatings, adhesives, lastomers,super absorbent polymers, flocculants as well as fibres and plastics.Acrylate polymers show a widerange of properties dependent on the type of the monomers and reaction conditions.

Methyl methacrylate (MMA) is ester of the unsaturated C4 carboxylic acid. The term of metha indicates an additional methyl group attached to the alpha carbon of acrylic acid.Methyl methacrylate is a flammable, colorless liquid; melting at 48^{0C},boiling at 101^{0}C, soluble in the most organic solvents but insoluble in water. It isprepared by the esterification of methacrylamidesulfate with methanol.(The reaction of acetone and hydrogencyanide forms acetone cyanohydrin, which is further treated with sulfuric acid to produce methacrylamidesulfate). Ammonium bisulfate is a byproduct.MMA is produced commercially also from C4 rout(isobutylene and tertbutylalcohol) through two oxidation process. This process don't need sulphuric acid and no acidic by products.MMA is the monomer to make polymethyl methacrylate (PMMA) used as a shatter proof replacement for glass.

7.2.Production and properties:

More than 3 million tons of methyl methacrylate (MMA) are produced annually. In one route, acetone cyanohydrin is converted to methacrylamidesulfate using sulfuric acid.That compound is hydrolyzed to methacrylic acid, or it can be converted into methyl methacrylate in one step. In the second route, isobutylene or tertbutanol are oxidized to methacrolein, then methacrylic acid. Methacrolein for this purpose can also be obtained from formaldehyde and ethylene.Isobutyric acid can also be dehydrogenated to methacrylic acid.[3] Methacrylic acid was first obtained in the form of its ethyl ester by treating phosphorus pentachloride with oxyisobutyric ester[4]. It is, however, more readily obtained by boiling citraormesobrompyrotartaric acids with alkalis.It crystallizes in prisms.When fused with an alkali, it forms propanoicacid.Sodiumamalgam reduces it to isobutyric acid.A polymeric form of methacrylic acid was described in 1880[5].
Molecular Weight: 86.08924 g/mol

7.3.Chemical and Physical Properties:

Molecular Weight	86.08924 g/mol
Molecular Formula	$C_4H_6O_2$
XLogP3	0.9
Hydrogen Bond Donor Count	1
Hydrogen Bond Acceptor Count	2
Rotatable Bond Count	1
Exact Mass	86.036779 g/mol
Monoisotopic Mass	86.036779 g/mol
Topological Polar Surface Area	37.3 A^2
Heavy Atom Count	6
Formal Charge	0
Complexity	83.5
Isotope Atom Count	0
Defined Atom Stereocenter Count	0
Undefined Atom Stereocenter Count	0
Defined Bond Stereocenter Count	0
Undefined Bond Stereocenter Count	0
Covalently-Bonded Unit Count	1

7.4.Physical Description:

Methacrylic acid is a clear colorless liquid (or low melting solid) with a pungent odor.Corrosive to metals and tissue.Flash point 170°F.Melting point 61°F.Maypolymerize exothermically if heated or contaminated.If the polymerization takes place inside a container,the container may rupture violently. Less dense than water.Vapors heavier than air.Used to make plastics.

Methacrylic acid inhibited is a clear colorless liquid with a pungent odor.Corrosive to metals and tissue.Combustible.Flash point 170 °F.Melting point 61 °F. May polymerize if contaminated or heated.If polymerization takes place inside a closed container the container may violently rupture.Less dense than water and is soluble in water.Vapors heavier than air.Used to make plastics.

7.4.1.Color:

Clear colorless liquid or colorless crystals.

7.4.2.Odor:

Acrid, repulsive odor.

7.5.Pharmacology and Biochemistry:

7.5.1.Absorption, Distribution and Excretion:

Methacrylic acid is readily absorbed through mucous membranes of the lungs and gastrointestinal tract and the skin, and is rapidly distributed to all major tissues.

7.6.1.**Metabolism/Metabolites:**

Methacrylates are metabolized via two basic pathways, hydrolysis and conjugation.Methacrylic acid is a physiological substrate of the valine pathway and ismetabolized toCO_2 by two substrates of the citric acid cycle,methylmalonyl and succinylCoA.MaleWistar rats dosed orally with radiolabelled methyl methacrylate in corn oil revealed that endogenously generated methacrylic acid (0.08% of the dose) wasmetabolized using the pathway present in mammalian cells for the metabolism of valinewith CO_2 and water as the ultimate metabolites.Methacrylic acid is a physiological metabolite of the Valine pathway.After activation with AcetylCoAit is converted into methylmalonylCoA and SuccinylCoAwhich enters the citric acid cycle.

Methacrylic acid is metabolized primarily through B12dependentpathway of propionate metabolism.It is first converted to the coenzymeA to ester. This catabolicpathway leads to the tricarboxylic acid (TCA) cycle and ultimately to CO_2.

7.7.Polymerization:

Polymerizes are easilyessape on heating or in presence of traces of hydrochloric acid,Hazardouspolymerizaton may occur.Usually contains inhibitors to prevent polymerization.Polymerizaton may be caused by elevated temperature,oxidizers,peroxides or sunlight.Uninhibited monomer vapor may form polymer in vents and other confined spaces.Methacrylic acid inhibited drum of the uninhibited methacrylic acid which had been stored outside under winter conditions was transferred into a warm room to liquefy the acid. Later,exothermic polymerization led to bulging of the drum and leakage of the acid vapor.

REFERENCES:

1. CID 4093 (https://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=4093) fromPubChem

2. "NIOSH Pocket Guide to Chemical Hazards #0386". National Institute forOccupational Safety and Health (NIOSH).

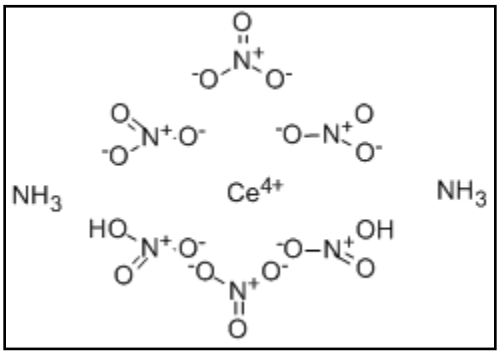
3. William Bauer, Jr. "Methacrylic Acid and Derivatives" in Ullmann's Encyclopedia ofIndustrial Chemistry 2002, WileyVCH,Weinheim. doi:10.1002/14356007.a16_441 (https://dx.doi.org/10.1002%2F14356007.a16_441). Article Online Posting Date:June 15, 2000

4. Edward FranklandAnnalen, 1865, 136, p. 12

5. F. Engelhorn et al. Ann., 1880, 200, p. 70.

8.2.2. CERRIC AMMONIUM NITRATE[1,2]:

- **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

8.2.2.1.PHYSICAL AND CHEMICAL PROPERTIES:

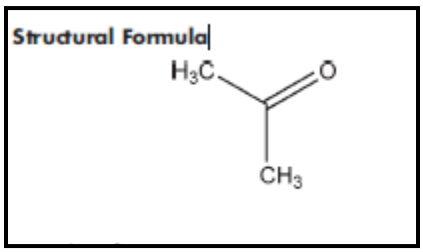
- **Appearance**: Small, orange-red, monoclinic crystals.
- **Odor:** Slight characteristic odor.
- **Solubility:** 141g/100ml water at 25℃ (77F).
- **Density:** 1.10g/ml at 20°C.
- **pH:** No information found.
- **Percent volatiles by volume:** 0 (at 21°C or 7^0F).
- **Boiling Point:** No information found.
- **Melting Point:** 107-108°C.
- **Vapor Density (Air=1):** No information found.
- **Vapor Pressure (mm Hg):** No information found.
- **Evaporation Rate (BuAc=1):** No information found.
- **Stability and reactivity:** Stable under ordinaryconditions of use and storage.
- **Hazardous Decomposition Products:** Oxides of nitrogen.
- **Hazardous Polymerization:** Will not occur.
- **Conditions to Avoid:** Heat, shock, friction, incompatibles.
- **Aggravation of Pre-existing Conditions:** No information found.
- **Incompatibilities:** Flammable and organic materials, reducing agents, powdered aluminum, boron phosphide, cyanides, esters, phosphate, phosphorus, sodium cyanide, sodium hypophosphite, stannous chloride, and thiocyanates**.**

8.2.2.2.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.

8.2.3. ACETONE[3]:

- **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.

8.2.3.1.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.

8.2.4. METHANOL[4]:

- **Common Synonyms:** Methyl alcohol, methyl hydrate, wood spirit, methyl hydroxide
- **Molecular structure:** $H_3 – C – OH$
- **Molecular formula:** CH_3OH
- **Molecular weight:** 32

8.2.4.1.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.

8.2.4.2.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.

8.2.4.3.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.

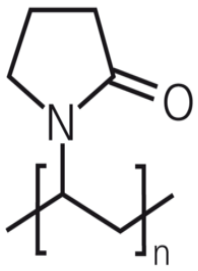
8.2.4.4.Medical Conditions Aggravated by Exposure: Emphysema or bronchitis.

8.2.4.5.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.

8.2.4.6.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.

8.2.5. POLYVINYLPYRROLIDONE[5-7]:

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



- **Molecular formula:** $(C_6H_9NO)_n$
- **CAS No:** 9003-39-8

8.2.5.1.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

8.2.5.2.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.

8.2.6. TALC[8]:

- **Common Synonyms:** Altalc, E553b, Hydrous magnesium calcium silicate, Hydrous magnesium silicate, Imperial, Luzenac Pharma, Magnesium hydrogen metasilicate, Magsil Osmanthus, Magsil Star, Powdered talc, Purified French chalk, Purtalc, Soapstone, Steatite, Superiore, Talcum.
- **CAS No:** 14807-96-6
- **Functional Category:** Anticaking agent, Glidant, Tablet and Capsule diluents, Tablet and capsule lubricant.

8.2.6.2.Description:

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Applications in Pharmaceutical Formulation or Technology:

- Talc was once widely used in oral solid dosage formulations as a lubricant and diluents although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations in a novel powder coating for extended-release pellets and as an adsorbant.

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves; Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting Powder. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant property.

Uses of Talc:

Use	Concentration (%)
Dusting powder	90-99
Glidant and Tablet Lubricant	1.0-10
Tablet and Capsule Diluent	5-30

8.2.6.3.Stability and Storage Conditions:

Talc is a stable material and may be sterilized by heating at 160C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Incompatible with quaternary ammonium compounds.

8.2.7. MAGNESIUM STEARATE[9,10]:

- **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.

8.2.7.2.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. http://www.cen.iitb.ac.in/cen/usage-policies/msds/ceric_ammonium_nitrate.pdf
2. http://www.chemicalbook.com/ChemicalProductProperty_EN_CB2302090.htm
3. Rowe RC., Sheskey PJ., Quinn ME. Handbook of pharmaceutical excipients. 6th Edn., Royal Pharmaceutical Society, United Kingdom, 7-8, 2009.
4. http://www.cen.iitb.ac.in/cen/usage-policies/msds/methanol.pdf.
5. Lieberman HA., Rieger MM., Banker GS. Pharmaceutical Dosage Forms: Disperse Systems, volume 3, 2nd Edn., Marcel Dekker, Inc., 282, 2008.
6. Evaluation of certain food additives and contaminants. WHO technical report series, No. 751 FAO/WHO Rep. 30th report, 30 – 31, Geneva, 1987.
7. Neumann A., Leuschener A., Schwertfeger W., Dontenwill W. Study on the acute oral toxicity of PVP in rabbits, unpublished report to BASF, 1979.
8. http://en.wikipedia.org/wiki/Talc.
9. Rowe RC., Sheskey PJ., Quinn ME. Handbook of pharmaceutical excipients. 6th Edn., Royal Pharmaceutical Society, United Kingdom, 404-407, 2009.
10. Rowe RC., Sheskey PJ., Quinn ME. Handbook of pharmaceutical excipients. 6th Edn., Royal Pharmaceutical Society, United Kingdom, 728-730, 2009.

9. 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 like 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). Concurrent formation of homopolymer during graft copolymerization is the main constraint

resulting a low grafting yield (Singh, Tripathy, Tiwari, & Sanghi, 2006). 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).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.

Therefore the main objectives of the study are:

9.1. **To perform grafting of Gellan gum with some synthetic polymers**.

1. **Characterization of the grafted Gellan gum**

   - Elemental analysis.
   - Viscosity measurement.
   - FT-IR spectroscopy.
   - DSC and TGA study.
   - X- Ray Diffraction Study
   - SEM study.
   - 13c nmr spectroscopy.
   - Swelling study in different pH media.
   - Rheology study.
   - Acute oral toxicity study.

2. **Characterization of the drug**

   - UV-Visible spectroscopy.
   - FT-IR spectroscopy.
   - Assay.
   - 13c nmr spectroscopy.
   - Rheology study.
   - Preparation of standard calibration curve in different medium.

3**. To develop matrix tablet of Vinpocetine as model drug and analyse various parameters.**

- Potency
- Weight variation
- Thickness and Diameter
- Hardness
- Friablity
- Disintegration test
- Drug content

4. **In-vitro release kinetics**

- Effect ofdrug/polymer ratio.
- Effect of cross-linking agent.
- Effect of pH.

10.1: Drug used: VinpocetineHydrochloride,gifted from **La ChemicoPvt. Ltd.**, Kolkata, India.

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

Table10.1:List of various chemical used in project work

Sl. No	Chemical Used	Manufacturer
1.	Gellan Gum	Sigma aldrich
2.	Methacrylic acid	LobachemiePvt.Ltd,Mumbai
3.	Cerric Ammonium Nitrate	Qualigens Fine Chemicals,Mumbai
4.	Ethanol	Sigma aldrich
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.	Talc	New Bengal Drug House, Kolkata
9.	Magnesium stearate	LobaChemiePvt. Ltd. Mumbai

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

Table10.2: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.	Rheometer	Rotating rheometer with coaxial cylinders	BiolinxLabsystemsPvt. Ltd.
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.	Solid State NMR	Bruker DSX 400 spectrometer	JEOL INDIA Pvt. Ltd.

10.4.METHODS:

10.4.1.Preparation of Standard Calibration Curve of VinpocetineinPhosphate Buffer PH 6.8:

10.4.1.1.Preparation of phosphate buffer PH 6.8[1]:

About 28.80 gm of disodium hydrogen phosphate was accurately weighed out and taken into a 1000ml volumetric flask. About 11.45 gm of potassium dihydrogen phosphate in sufficient water to produce 1000ml was made upto the mark with distilled water with continuous stirring.

10.4.1.2.Preparation of Standard Curve of vinpocetine[2]:

100 mg vinpocetinewas accurately weighed and dissolved in phosphate bufferpH 6.8and volume made up to 100ml (**Solution1**). 10ml of **solution 1** was diluted withphosphate bufferPH 6.8to make 100ml (**Solution 2**). The concentration of **solution 2** was 100µg/ml. Suitable volume of **solution 2** was taken in different 25 ml volumetric flask to produce different standard solutions with concentrations of 2,4,6,8,10, 12µg/ml. Finally, volume wasadjusted to 25ml with same buffer solution. One of the standard solutions was then scanned from 190nm to 1100nm and 500nm to 1100nm sing UV-Visible Spectrophotometer. Then absorbance of all standard solutions was measured at observed λ_{max}. 276. 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.

10.4.3. Synthesis of polymethacrylic acid – grafted – GellanGum(GG):

10.6.4.3.1. Free radical initiation synthesis:

At first,the synthesis of polymethacrylic acid grafted GG was tried only by free radical initiator(cerric ammonium nitrate) at 60^{o}C (**Batch S1,S2,S3,S4**).1gm GG was dissolved in 100 ml of water (**Solution A**) and specified amount of methacrylic acid was dissolved in 25 ml water (**Solution B**). **Solution B** was then added to **Solution A** and stirred for 1 hour. Specified amount of cerric ammonium nitrate was dissolved in 25ml water and mixed with the previous mixture with constant stirring for 2 hours. Then it was left for overnight. Acetone was added to it in 1:2 ratios (reaction-mixture:acetone) for precipitation of the grafted GG. The precipitate was collected and added in 50 ml of 20% v/v aqueous methanol (20% methanol and 80% water) to remove the un-reacted free monomer and the homopolymer (polymethacrylic acid) formed during graft reaction. After stirring for 1 minute

it was allowed to stand for further precipitation. The precipitate was collected and finally washed with distilled water and dried at 40^0C to get a constant weight. The dried grafted GG was then powdered using pestle and mortar and passed through #100 mesh. Different grafting parameters such as percentage grafting (%G), grafting efficiency (%GE) and percentage conversion (%Cn) were calculated using following formula to assess the efficiency of the synthesis[3,4].

10.4.3.2. Microwave promoted synthesis[5]:

Microwave-promoted free radical initiation methodwas employed for the synthesis of polymethacrylic acid-grafted-gellangum (PMa-g-GG). Amount of methacrylic acid (Ma), cerric (IV) ammonium nitrate (CAN) and microwave irradiation time were taken as independent variable synthetic parameters. A total of eight batches of grafted TKP with different synthetic conditions were prepared as shown in **Table 6.3**. 1gmGG was dissolved in 100 ml water (**Solution A**) and specified amount of methacrylic acid was dissolved in 25 ml water (**Solution B**). **Solution B** was then added to **Solution A** and stirred for 1 hour. Specified amount of CAN was dissolved in 25 ml water and mixed with the previous mixture. The mixture was then exposed to microwave in a domestic microwave oven (**Electrolux, C23K101.BB, India**) at 500 Watt for a specified timefollowing one minute heating and one minute cooling cycle. Then it was left for overnight. Acetone was added to it in 1:2 ratios (reaction-mixture: acetone) for precipitation of the graftedGG. The precipitate was collected and added in 50 ml of 20% v/v aqueous methanol (20% methanol and 80% water) to remove the un-reacted free monomer and the homopolymer (polymethacrylic acid) formed during graft reaction. After stirring for 1 minute it was allowed to stand for further precipitation. The precipitate was collected and finally washed with distilled water and dried at 40^0C to a get constant weight. The dried grafted GG was then powdered using pestle and mortar and passed through #100 mesh. Different grafting parameters such as percentage grafting (%G), grafting efficiency (%GE) and percentage conversion (%Cn) were calculated using following formula to assess the efficiency of the synthesis.

$$\textbf{Percent grafting (\% G)} = (W_1 - W_0) \times 100 / W_0$$

$$\textbf{Percent grafting efficiency (\% GE)} = (W_1 - W_0) \times 100 / W_2$$

$$\textbf{Percent conversion (\% Cn)} = W_1 \times 100 / W_2$$

Where, W_0 = Weight of native Gellan Gum (GG)

W_1 = Weight of grafted GG

W_2 = Weight of methacrylic acid

Table 10.3.Synthetic details of methacrylic acid-grafted gellangum

Batch Code	Amount of CAN (mg)	Amount of MCA (ml)	Microwave irradiation time (min.)
GG	-	-	-
S 1	400	10	-
S 2	200	10	-
S 3	400	5	-
S 4	200	5	-
MS 1	200	5	1
MS 2	400	5	5
MS 3	200	5	1
MS 4	400	5	5
MS 5	200	10	1
MS 6	400	10	5
MS 7	200	10	1
MS 8	400	10	5

10.4.4.Characterization of grafted gellangum:

10.4.4.1.Rhelogical Study:

The rheological measurements were carried out using (Rotating rheometer with coaxial cylinders) a controlled rate instrument of couette type (Bohlin, 1988)in the dynamic oscillation mode. The measuring systemused was a concentric cylinder, C14. Silicone oil wasadded to the surface of the sample to prevent evaporationduring measurements.The hot, freshly prepared sample solutions were pouredinto the similarly heated measuring geometry. The samples were then kept at 90.8^{0C} for an additional 20 min before the actual measurements started.

10.4.4.2.Solid-State NMR Study:

Solid-state 13C CP/MAS NMR spectra were recorded on a BrukerDSX 400 spectrometer (Bruker BioSpin, Rheinstetten, Germany)operating at 400.61 MHz (1H) and 100.13 MHz (13C), powder sampleswere spun at 10 kHz in a 4 mm ZrO2 rotor using a doubleair-bearing probehead (Bruker PH MAS VTN 400WB BL4). Acquisitionwas performed with a standard CP pulse sequence withramped CP scheme and two-pulse phase modulation decouplingscheme, using 3.2_s proton 90◦ pulse, 2 ms contact time and repetition times ranging from 5s to 1200s. The decoupling field strengthwas set to 78 kHz. Glycine was used for the Hartmann–Hahn matchingprocedure and as an external standard; 13C chemical shifts werereferenced to glycine CO at 176.5 ppm. Chemical shifts were calibratedrelative to TMS. For all the experiments 0.755 Hz digital FIDresolution, 32 K time domain and 24 752 Hz spectral width wereapplied.

10.4.4.3. Infrared Spectral Analysis[6]:

FTIR spectra of GG, PMa-g-GG were obtained to predict the possible changes of functional groups of grafted GG 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}. Vinpocetineand its tablet formulation were also analyzed by FTIR to predict the possible interactions between drug and modified polymer by same process.

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

DSC and TGA thermograms of GG, PMa-g-GG, vinpocetineand 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.

10.4.4.5. Powder X-ray diffraction[8]:

X-ray powder diffractometry of vinpocetineand its tablet formulation were recorded using X-ray diffractometer. The diffractometer was run at a scanning speed of 2^0/min and a chart speed of 2^0/2cm per 2θ and the angular range fixed was from 10^0 to 80^0.

10.4.4.6. Scanning electron microscopy:

The morphology of the GG andPMa-g-GG was undergone SEM analysis. The sampleswere coated using gold to increase the conductivity of the electron beam. The operating conditions were an accelerating voltage of10 kV, the working distance were 12 mm at spot size of 45.

10.4.5.Preparation of sustained release monolithic matrix tablet of vinpocetine HCL:

Monolithic matrix tablets of a water soluble drug vinpocetine were prepared with GG and grafted GG of different 4 batches (GG, GG1,MS6, $MS6^2$) employing wet granulation method. Semisolid dough was prepared from the GG or grafted gum with minimum amount of water and then polyvinyl pyrrolidone K30 (as binder) and drug were mixed intimately with it. The mass was then passed through #18 mesh to obtain granules. These granules were dried at 60^0C for 20 mins and passed through # 18 mesh. The granules were lubricated with purified talc and magnesium stearate. The tablets were compressed at an average weight of 245 mg in a rotary tablet machine with 9 mm single punch diameter keeping the hardness within the range of 4-5 kg/m^2. The amounts of drug and excipients mentioned were for one tablet.

Table 10.4. Composition of matrix tablets of vinpocetine HCL

Batch code	Drug (mg)	Polymer (mg)		PVP K - 30 (mg)	Talc (mg)	Magnesium stearate (mg)
		pure	Grafted			
GG	120	100	-	20	2.5	2.5
GG1	120	-	100	20	2.5	2.5
MS6	120	-	100	20	2.5	2.5
$MS6^2$	120	-	100	20	2.5	2.5

10.4.6.*In-vitro* drug release study:

In vitro dissolution studies were carried out in USP type-II dissolution apparatus using 900ml phosphate buffer PH 6.8 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 5 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 276 nm using UV-Visible spectrophotometer. All the studies were conducted in triplicate.The results of *in vitro* release data were fitted in to following mathematical models fordescribing the drug release pattern:

- ✓ **Zero order kinetics[9]:**

  Zero order release would be predicted by the following equation:

$$A_t = A_O - K_O t$$

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[10]:**

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[11]:**

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:

$$\mathbf{Q = Kt^{½}}$$

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

- ✓ **KorsmeyerandPeppasModel[12]:**

  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. 1st Edn.,S. Chand, New Delhi, 245-264, 1980.
3. Jana S., SahaA.,NayakAK,.SenKK., BasuSK.Aceclofenac-loaded chitosan-gellanpolysaccharide interpenetrating polymeric network microparticles. Colloids and Surfaces B: Biointerfaces, 105: 303-309, 2013.
4. AthawaleVD.,Lele V. Graft co-polymerization onto starch. II: Grafting of acrylic acid and preparation of its hydrogels. Carbohydrate Polymers, 35: 21-27, 1998.
5. Vijan V.,Kaity S.,Biswas S.,Isaac J.,Ghosh A. Microwave assisted synthesis and characterization of methacrylic acid grafted gellan, application in drug delivery. Carbohydrate Polymers, 90: 496-506, 2012.
6. SilversteinRM., BasslerGC,.Morrill TC. Spectrometric Identification of Organic Compounds. 4th Edn.,Wiley, New York, 166, 1981.
7. Skoog DA.Principles of instrumental analysis. 5th Edn.,Harcourt Publishers, 203-221, 2001.
8. Maslen EN.,FoxAG.,O'Keefe MA. X-ray Scattering, In: Prince E. (Ed), International Tables for Crystallography, Volume C. Kluwer Academic, Dordrecht, 554, 2004.
9. Baveja SK., Rao R.,Devi KPV. Zero-order release hydrophilic matrix tablets of beta-adrenergic blockers. Int. J Pharm, 39: 39-45, 1987.
10. Narashimhan B., MallapragadaSK., PeppasNA.Release kinetics, data interpretation, In: Encyclopedia of controlled drug delivery, Mathiowitz E. 2nd Edn., John Wiley and Sons, Inc, New York, 921-951, 1999.
11. 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.
12. CostaP., Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci, 13: 123-133, 2001.

11. RESULTS AND DISCUSSION:

11.1. EVALUATION OF DRUG:

11.1.1. Standard calibration curve of Vinpocetine in Phosphate buffer pH 6.8:

Table 11.1. Standard calibration curve of Vinpocetine in phosphate buffer pH -6.8.

Sr. No	Concentration (µg/ml)	Absorbance			Average absorbance ± SD	Equation	R^2 Value
		1	2	3			
1	0	0	0	0	0 ± 0	y = 0.056x - 0.001	R^2 = 0.999
2	2	0.112	0.111	0.110	0.218 ± 0		
3	4	0.225	0.224	0.225	0.32 ± 0.001		
4	6	0.332	0.333	0.332	0.431± 0.002		
5	8	0.449	0.449	0.449	0.535 ± 0		
6	10	0.562	0.562	0.563	0.641± 0.002		
7	12	0.674	0.675	0.675	0.748 ± 0		

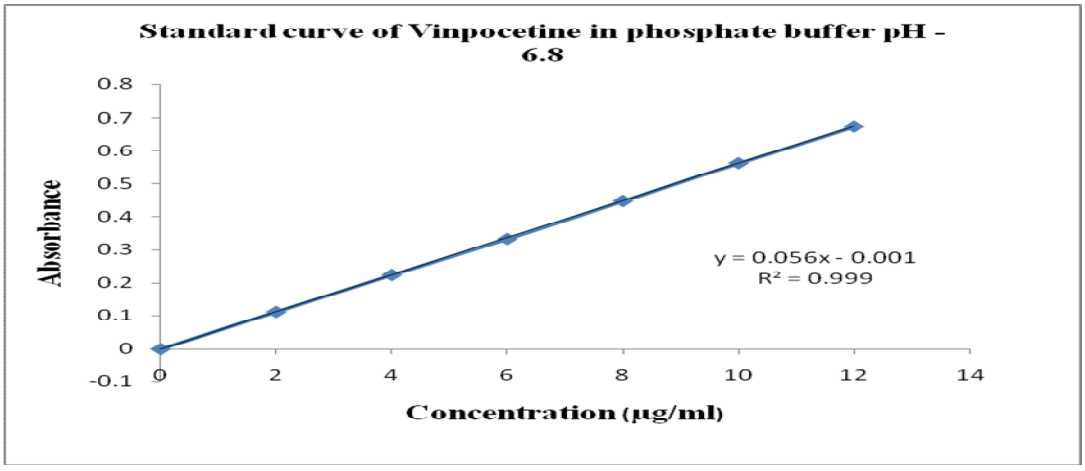


Figure 11.1. Standard Calibration Curve of Vinpocetine in Phosphate Buffer PH-6.8

Table 11.2. Standard calibration curve of Vinpocetine in 0.1(N) HCL:

Sr. No	Concentration (µg/ml)	Absorbance			Average absorbance ± SD	Equation	R^2 Value
		1	3	3			
1	0	0	0	0	0 ± 0	y = 0.036x + 0.005	R^2 = 0.998
2	2	0.076	0.076	0.076	0.076 ± 0		
3	4	0.152	0.152	0.153	0.153± 0.001		
4	6	0.230	0.228	0.228	0.229 ± 0.001		
5	8	0.303	0.301	0.301	0.302± 0.001		
6	10	0.358	0.358	0.358	0.358 ± 0		
7	12	0.435	0.436	0.437	0.436 ± 0.001		

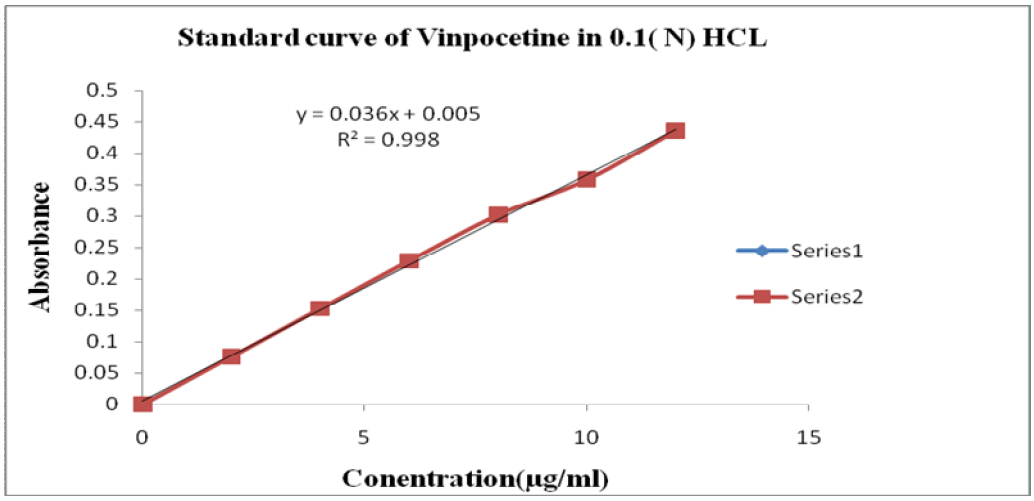


Figure 11.2. Standard Calibration Curve of Vinpocetine in 0.1 (N) HCL

Discussion:

Graph of absorbance versus concentration was plotted and found to be linear over the range of 2 to 12 µg/ml, indicating its compliance with Beer's Lambert's Law.

11.2. Synthesis of polymethacrylic acid-g-GG (Pma-g-GG)

Graft co-polymerization of methacrylic acid on to Gellan gum was carried out employing grafting technique by free-radical initiation. In several study, Cerric (IV) ammonium nitrate was used as free-radical initiator (Mishra & Pal, 2007; Fares, Assaf, & Abul-Haija, 2010; Bharaniraja, Kumar, Prasad, & Sen, 2011; Adhikary, Krishnamoorthi, & Singh, 2011). Alongwith free-radical initiator, microwave-promoted graft-copolymerization have also been reported (Tiwari, & Singh, 2008; Singh, Kumari, Tiwari, & Pandey, 2010).

Table 11.2 presents the different synthetic conditions of conventional heat-induced and microwave-promoted; cerric (IV) induced graft copolymerization, % grafting, % grafting efficiency, % conversion of native Gellan gum and its grafted forms. Initially the synthesis was tried without application of microwave radiation following normal heating the reaction mixture at 60^{o}C in water bath. But the results showed no significant yield of grafted gum indicating the fact that the only combination of free radical initiator and supply of energy in form of normal heat was not sufficient for grafting in non-nitrogen environment. In the microwave promoted synthesis, amount of CAN, methacrylic acid and microwave irradiation time were taken as independent synthetic variables by keeping the other parameters constant for the optimization of the synthetic conditions. The values of different grafting parameters shown in Table7.1 reveal that combination of higher amount of CAN and microwave irradiation for 1min has major positive influence on the higher grafting efficiency. The anomeric –CHOH on GG-backbone is the reactive vicinal group, where the grafting is initiated. The overall reaction mechanism is that, cerric (IV) ammonium nitrate gets dissociated into Ce^{4+}, ammonium and nitrate ions and then cerric (IV) ion attacks the GG macro chains 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 is required for the formation of the free radical. The grafting of Mca onto GG was then initiated

by the free radical reacting with the monomer. In the presence of Mca, the GG free radical is chemically coupled to the monomer unit, thereby resulting in a covalent bond between Mca and GG to create the chain reaction for propagation. Cerric ions also attack monomer resulting the formation of methacrylic acid 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 radical or between GG-propagating-free-radical and homopolymer-propagating-free radical (composed of only monomers). Homopolymer is formed due to termination by coupling between two homopolymer-free-radicals. The microwave irradiation provides rapid transfer of energy in the bulk of the reaction mixture, which reduces reaction time therefore it acts as a catalyst and gives a synergistic activity.

This phenomenon substantiates the results of the cerric (IV) initiated microwave-promoted graft copolymerization. The synthetic conditions for the synthetic batches MS3and MS7 result in lowest grafting whereas the batch MS6 results highest yield. The degree of grafting was shown to increase with the increase in concentration level of methacrylic acid at both higher and lower level of two other independent synthetic factors. Similarly, grafting efficiency and other grafting parameters are proportional to the concentration of cerric ammonium nitrate. % grafting was shown to be inversely proportional to microwave irradiation time. This may be due to the fact that a saturation of free radical points on gelrite backbone gets generated in a certain time period of microwave irradiation. After that a further irradiation results in the breakage of propagated chains on the free radical sites and premature advance termination (Vijan, Kaity, Biswas, Isaac, & Ghosh, 2012).

Table 11.3. Synthetic details of methacrylic acid-grafted-gellan gum

Table 11.3.1.

Batch Code	Amount of CAN (mg)	Amount of MCA (ml)	Microwave irradiation time (min.)
GG	-	-	-
S 1	400	10	-
S 2	200	10	-
gS 3	400	5	-
S 4	200	5	-
MS 1	200	5	1
MS 2	400	5	5
MS 3	200	5	1
MS 4	400	5	5
MS 5	200	10	1
MS 6	400	10	5
MS 7	200	10	1
MS 8	400	10	5

Batch no	Amt of methacrylic acid (g)	Amt of cerric ammonium nitrate (mg)	Microwave (min)	Amt of grafted gum(g)	%G	%GE	%C
S1	10.14	400	----	1.9041	90.41	8.916	18.778
S2	10.14	200	-----	1.3536	35.36	3.487	13.349
S3	5.07	400	-----	2.4207	142.07	28.022	47.746
S4	5.07	200	-----	2.1388	113.88	22.462	42.185
MS1	5.07	200	1	2.2057	120.57	23.781	43.505
MS2	5.07	400	1	3.4420	244.20	48.166	67.890
MS3	5.07	200	5	1.0441	4.41	0.870	20.594
MS4	5.07	400	5	2.5671	156.71	30.910	50.633
MS5	10.14	200	1	1.0786	7.86	0.775	10.637
MS6	10.14	400	1	5.4855	448.55	44.236	54.098
MS7	10.14	200	5	1.1200	12.00	1.183	11.045
MS8	10.14	400	5	1.3494	34.94	3.346	13.308

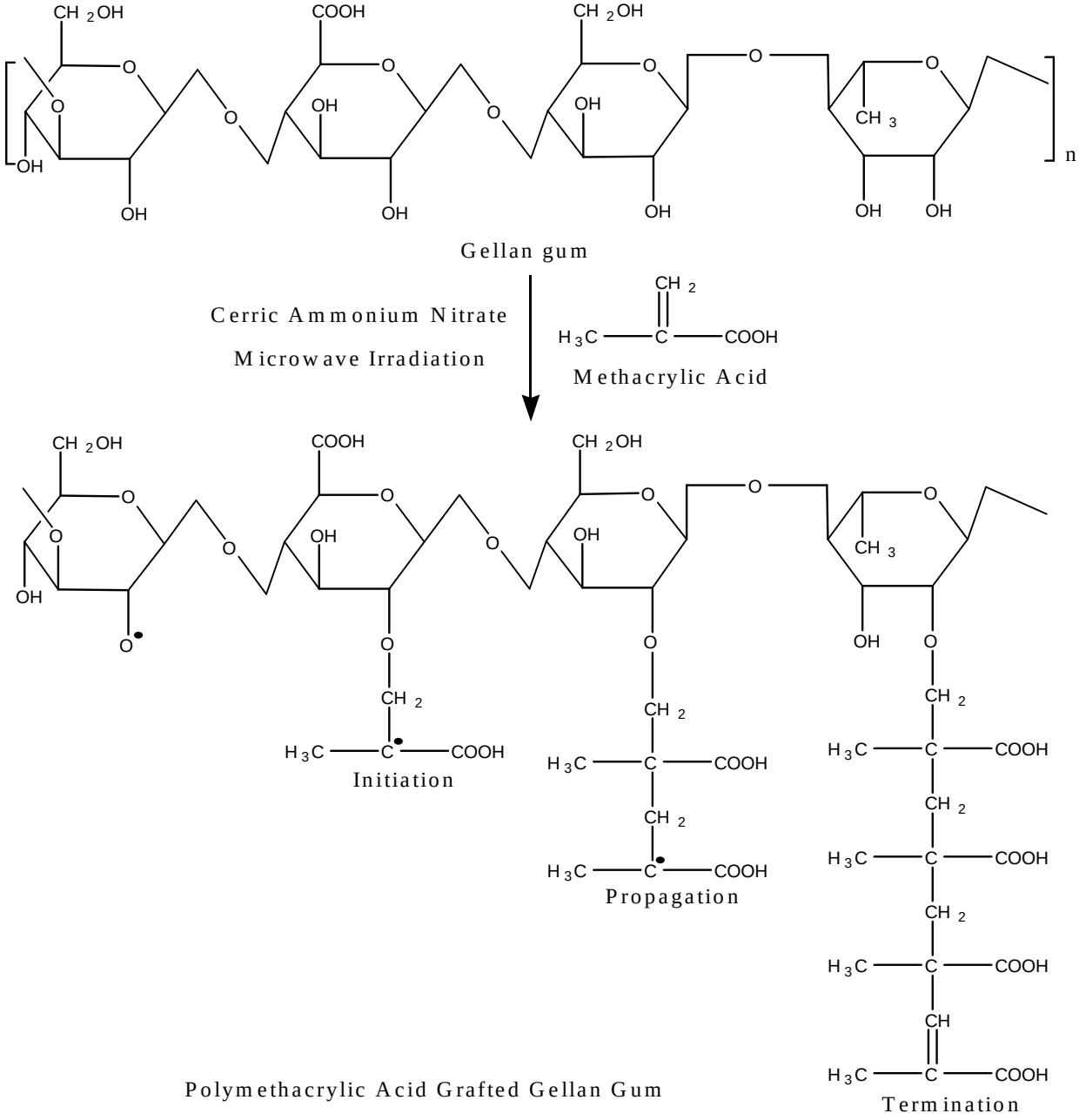


Figure 11.3. The structures of native GG and Pma-g-GG

11.3. EVALUATION OF GRAFTED GUM:

Rheology parameters:

The rheological property of Gellan Gum and different grafted gellan gum were dittermined by analaying their individual viscosity, shear rate, shear stress and storage modulus.

Low amplitude oscillatory shear tests were carried out in a controlled strain rheometer (Rheometrics Fluid Spectrometer RFS II) using the coaxial cylinders fixture (inner diameter: 32 mm; outer diameter: 34 mm, immersion length: 33 mm). The samples were poured into the preheated geometry (65–60 ^{0}C) and then cooled to 25 ^{0}C under a constant oscillation frequency of 1 rad/s to get the temperature evolution of dynamic moduli. A time sweep at 1 rad/s was also performed to determine the equilibrium values of the dynamic moduli. The moduli reached their equilibrium value in 15–30 min depending on gellan concentration. Thereafter, the mechanical spectra were obtained from 1022 to 102 rad/s and strain sweeps were completed to verify that all measurements were carried out within the linear region of viscoelasticity. All samples were covered with a thin layer of paraffin oil to avoid dehydration. Gellan concentrations higher than 0.05% were studied under low amplitude oscillatory shear tests in a HAAKE RV20 CV 20N using the plate–plate fixture (diameter ¼ 19.25 mm, Dh ¼ 3 mm) both plates were covered with fine sand (mesh 100) to avoid slippage during oscillation. Strain sweeps were performed previous to each was 36.5 ^{0}C, which was taken as the coil-helix transition temperature. In a previous work (Miyoshi, Takaya, Nishinari, 1994b) the exothermic peak temperature of 1% gellan with 6.8 mM CaCl2 was detected at 34.2 ^{0}C, which nearly corresponded to the temperature where G0 began to increase rapidly during the cooling process (35.8 ^{0}C) (Miyoshi, Takaya, & Nishinari, 1994a). Our results are close to those reported previously (Miyoshi et al., 1994b) in spite of the higher salt concentration used here. It has been reported that the conformational transition shifts to higher temperatures when salt concentration is increased (Kasapis et al., 1999; Miyoshi et al., 1994b; Nishinari, Watase, Rinaudo, Milas, & 1996) because of the higher stability of the double helix in excess of salt (Mazen, Milas, & Rinaudo, 1999). Thus, the slightly higher transition temperature observed can be due to the increase in CaCl2 concentration. Fig. 1 also shows the dynamic moduli evolution with temperature of 0.05% gellan

in the presence of 10 mM CaCl2 during the cooling process. At temperatures higher than 43.^{0C} the dynamic moduli were too small and hardly detected by the torque sensor of the rheometer. As soon as temperature reached 42.8 ^{0}C both moduli began to increase rapidly. This temperature coincided with the beginning of the coil-helix transition observed in DSC. Comparing the DSC peak with the G^{0} and G^{0} traces, it can be noticed that approximately at the temperature of the DSC peak (36.5 ^{0}C), the moduli, especially G^{0}, reached the equilibrium value corresponding to the ordered state (rigid helices). It is worth saying that the temperature evolution of the dynamic moduli was basically the same for all gellan concentrations (0.005–0.05%), but it was not possible to evaluate their thermal behavior by DSC for the reason mentioned above.

Storage Modulus vs Shear Stress:

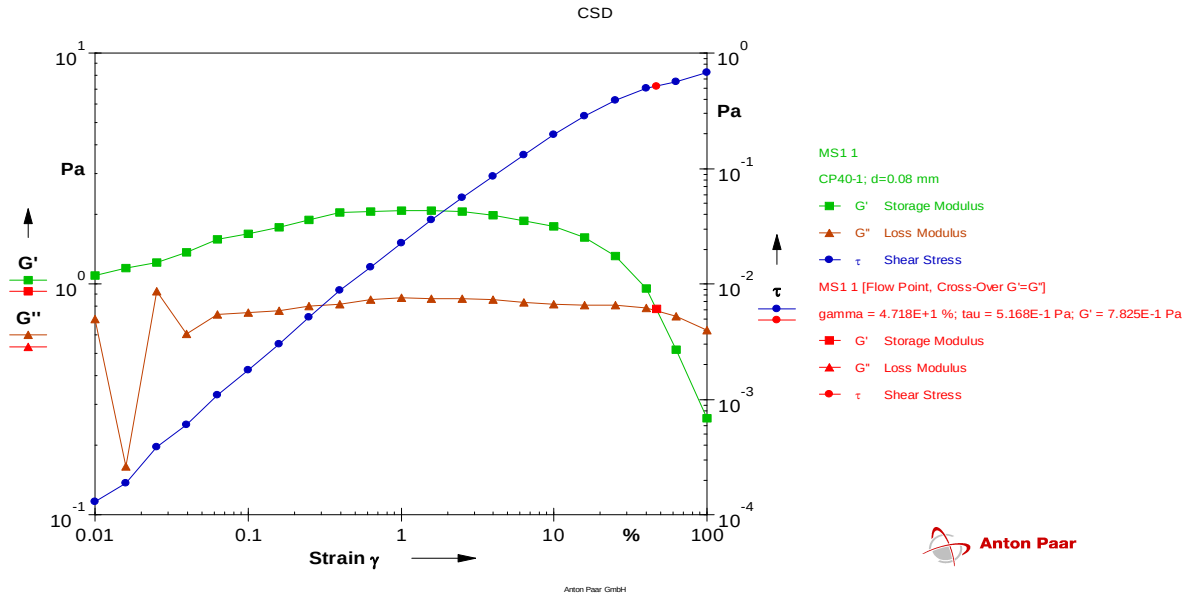


Fig:batch no ms1

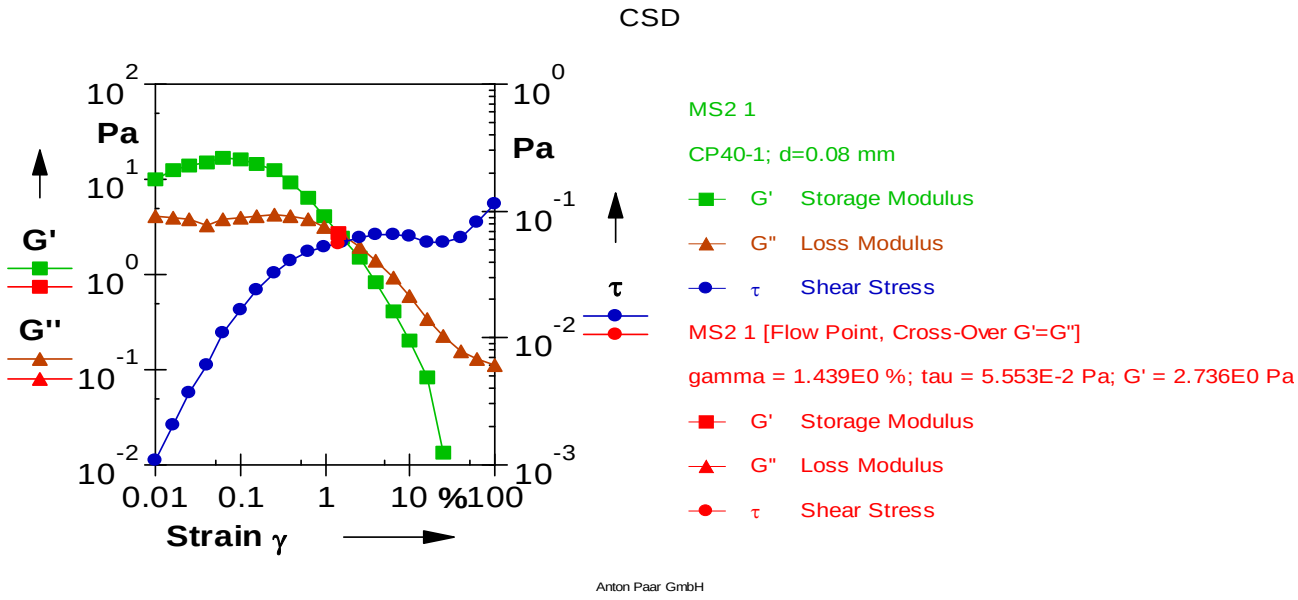


Fig:Batch No MS2

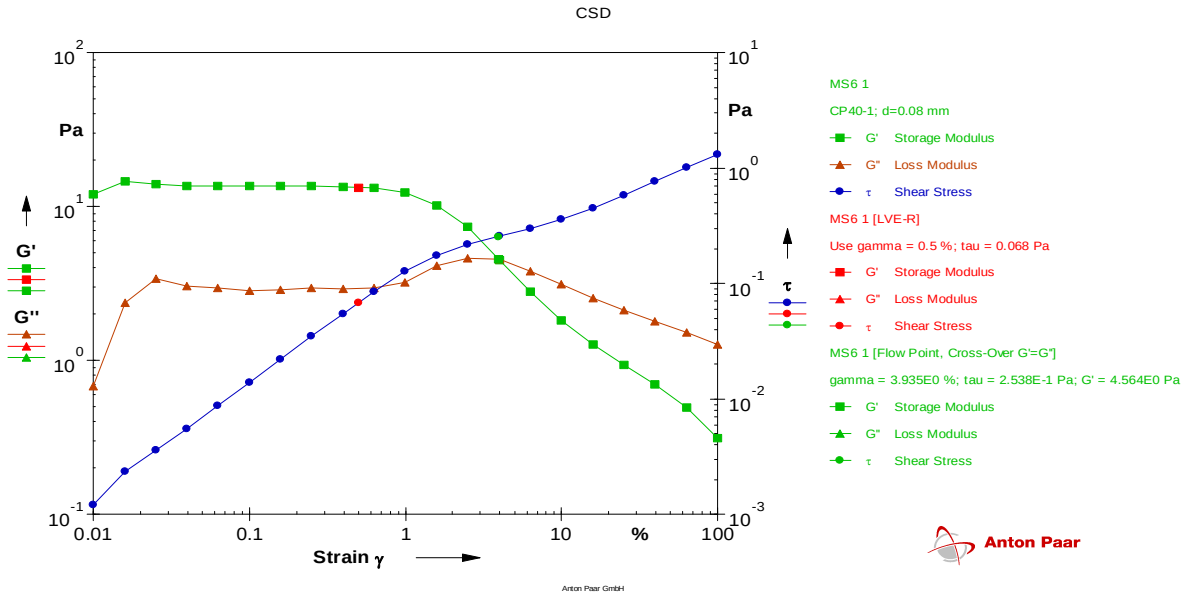


Fig:Batch No-MS6

Viscosity vs Shear Rate:

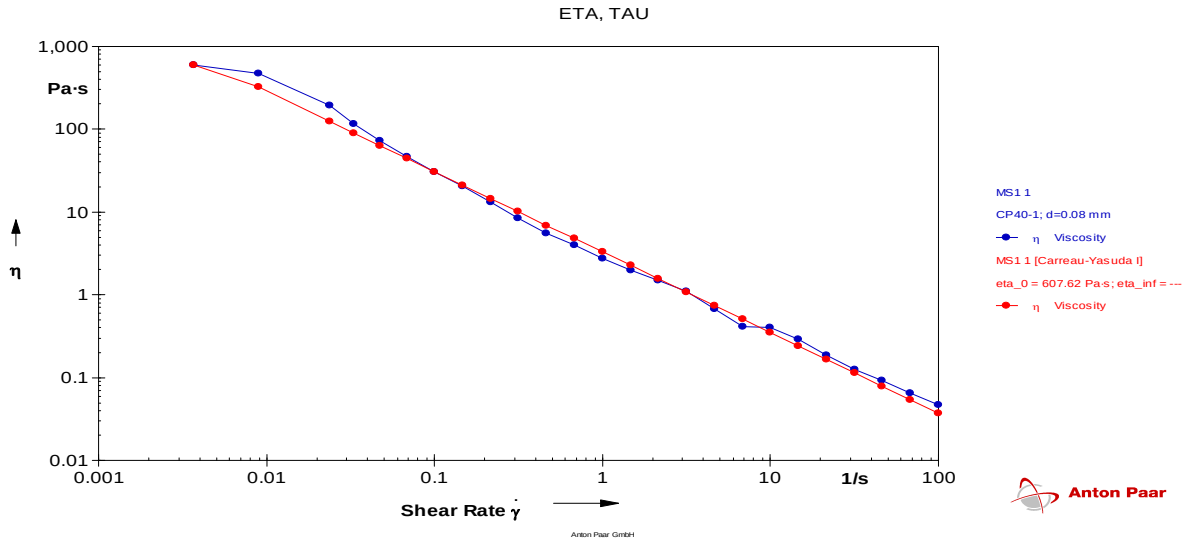


Fig: Batch No MS1

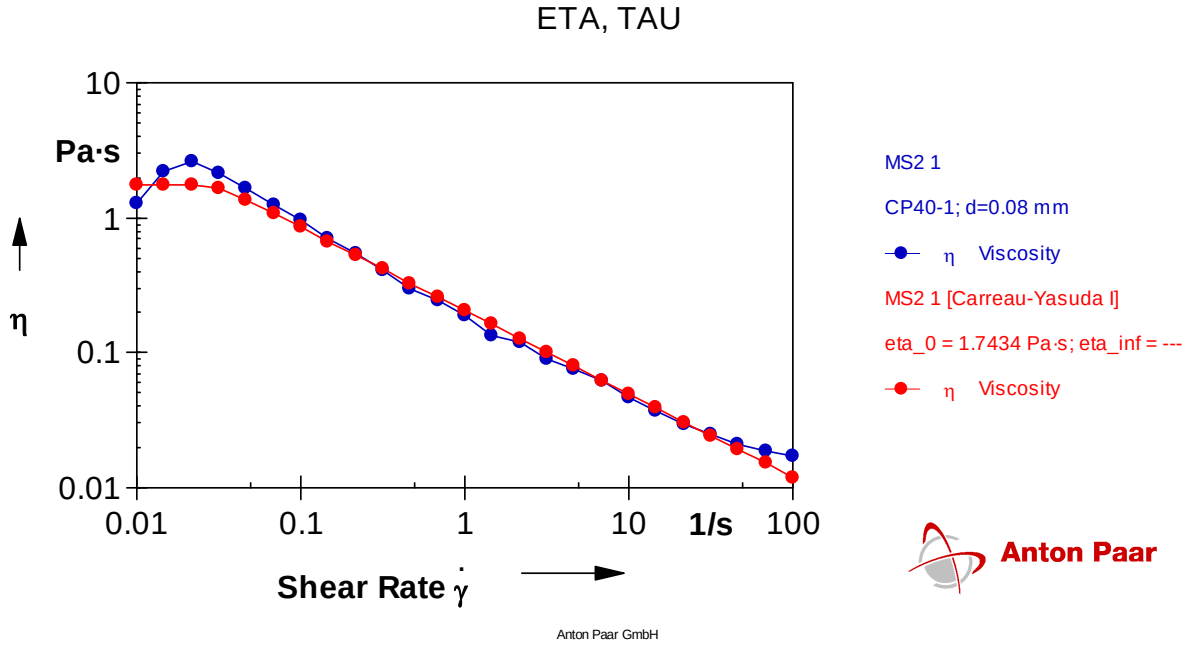


Fig:Batch No MS2

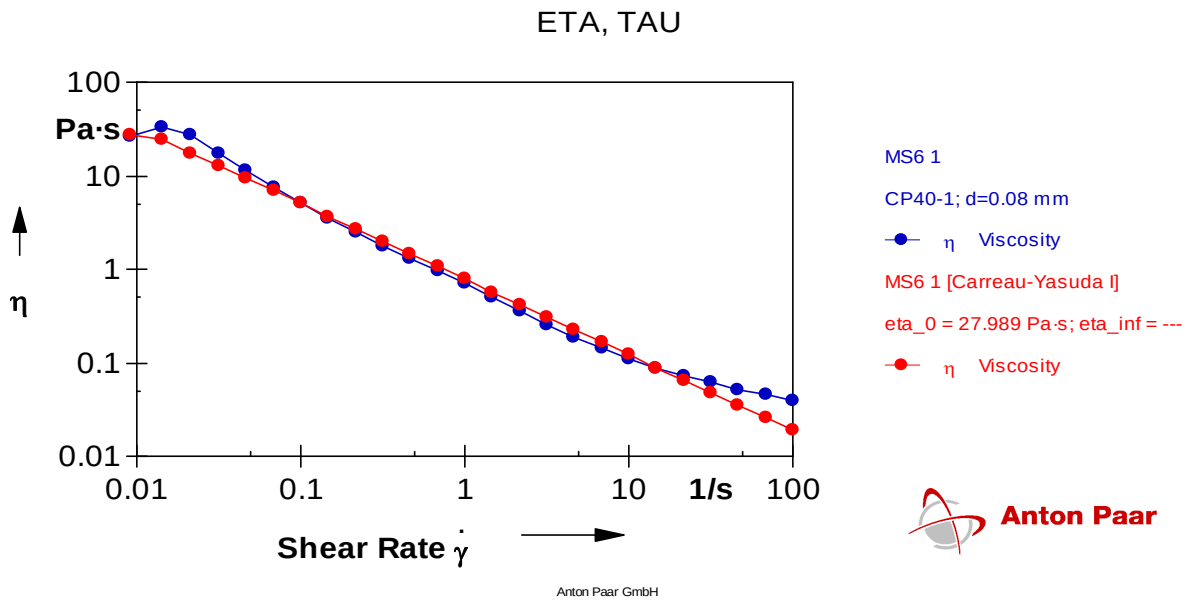


Fig:Batch No MS6

11.3.3. Infrared Spectral Analysis:

Infrared spectra of Gellan gum (GG) and grafted GG are shown in **Figure 11.4** and 11.**5** respectively. GG showed characteristic peaks at 3287.36 cm^{-1} for –OH group, at 1363.80 cm^{-1} for etheric and alcoholic –C-O group.

Some differences were observed in spectra of grafted GG compared to GG. The infrared spectra of methacrylic acid grafted GG shows characteristic peaks at 1715.70 cm^{-1} for –CH2OH group due to addition of methacrylic acid which was grafted onto GG. An additional peak at 1696.82 cm^{-1} has been observed due to -COOH bending. A peak observed at 1378.88 cm^{-1} indicates presence of –CH3 methyl bond in the grafted gum. A significant peak is also observed at 1378.88 cm^{-1} for $=CH_2$ group which occurs due to grafting reaction between OH group of C_2 of GG and π bond of methacrylic acid.

Infrared spectra of vinpocetine and tablet formulation are shown in **Figure 11.6.** and **11.7** respectively. Vinpocetine shows the characteristic peaks at 1715.01 $cm^{-1}$for N-H bending, at 1450.34 cm^{-1} for C-C in aromatic ring. Peaks at 1204.83 $cm^{-1}$and 1016.96 cm^{-1} indicate C-N stretching and ester C-O group respectively. Peaks at 764.81cm^{-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 grafted GG

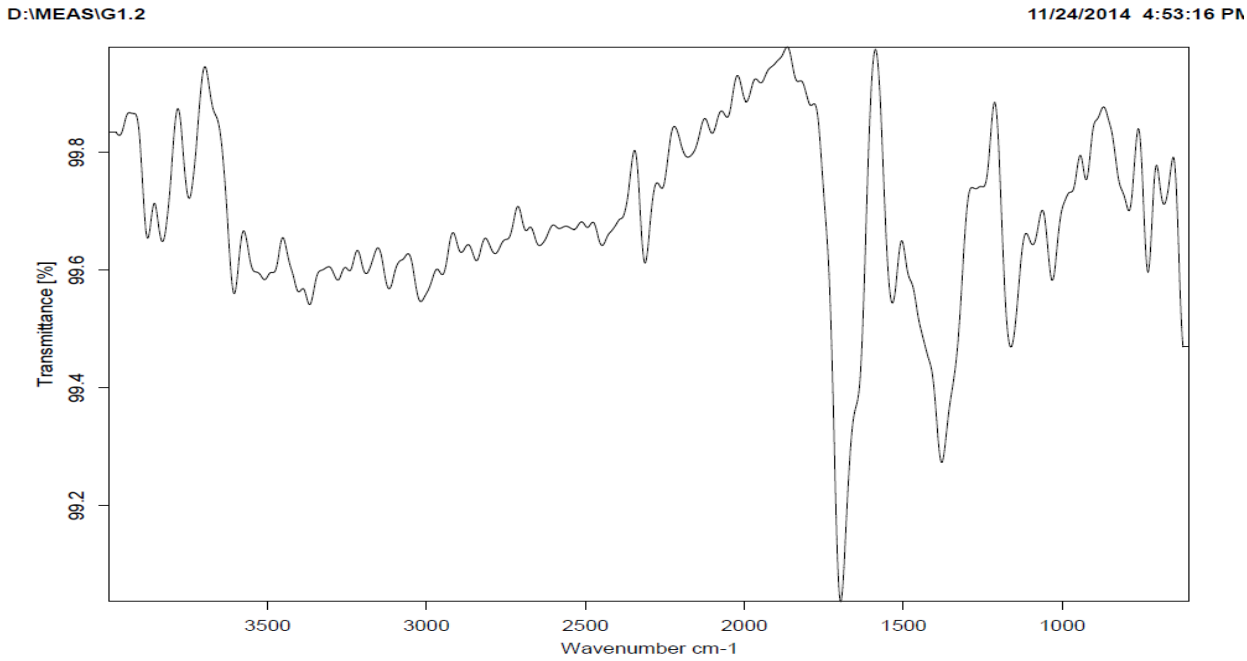


Figure 11.4. FTIR Spectrum of Isolated Gellan gum(GG)

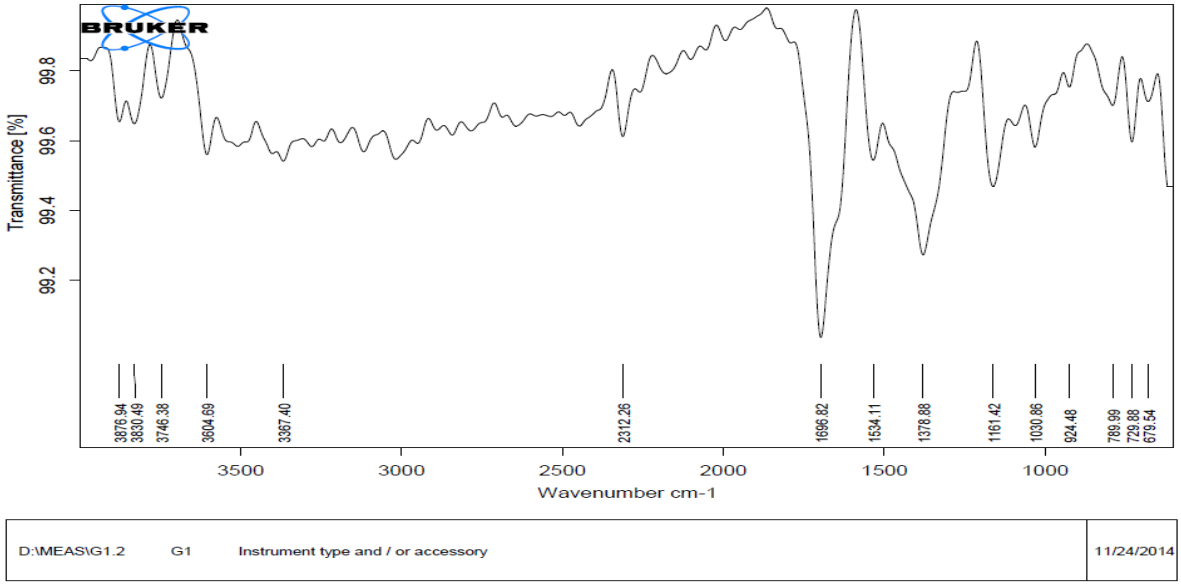


Figure 11.5. FTIR Spectrum of Polymethacrylic Acid Grafted GG (Pma-g-GG)

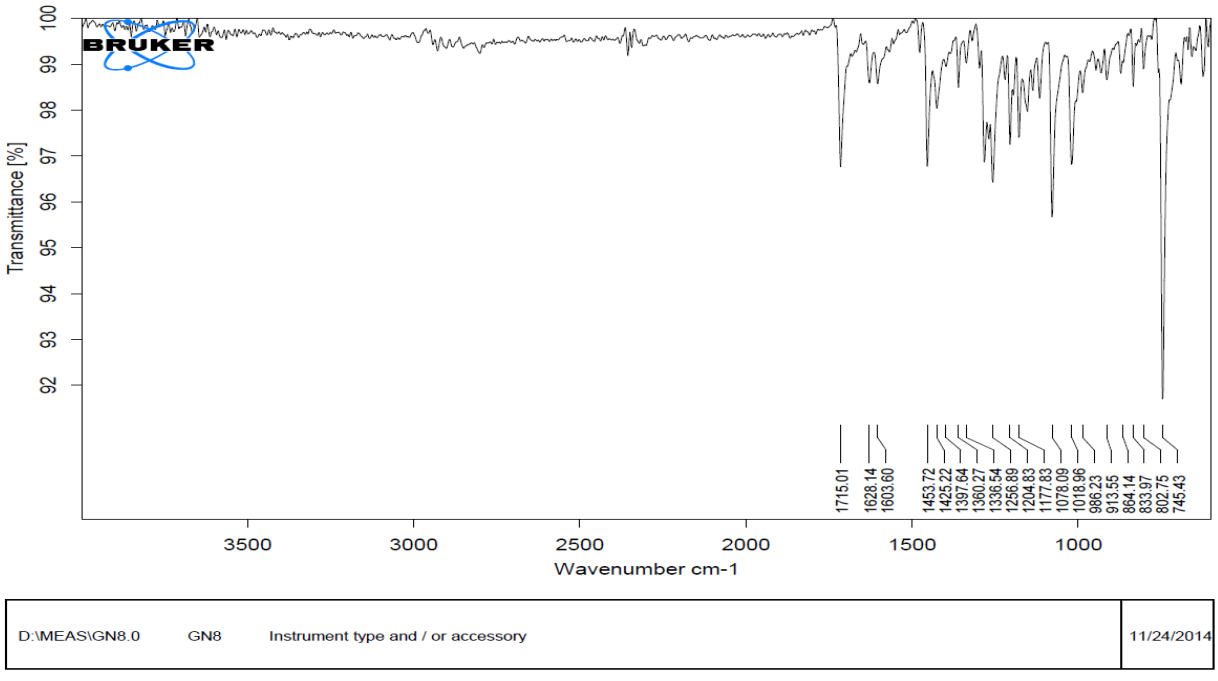


Figure 11.6. FTIR Spectrum of Pure Vinpocetine

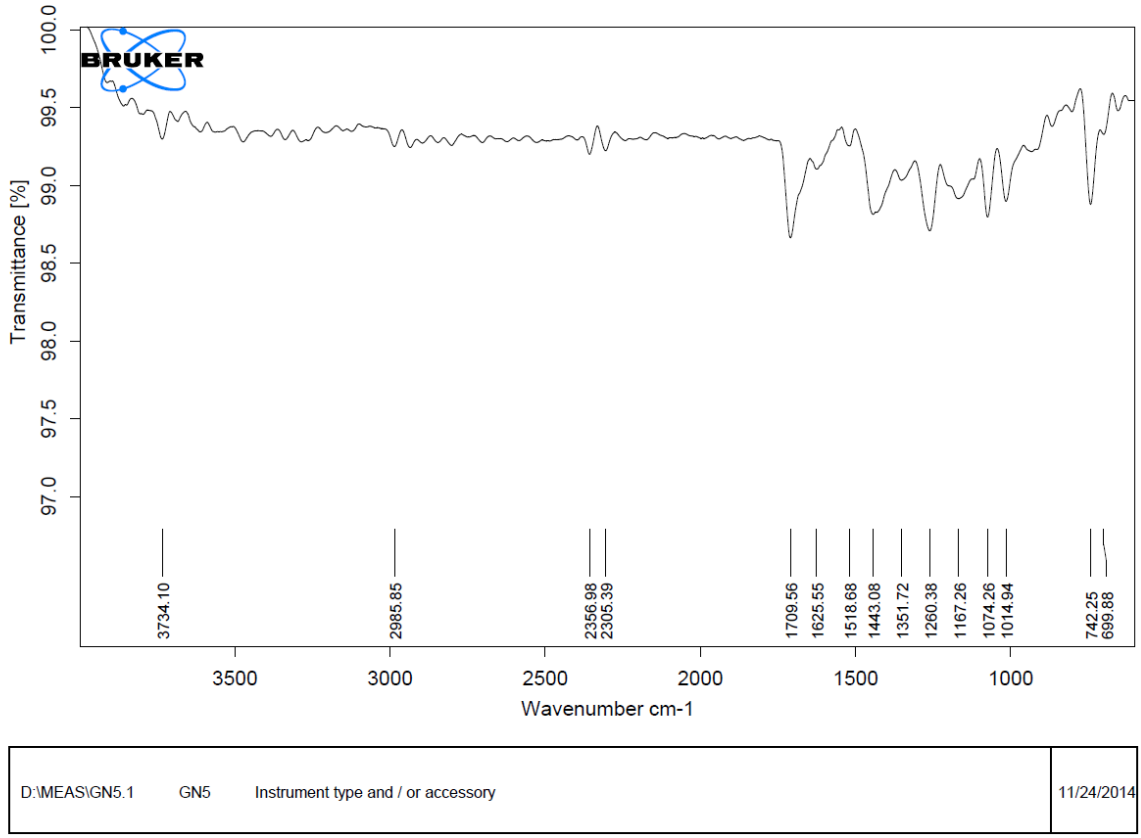


Figure 11.7. FTIR Spectrum of Graffed Gellan gum and Vinpocetine Mixture

11.3.4. Differential Scanning Calorimetry and Thermogravimetric Analysis:

DSC and TGA curves of GG, Pma-g-GG, vinpocetine and tablet formulation are shown in **Figure 11.8, 11.9, 11.10** and **11.11** respectively. An endothermic peak at 80^{o}C was recorded in DSC thermogram of GG. TGA thermogram of GG shows a 13% weight loss in the temperature range from 40^{o}C to 170^{o}C. The correlation between endothermic peak and simultaneous reduction in weight indicates the loss in moisture present in the GG. DSC thermogram of Paa-g-

GG shows an endothermic peak at 80^{o}C similarly with GG indicating loss in moisture content, which is further established by the 13% reduction in weight in the temperature range from 40^{o}C to 175^{o}C observed in corresponding TGA curve. An endothermic peak at 285.73^{o}C and an exothermic peak at 310^{o}C have been seen in DSC thermogram of vinpocetine, which indicates melting and subsequent thermal degradation respectively. Approximately 40% weight loss in the temperature range from 290^{o}C to 340^{o}C substantiates the thermal degradation of vinpocetine in the aforesaid temperature range. Two endothermic peaks at 80^{o}C and 240^{o}C observed in DSC curve for tablet formulation demonstrate moisture loss and melting point 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.

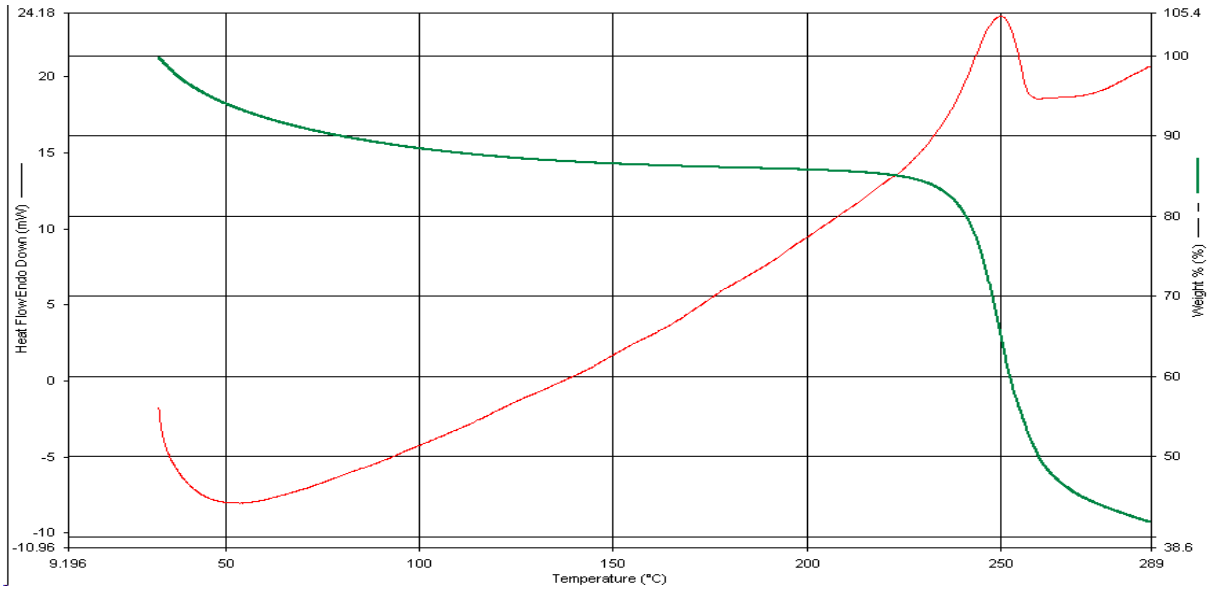


Figure 11.8. DSC Thermogram of Isolated Gellan Gum(GG)

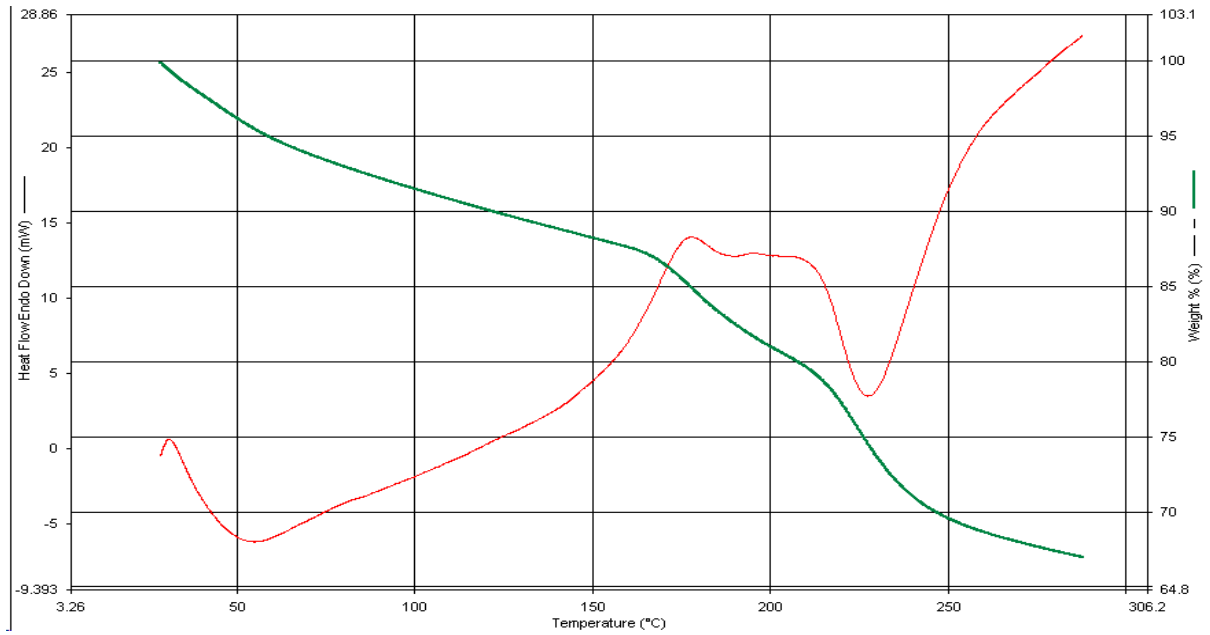


Figure 11.9. DSC Thermogram of Polymethacrylic Acid Grafted Gellan gum(Pma-g-GG)

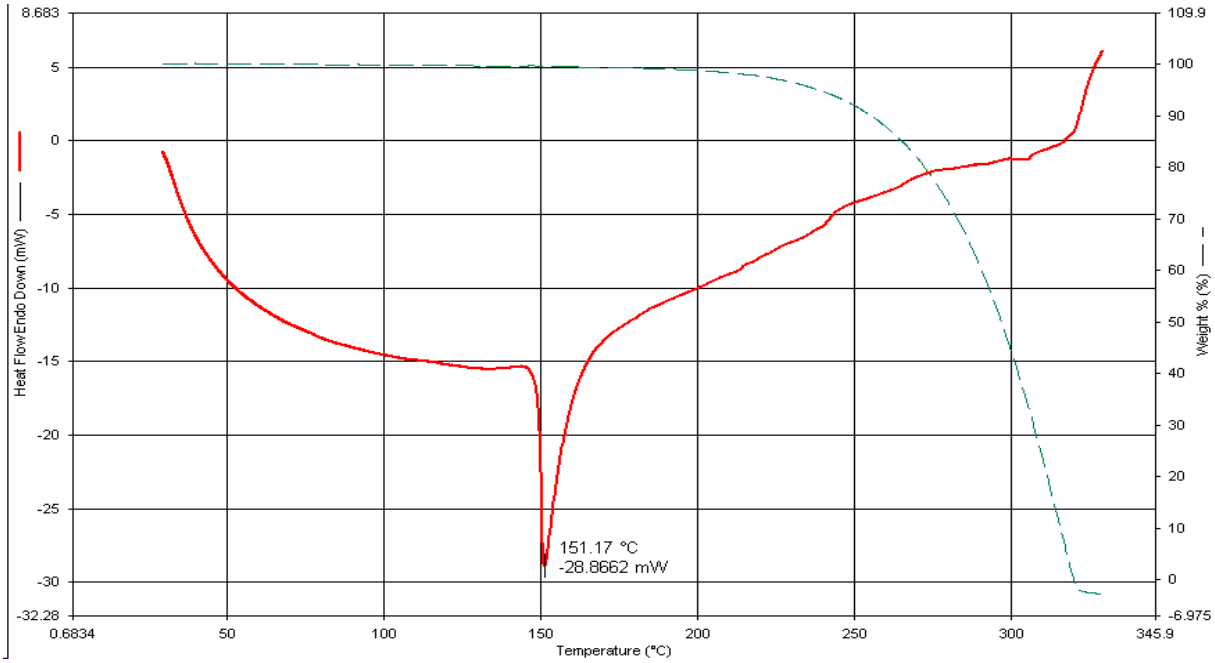


Figure 11.10. DSC Thermogram of Pure Vinpocetine

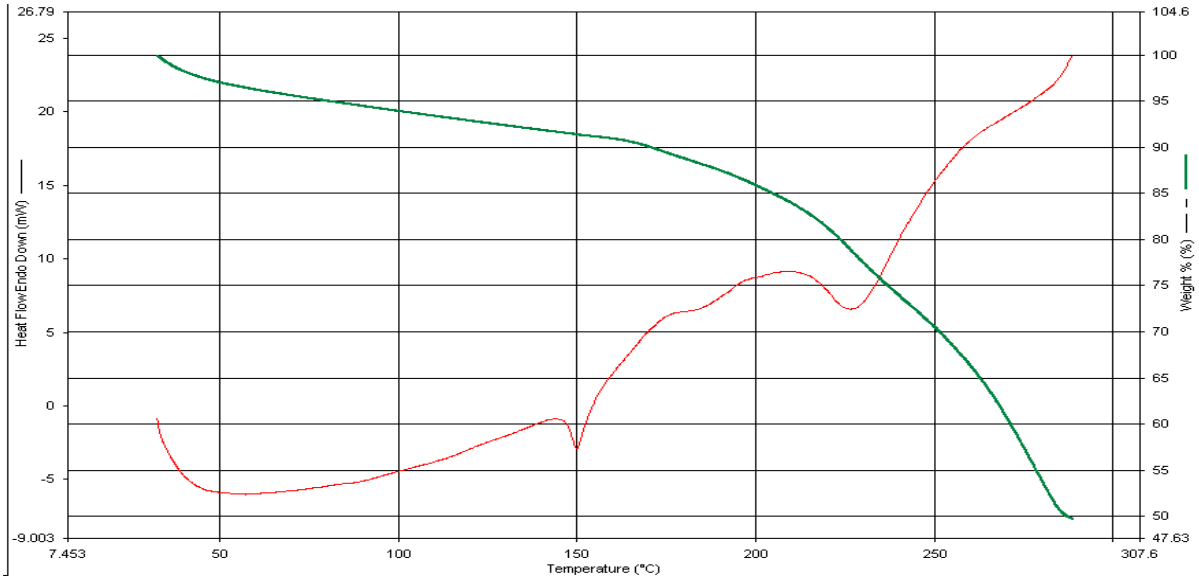


Figure 11.11. DSC of Vinpocetine and Gellan Mixture

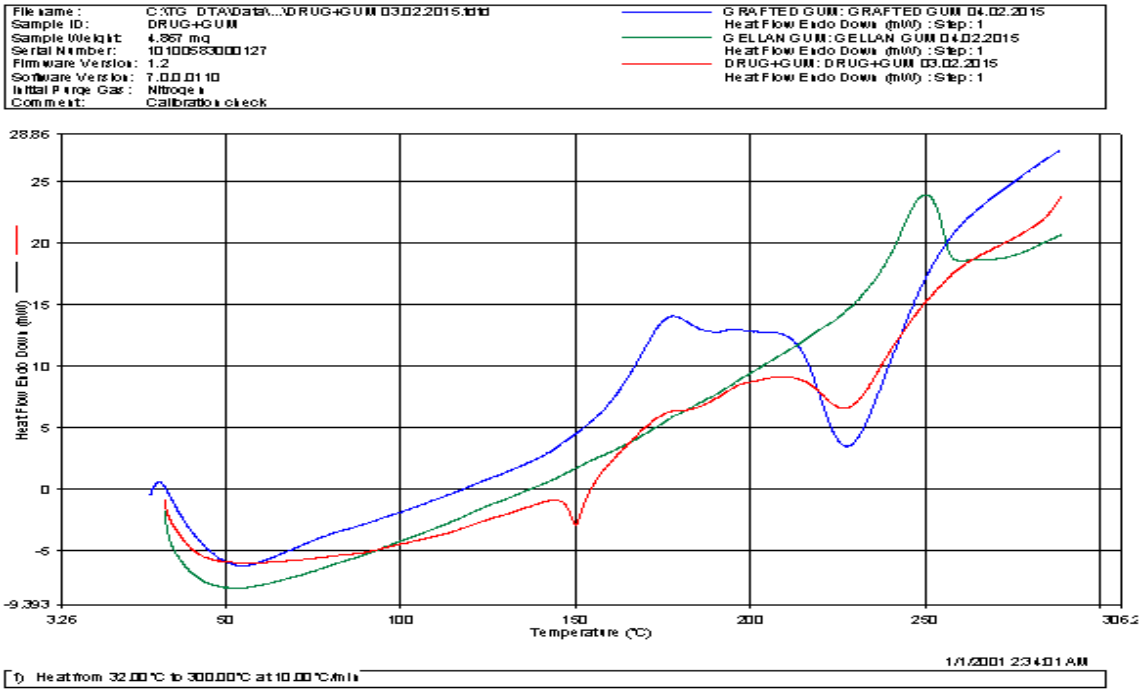


Fig. 11.12. DSC of Gellan,Vinpocetine and Grafted gum Mixture

11.3.5. Powder X-ray diffraction:

X-ray diffractogram of pure vinpocetine and tablet formulation containing drug were represented in **Figure 11.13** and **11.14.** From the diffractogram it can be said that the drug was of crystalline nature in its pure form as well as in tablet because it showed several peaks rather than hump and less noise. The diffractograms portray that the intensities at various 2θ values for pure drug were retained in tablet formulation attributing to the absence of incompatibility between drug and other formulation components.

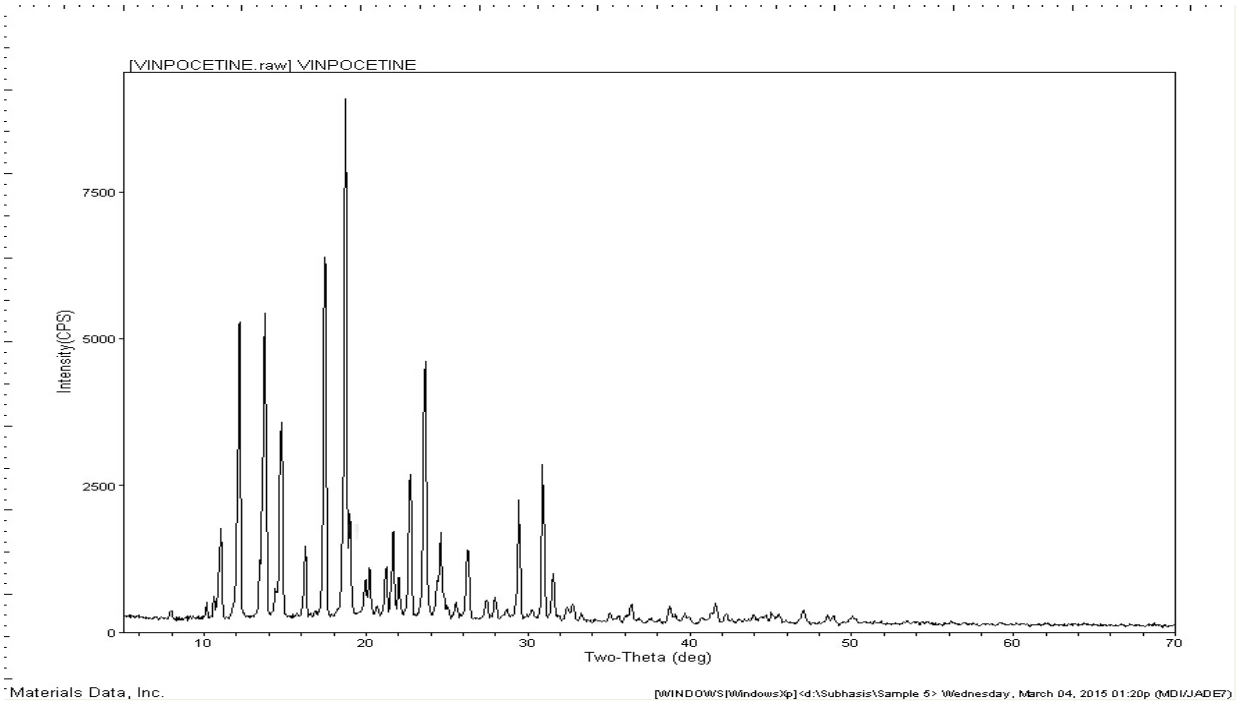


Figure 11.13. X-ray Diffractogram of Pure Vinpocetine

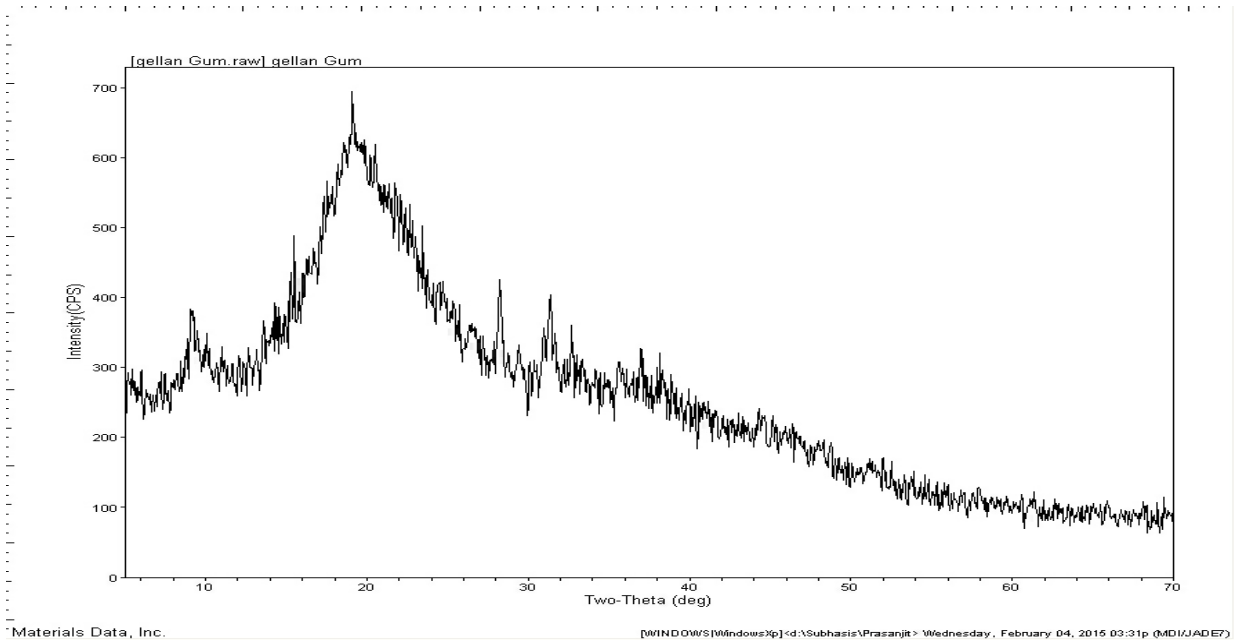


Figure 11.14. X-ray Diffractogram of Gellan gum

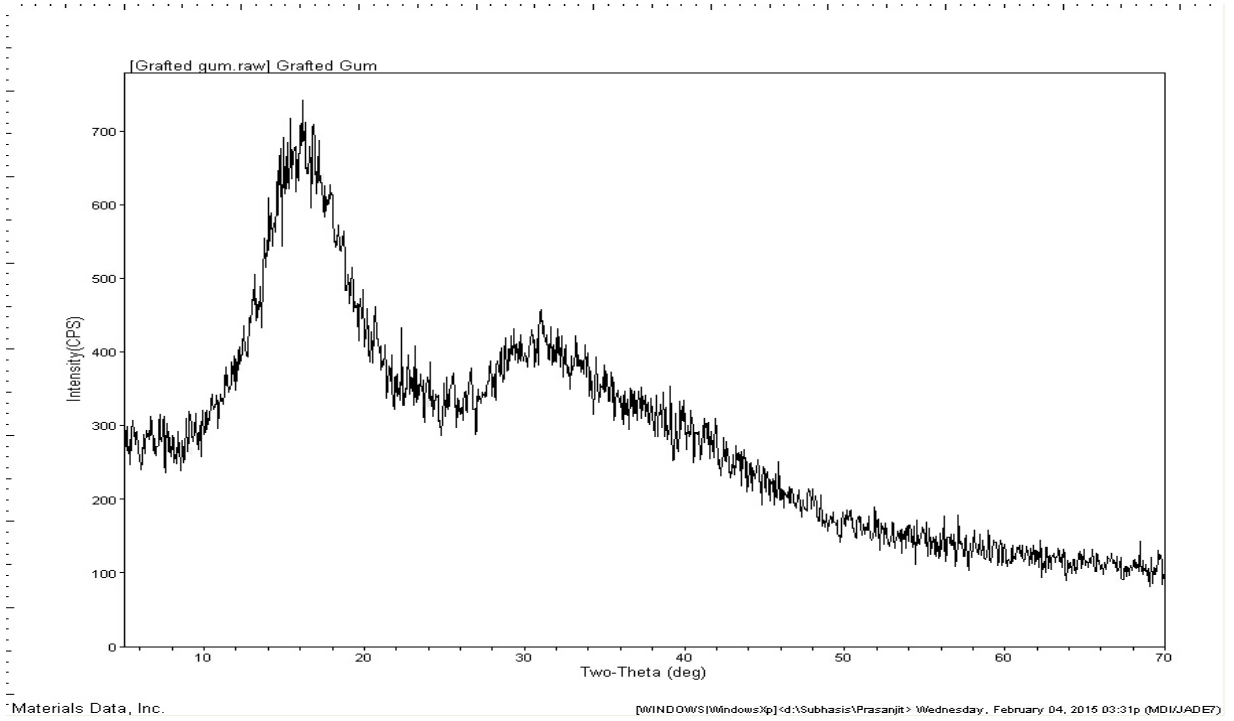


Figure 11.15. X-ray Diffractogram of Graffted Gellan Gum

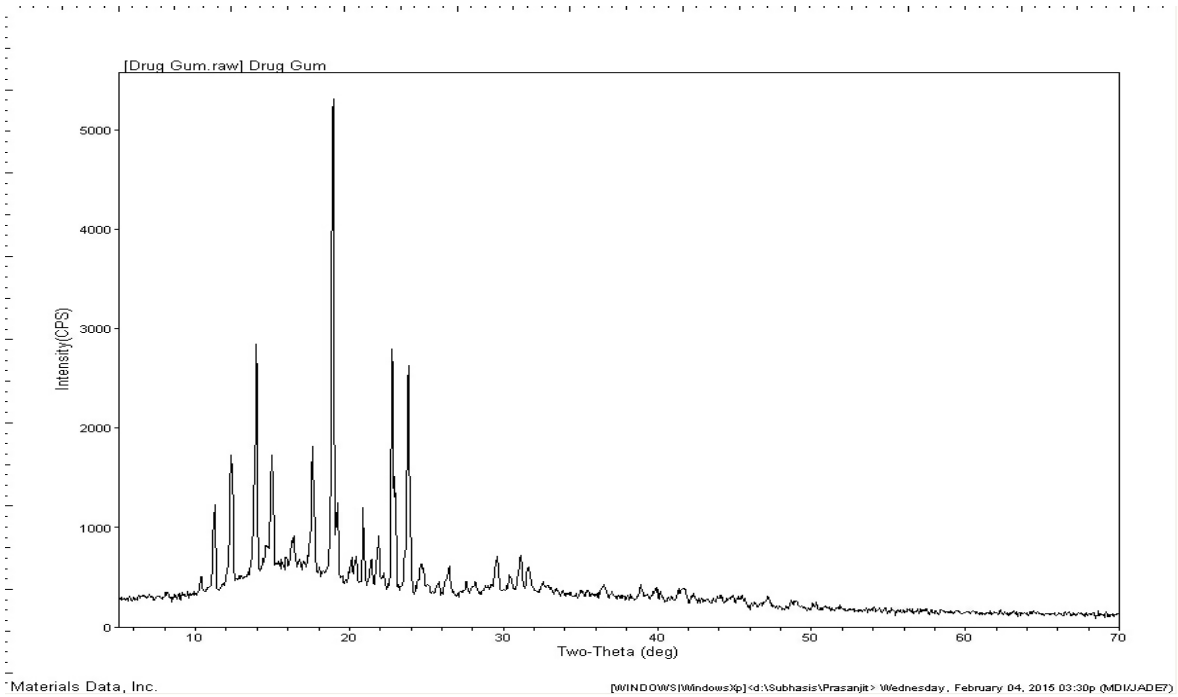


Figure 11.16. X-ray Diffractogram of Graffted Gellan Gum and Vinpocetine

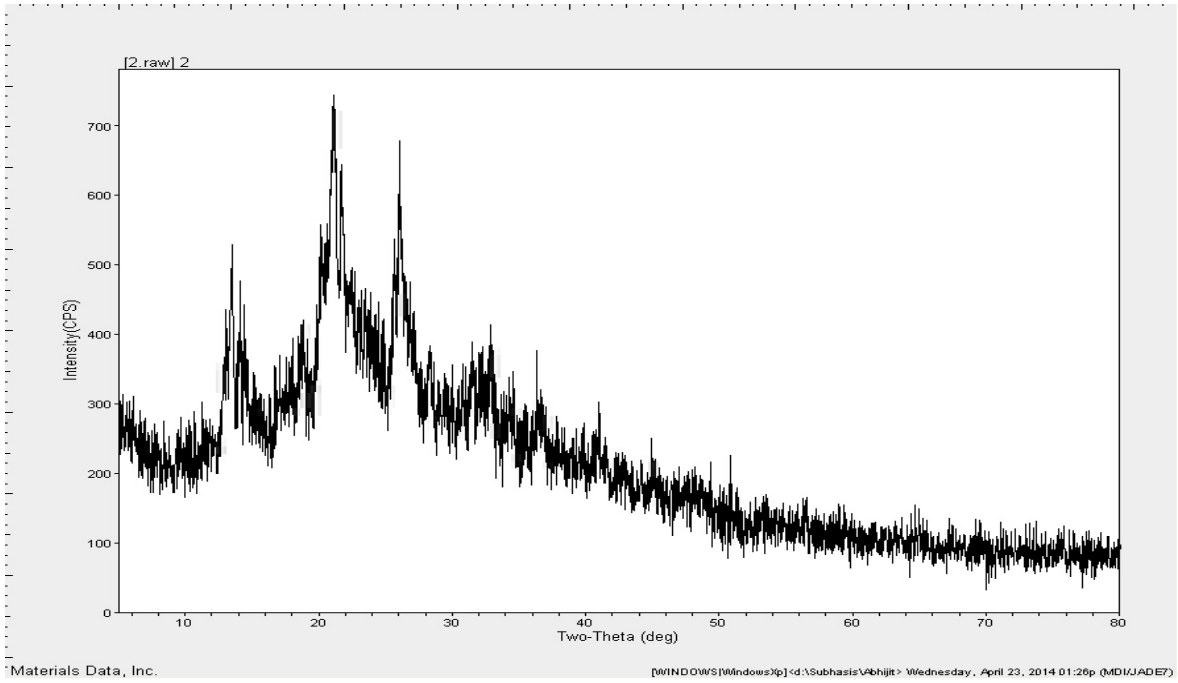


Figure 11.17. X-ray Diffractogram of Prepared Tablet Formulation.

11.3.6. Scanning Electron Microscopy:

Figure 11.18 and **11.19** shows the scanning electron micrographs of Gellan gum and its grafted form. The methacrylic acid particles are polyhedral in shape, while the Gellan gum particles are fibrous in nature. The SEM images of grafted copolymer show that the grafting of methacrylic acid onto GG brings about the change in the surface morphology, texture and topography of the GG particles. The irregular morphology as a lobule aggregate with higher heterogeneity is shown in case of grafted copolymer.

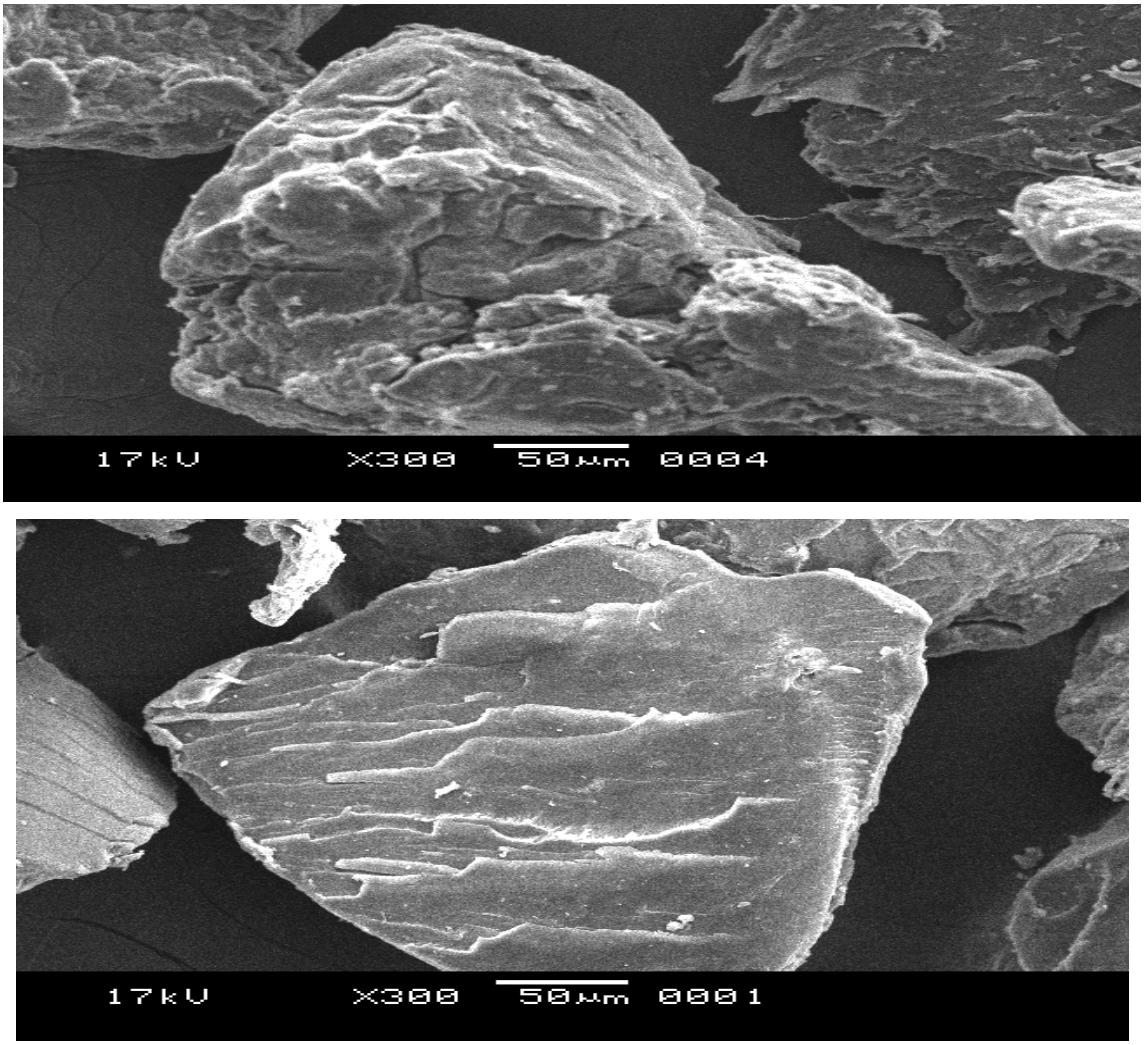


Figure 11.18. SEM image of isolated Gellan gum(GG)

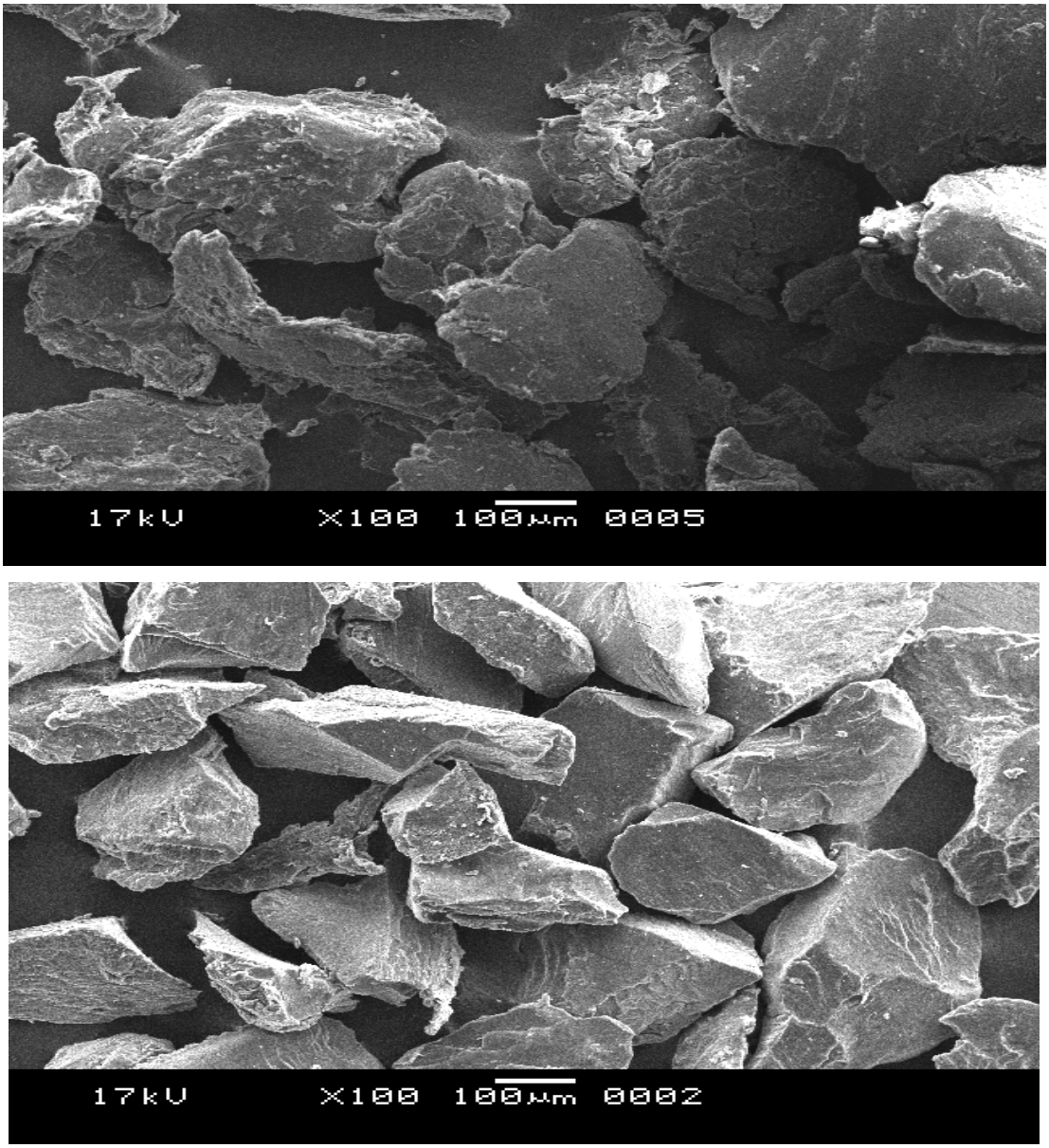


Figure 11.19. SEM image of Polymethacrylic acid grafted Gellan gum(Pma-g-GG)

11.3.7.High Resolution Solid-State NMR Spectroscopy:

13C cross polarization magic angle spinning (CP MAS) and 2D1H–13C NMR spectra were recorded using 4 mm zirconium oxide rotors spun at 5 kHz on a Varian Infinity-Plus 300 spectrometer operating at 299.78 and 75.39 MHz for 1H and for 13C, respectively. For the CP experiment, the Jeol solution for innovation matching condition was optimized using hexamethylbenzene (HMB). The 13C chemical shift was referenced to a solid HMB sample externally as 17.35 ppm for the methyl groups. The Solid state NMR spectroscopy experiment is done for the following samples.

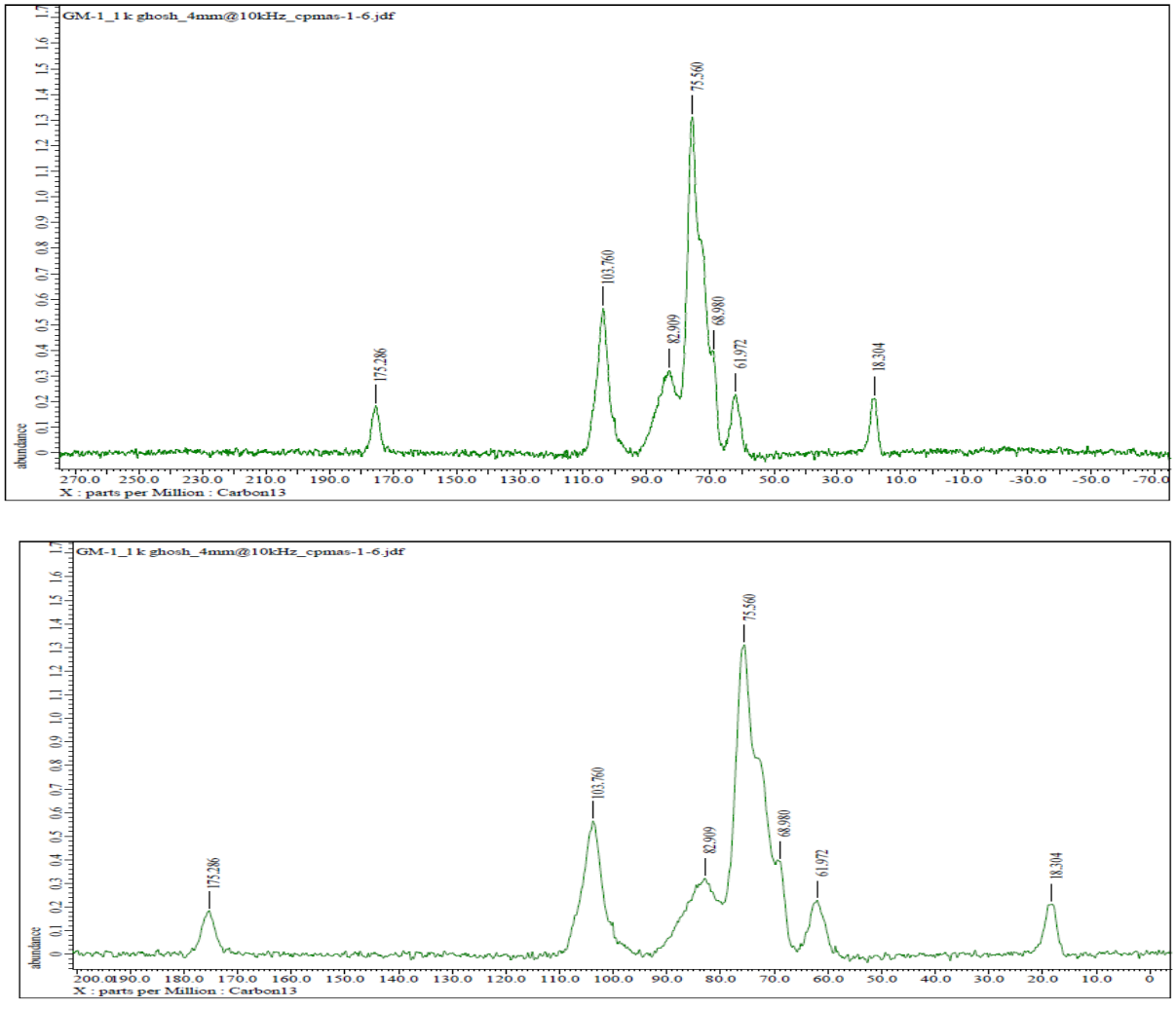
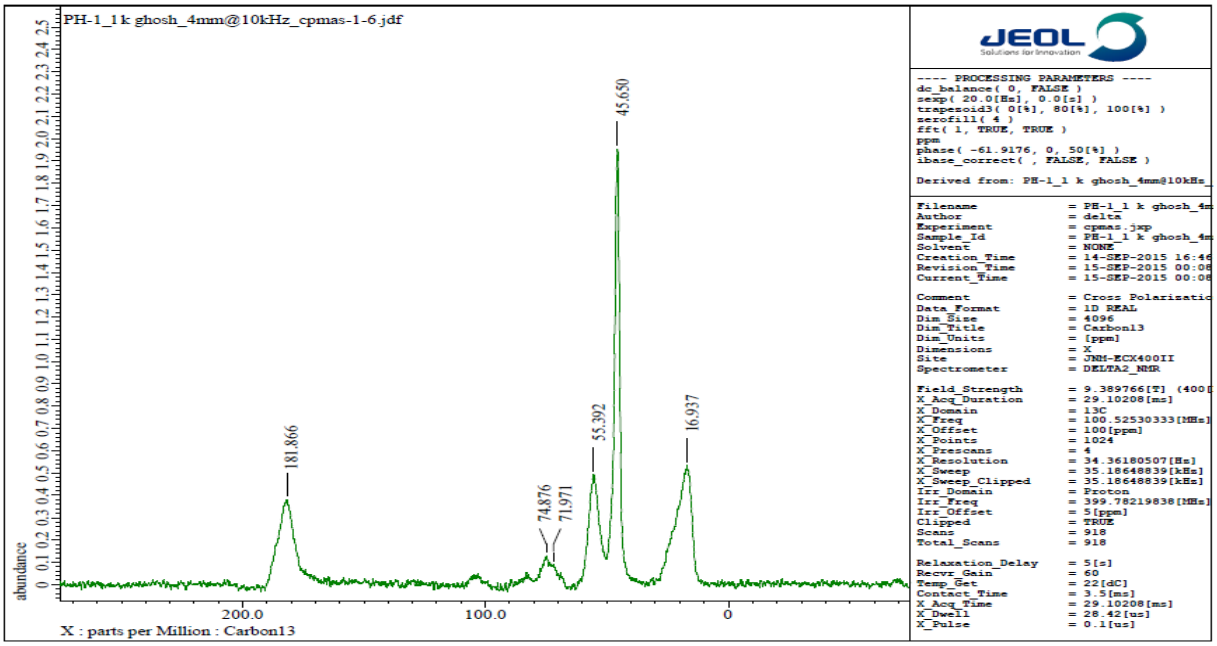


Fig11.20:Solid state NMR of Gellan Gum



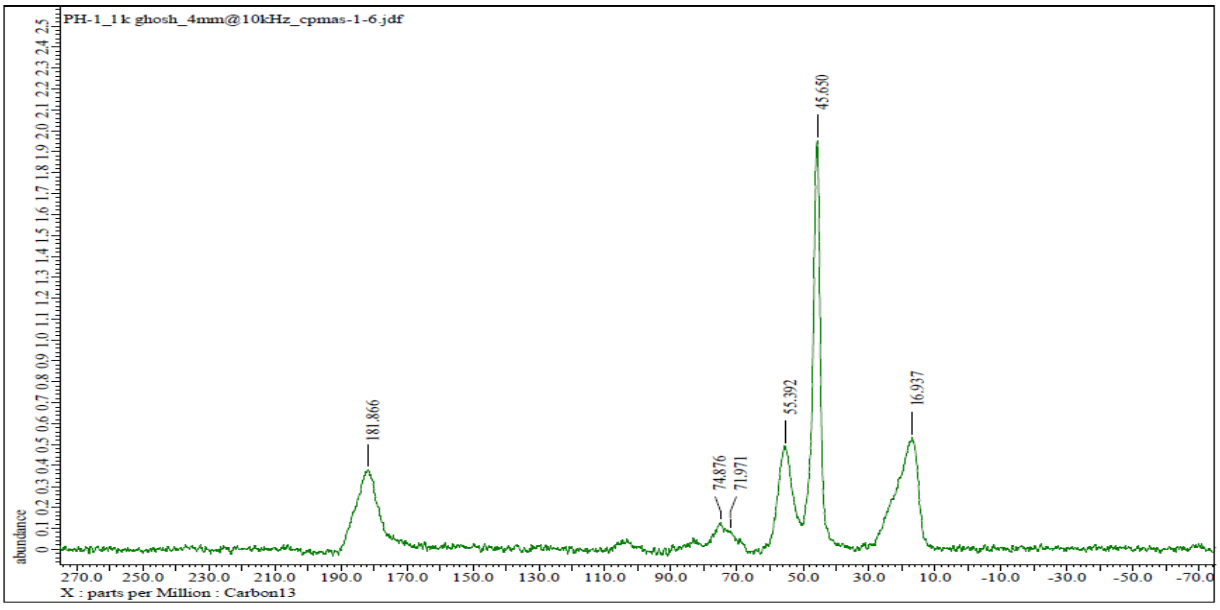


Fig11.21:Solid state NMR of Graffted Gellan Gum

11.3.8.In-Vitro Swelling Study:

The Sustained Released tablet contained grafted polymer, vinpocetine and meagnasim stearate These usually uptake water and get swelled in contract with water. This water uptake and swelling property have greater influence on drug release from the sustain tablets.

11.3.8.1.Method:

One tablet was weighted accurately and placed in a small metal basket of previously weighted. Then the basket with the tablet was immersed in 100ml of 0.1(N) HCL and phosphate buffer of PH-6.8 in a beaker at 37-+0.5c. At different time intervals the system was taken out from the buffer and weighted after soaking with tissue paper to remove the buffer on its surface.The final weight of tablet at each time intervals was measured by distracting the basket weight from combining weight of basket and tablet. The swelling index(%weight gain) was calculated using following equation:

Swelling Index=[(W1-W2)/W1]*100

Where,

W1=Initial weight of tablet.

W2=Final weight of tablet.

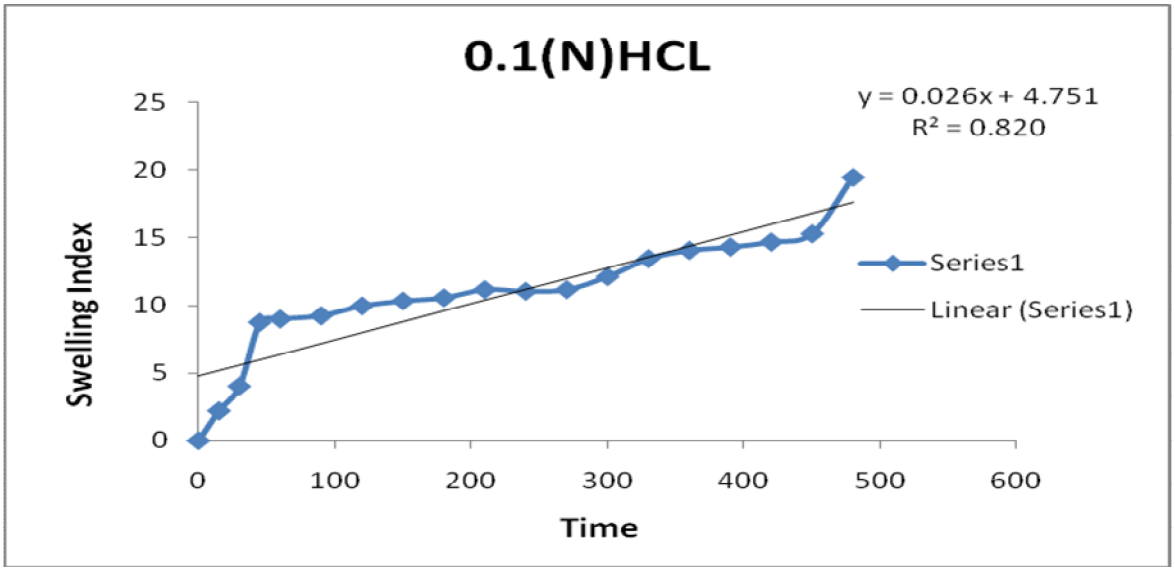
The swelling study of following batches of was carried out S1, MS3 and MS6 because this batches absorbed maximam water both from 0.1(N) HCL and phosphate buffer PH-6.8.

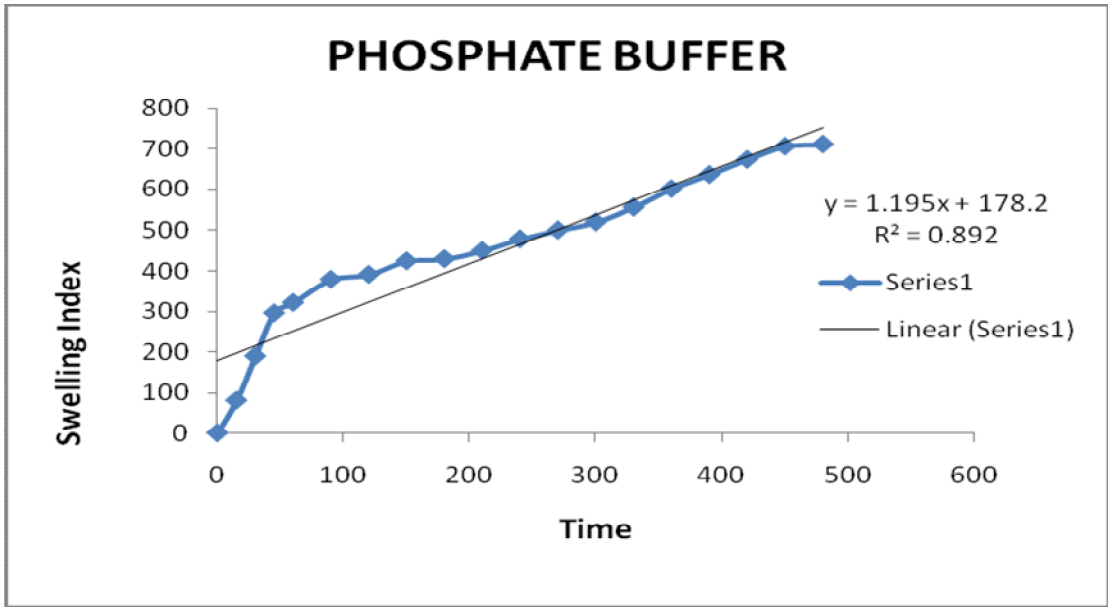
Table 11.4: In-Vitro Swelling study of different formulations.

Time(minite)	Batch No-S1				Batch No-S4				Batch No-MS6			
	0.1(N) HCL		Phosphate Buffer PH-6.8		0.1(N) HCL		Phosphate Buffer PH-6.8		0.1(N) HCL		Phosphate Buffer PH-6.8	
	Wt after specified time(mg)	Swelling Index(%)	Wt after specified time(mg)	Swelling Index(%)	Wt after specified time(mg)	Swelling Index(%)	Wt after specified time(mg)	Swelling Index(%)	Wt after specified time(mg)	Swelling Index(%)	Wt after specified time(mg)	Swelling Index(%)
0	0.0822	0	0.0815	0	0.1108	0	0.1443	0	0.1055	0	0.1084	0
15	0.0840	2	0.1417	81	0.1933	74	0.2749	91	0.1434	36	0.3875	258
30	0.0855	4	0.2356	189	0.2499	126	0.3201	122	0.2786	164	0.51	371
45	0.0894	8	0.3220	295	0.2878	160	0.4027	179	0.3065	191	0.6944	541
60	0.0896	9	0.3430	321	0.2925	164	0.4090	183	0.3858	266	0.7194	564
90	0.0898	9	0.3897	378	0.3037	174	0.4655	223	0.3966	276	0.8333	669
120	0.0904	10	0.3998	391	0.3124	182	0.4661	223	0.5374	409	0.8752	707
150	0.0907	10	0.4217	424	0.3169	186	0.4698	226	0.5935	463	0.9319	760
180	0.0909	11	0.4314	429	0.3362	203	0.4856	237	0.6305	497	1.0512	870
210	0.0912	11	0.4481	450	0.3647	230	0.5837	305	0.6309	498	1.0716	889
240	0.0913	11	0.4713	478	0.3811	244	0.6099	322	0.6922	556	1.0758	892
270	0.0914	11	0.4890	500	0.3853	248	0.6156	327	0.6991	563	1.095	910
300	0.0922	12	0.5052	519	0.4108	271	0.6657	361	0.7128	575	1.096	911
330	0.0933	13	0.5343	555	0.4175	277	0.7516	421	0.7388	613	1.1016	916
360	0.0938	14	0.5711	601	0.4388	296	0.8078	460	0.7523	613	1.1074	921
390	0.0940	14	0.5997	634	0.4562	312	0.8740	506	0.7953	654	1.1707	979

Time(minite)	Batch No-S1				Batch No-S4				Batch No-MS6			
	0.1(N) HCL		Phosphate Buffer PH-6.8		0.1(N) HCL		Phosphate Buffer PH-6.8		0.1(N) HCL		Phosphate Buffer PH-6.8	
	Wt after specified time(mg)	Swelling Index(%)	Wt after specified time(mg)	Swelling Index(%)	Wt after specified time(mg)	Swelling Index(%)	Wt after specified time(mg)	Swelling Index(%)	Wt after specified time(mg)	Swelling Index(%)	Wt after specified time(mg)	Swelling Index(%)
420	0.0943	14	0.6302	673	0.5160	365	0.8865	514	0.8421	698	1.1792	988
450	0.0948	15	0.6569	706	0.5198	369	0.9009	524	0.8531	709	1.1886	997
480	0.0982	19	0.6612	711	0.5203	370	0.9097	530	0.9035	756	1.2039	1011

Table of Batch No S1:





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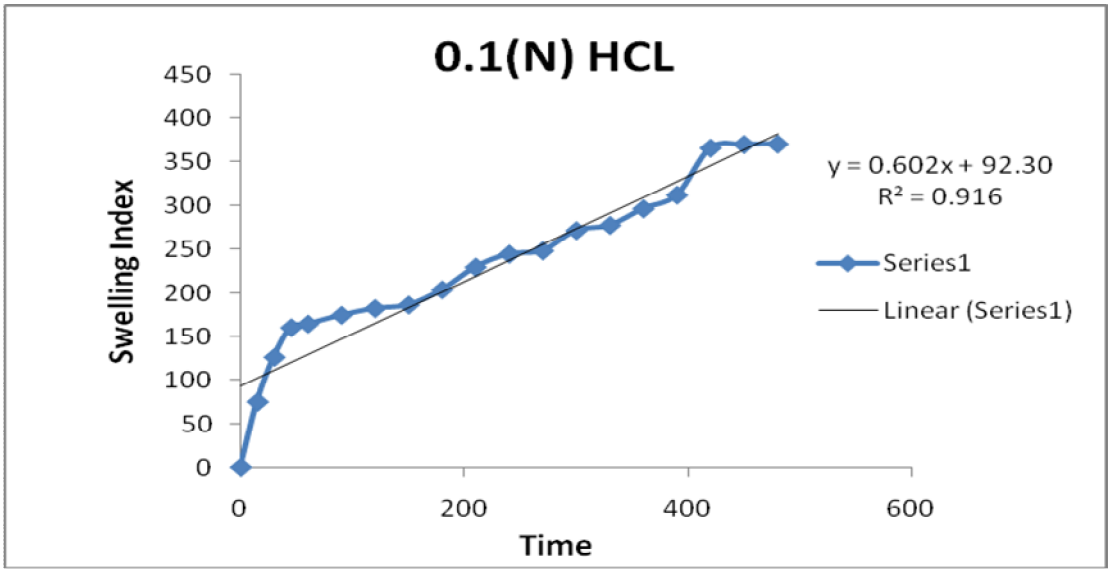


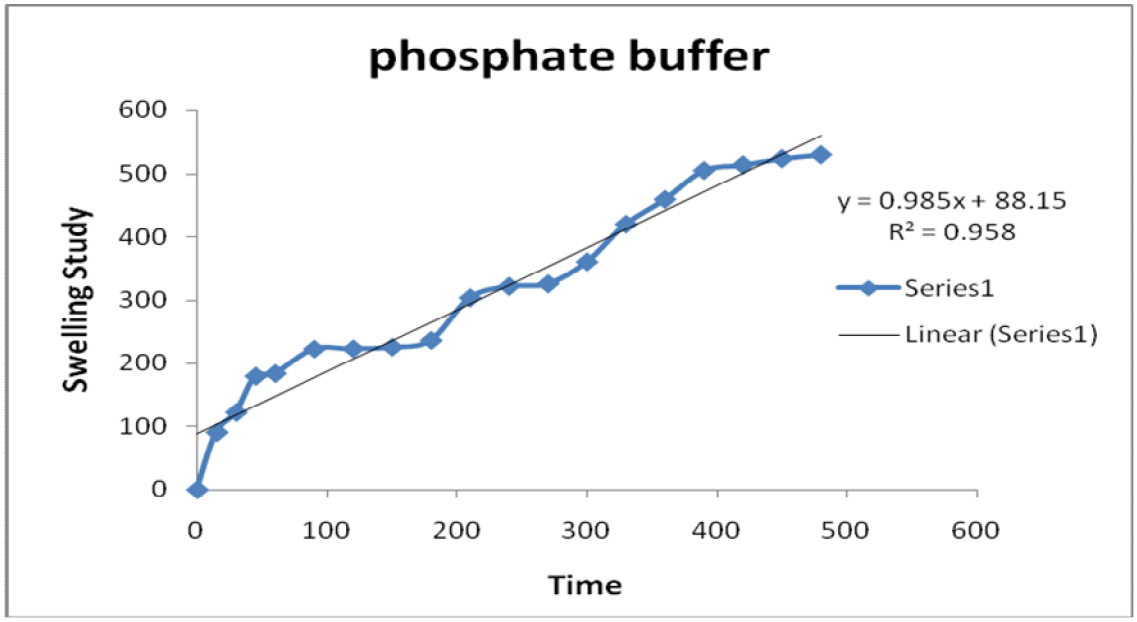
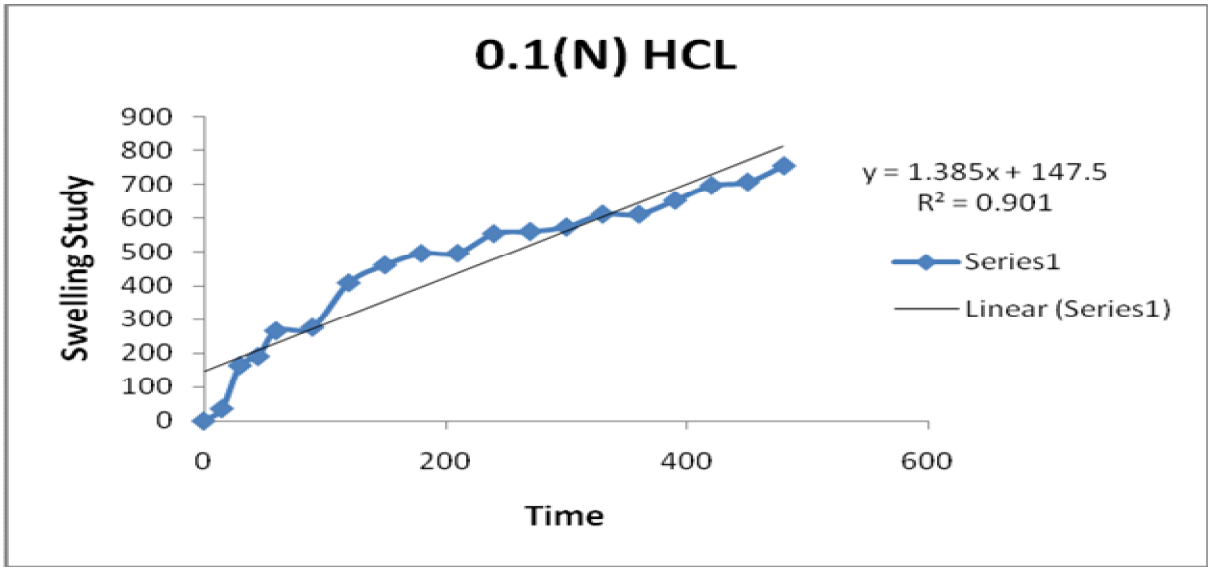


Table of Batch No MS6:



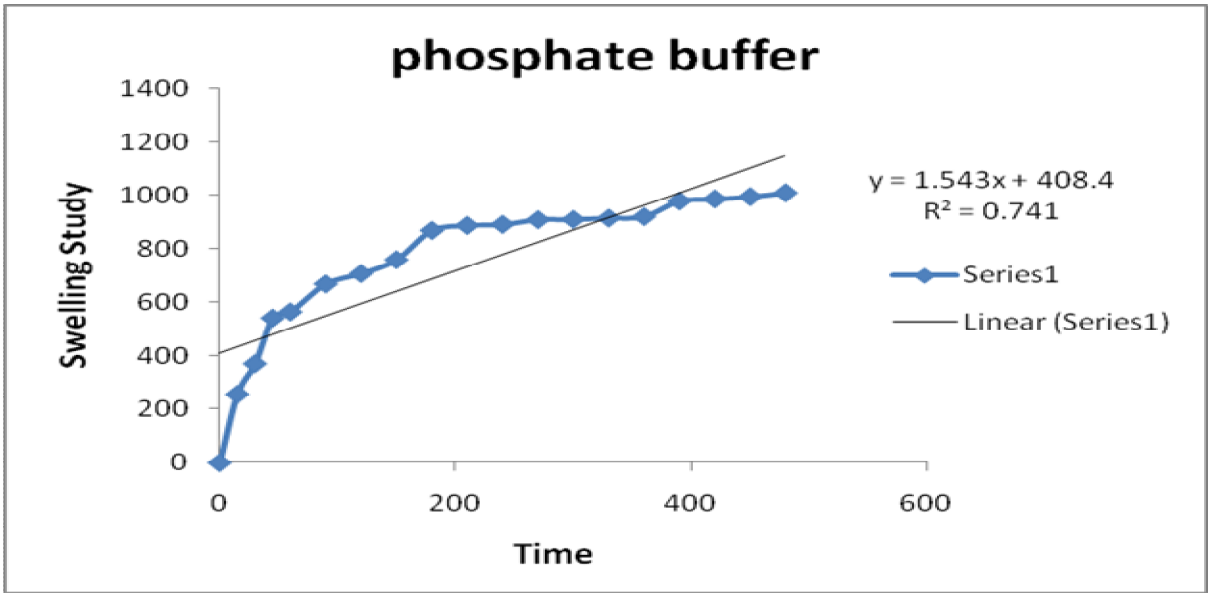
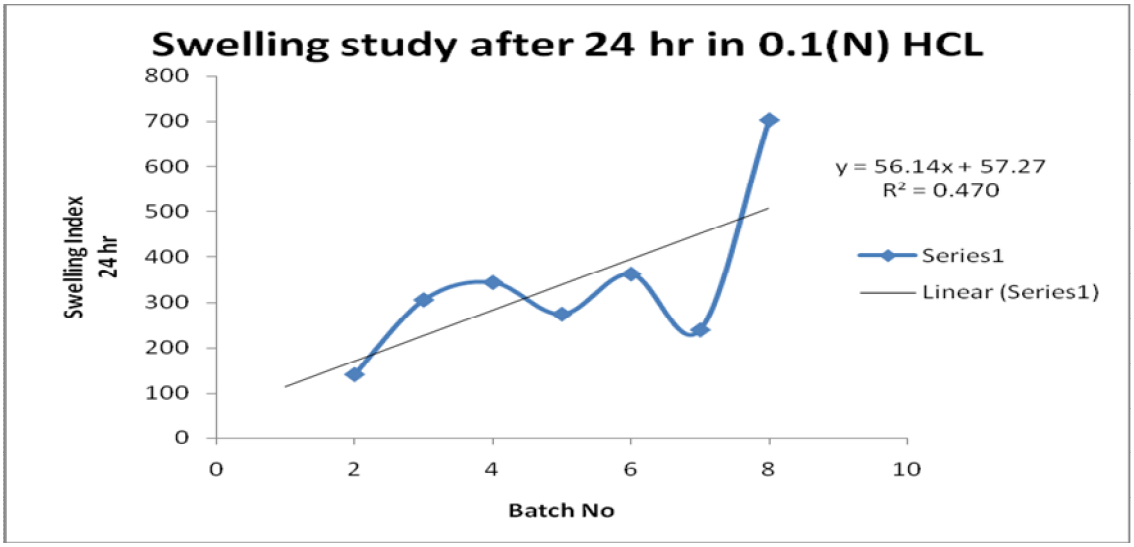
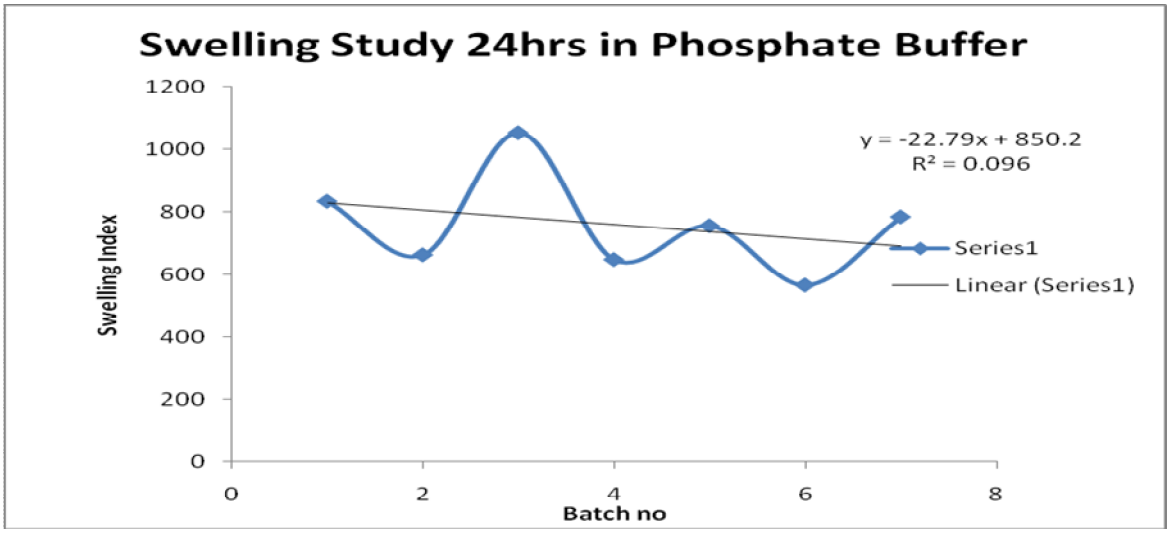


Table of Swelling Study after 24hrs:





11.4. *In vitro* drug release study and release mechanism:

The cumulative percentage of drug release versus time curves obtained from different formulations is shown in Figure 7.17. The cumulative percentage release at different time points profile (Table 7.5) portrays that the release of drug from the matrix tablet with GG is most rapid (83.9% drug release); intermediate in rate (50-60% within 4-5h) in case of MS_6 to a greater extent (80% drug release within 12h). This may be due to the fact that the matrix of the tablets is composed of only gellan gum thus these less branched network of the polymer leads to rapid water uptake, subsequent swelling and advance network relaxation of the matrix. In case of tablet obtained from Ms6 the matrix is composed of comparatively greater branched grafted GG having higher grafting efficiency, which leads to slow water uptake and swelling kinetic resulting sustained drug release over a period of 12h. The regression coefficient (R^2) values is shown in Table 7.6. The results demonstrate that most of the formulations follow Higuchi and Zero order release kinetic.The formulation of gellan gum and grafted gellan gum tablets release study is done both on 0.1(N) HCL and phosphate buffer of PH-6.8.The grafting gellan gum tablet well disperse in 0.1(N) HCL rather than Phosphate buffer Ph-6.8.

Table 11.5: Cumulative % drug release at different time points of different formulations.

Time(hour)	Curmulative % drug release(average)			
	Gellan Gum		Graffted Gellan Gum	
	0.1(N) HCL Buffer	Phosphate Buffer PH-6.8	0.1(N) HCL Buffer	Phosphate Buffer PH-6.8
0	0	0	0	0
0.25	12.1513875	6.53905	6.767381	6.620119
0.50	14.60335771	8.241378	8.250828	8.470903
0.75	20.44760472	9.822921	10.28707	11.41284
1	26.86286167	15.39193	12.688	13.43056
2	32.42735951	24.91902	14.63577	15.72425
3	40.34033889	32.13558	22.6991	17.85885
4	45.08016674	37.42328	28.21933	21.45849
5	50.67694333	38.37914	33.83233	25.41435
6	57.9029291	40.25854	39.39908	29.87417
7	64.09668903	40.43556	44.99234	33.27247
8	69.81610174	42.40444	49.53483	36.88576
9	73.47123632	45.0185	54.75424	40.41995
10	77.17739215	48.02135	60.53303	42.53462
11	80.99843257	51.00552	62.92787	44.48744
12	82.92503431	54.6039	66.67611	45.97755

Table11.6: R2 value of different kinetic models

Formulation Code	**R2 value(average)**					**Model of best Fit**
	Zero Order	**1st Order**	**Higuchi**	**Korsmeyer -Peppas**	**Hixion-Crowell**	
Gellan Gum in 0.1(N) HCL	0.950	0.993	0.996	0.992	0.950	Higuchi
Gellan Gum in Phosphate Buffer PH-6.8	0.991	0.992	0.969	0.976	0.991	Zero Order
Graffted Gellan Gum in 0.1(N) HCL	0.981	0.929	0.974	0.969	0.981	Zero Order
Graffted Gellan Gum in Phosphate Buffer PH-6.8	0.972	0.987	0.991	0.979	0.972	Higuchi

Drug release patter of Gellan gum in 0.1(N) HCL

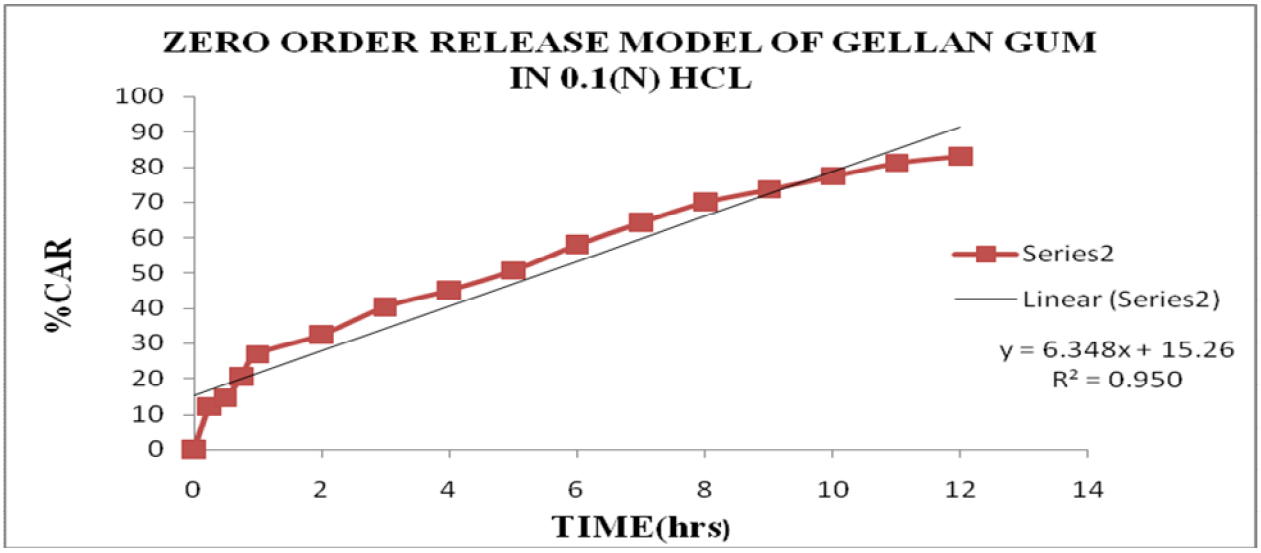


Figure 1:

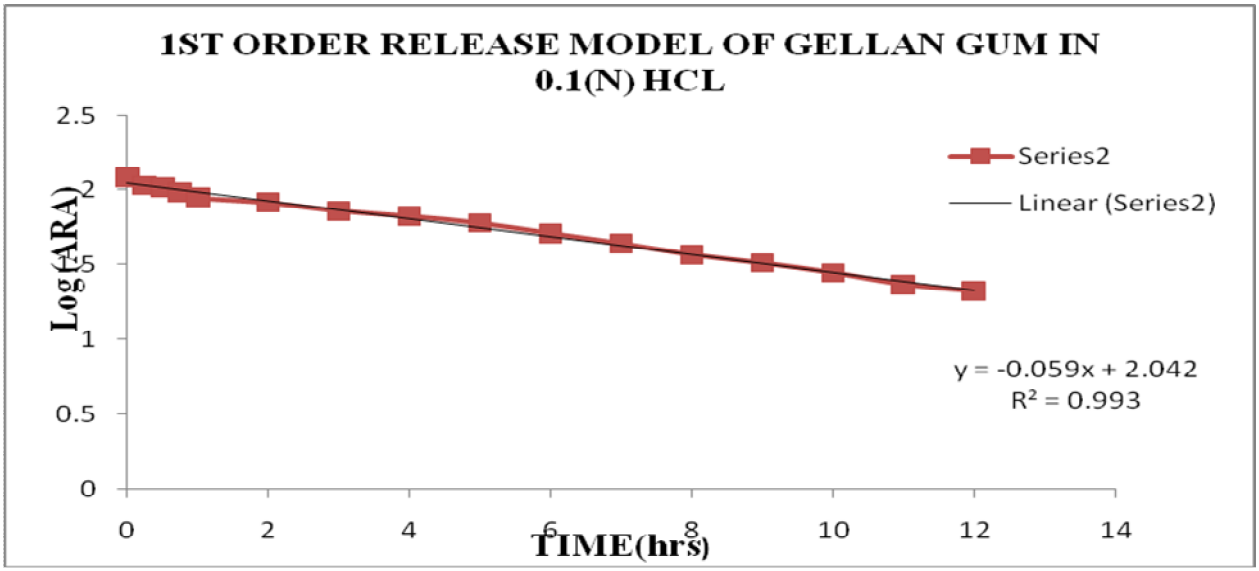


Figure 2:

Drug release patter of Gellan gum in 0.1(N) HCL

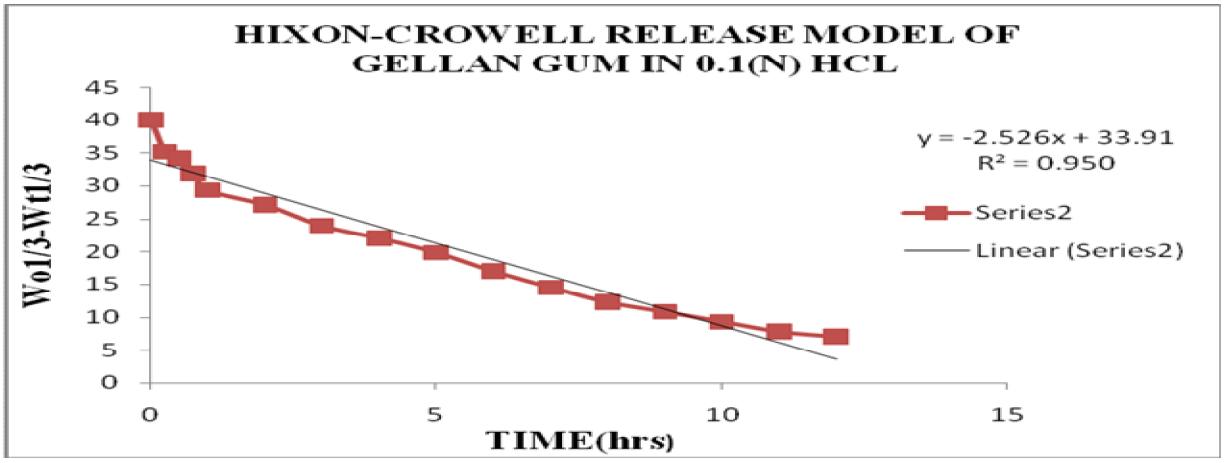


Figure 3:

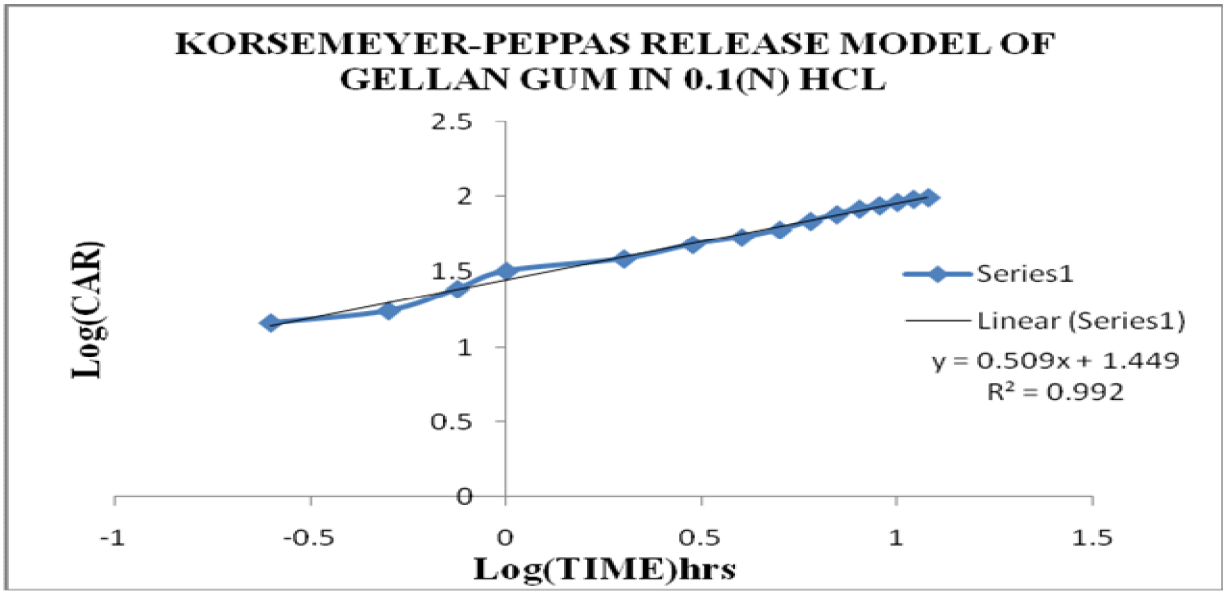


Figure 4:

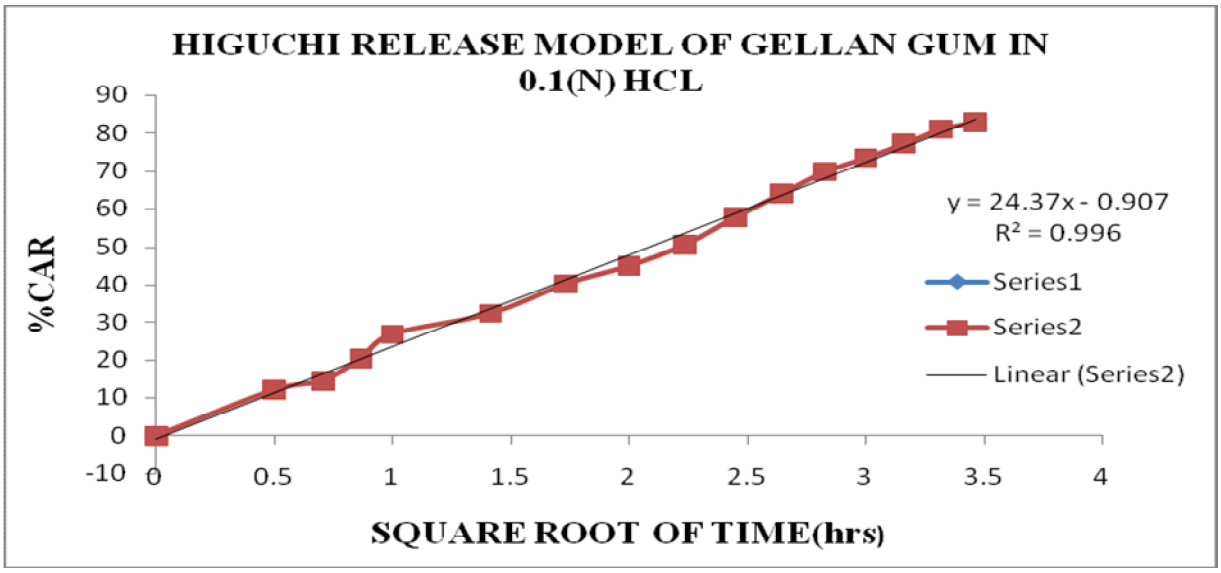


Figure 5:

Drug release patter of Graffted Gellan gum in 0.1(N) HCL

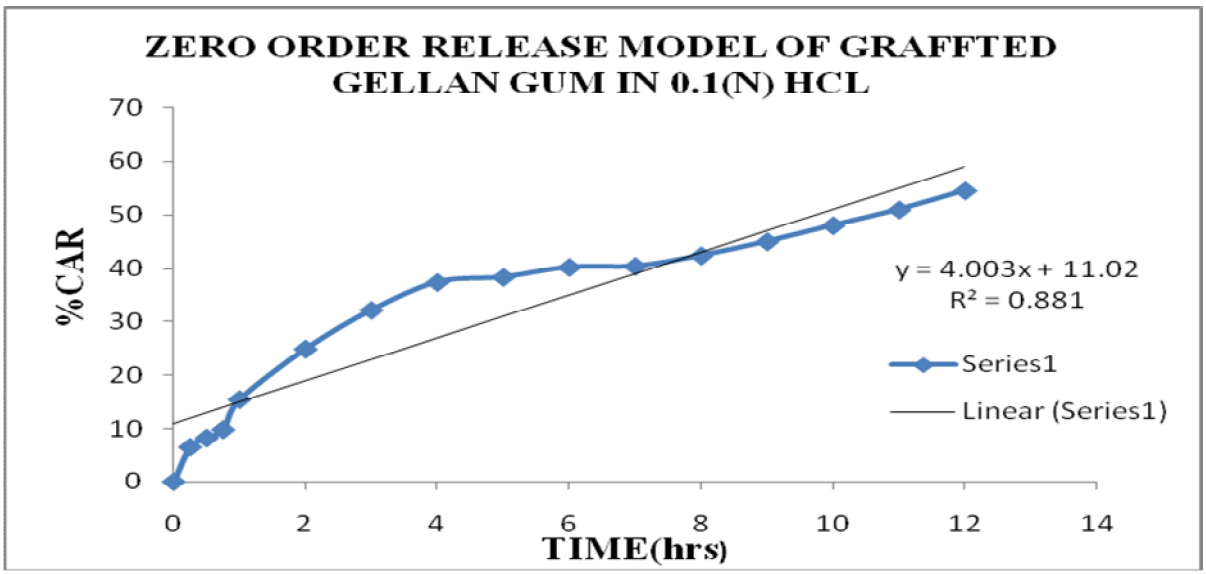


Figure 1:

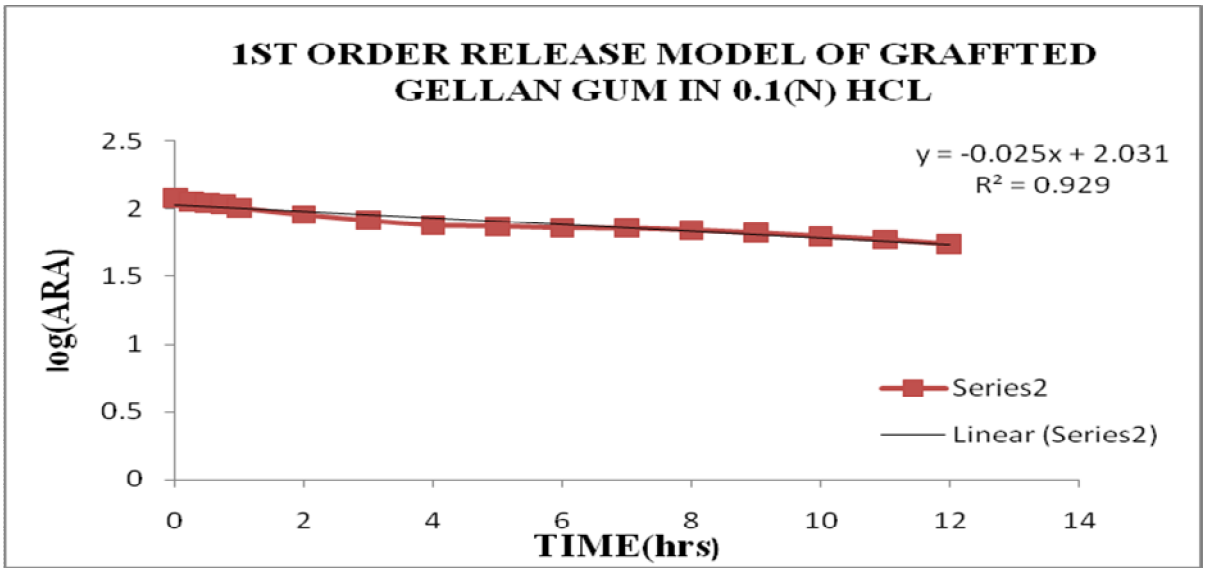


Figure 2:

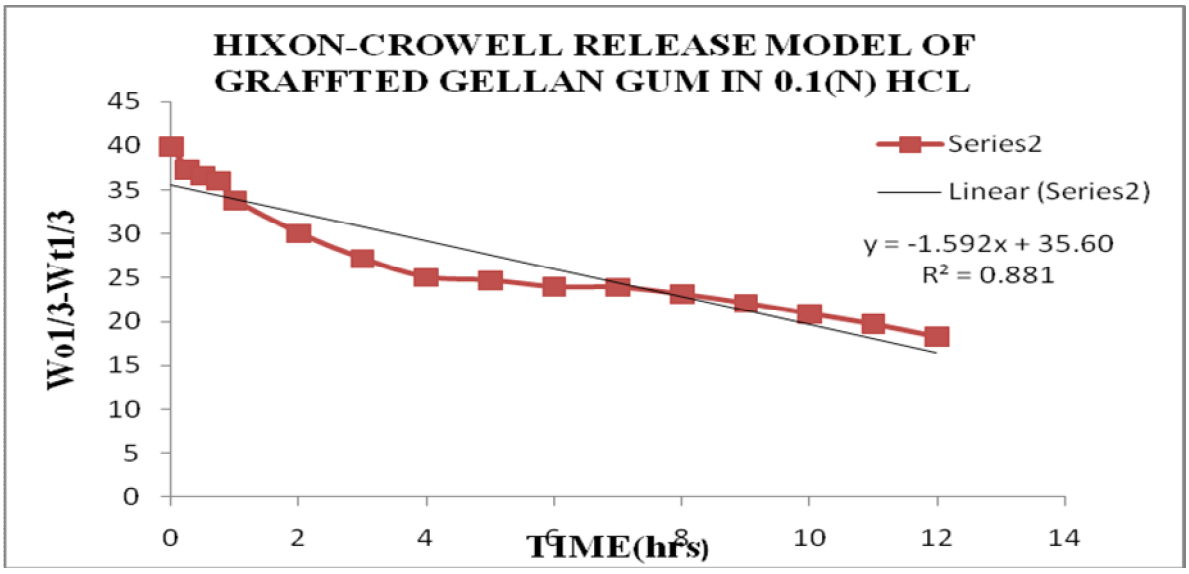


Figure 3:

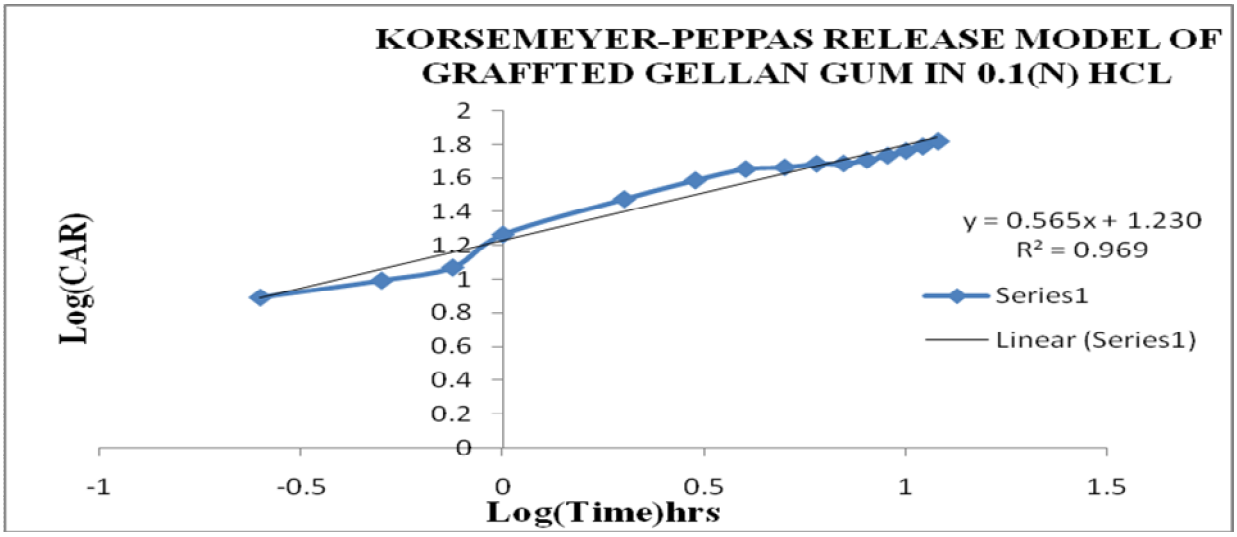


Figure 4:

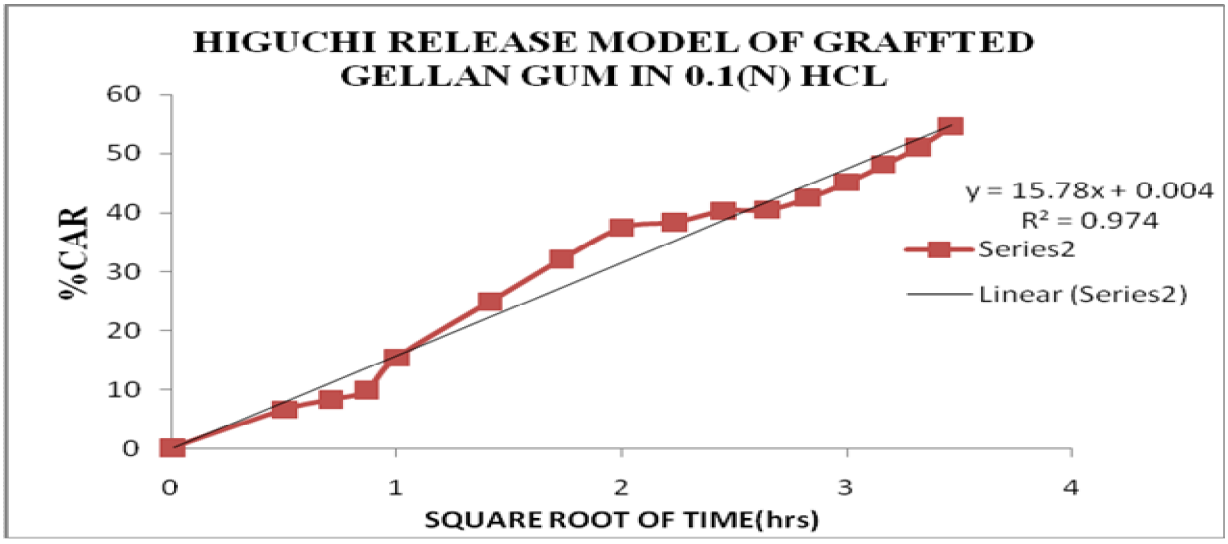


Figure 5:

Drug release patter of Gellan gum in phosphate Buffer PH-6.8

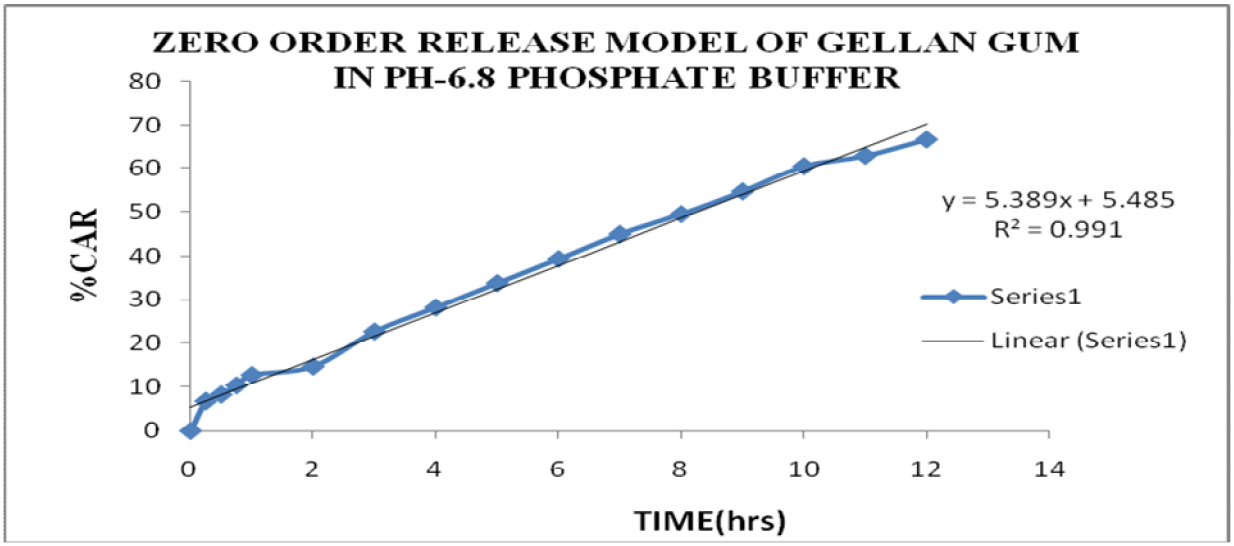
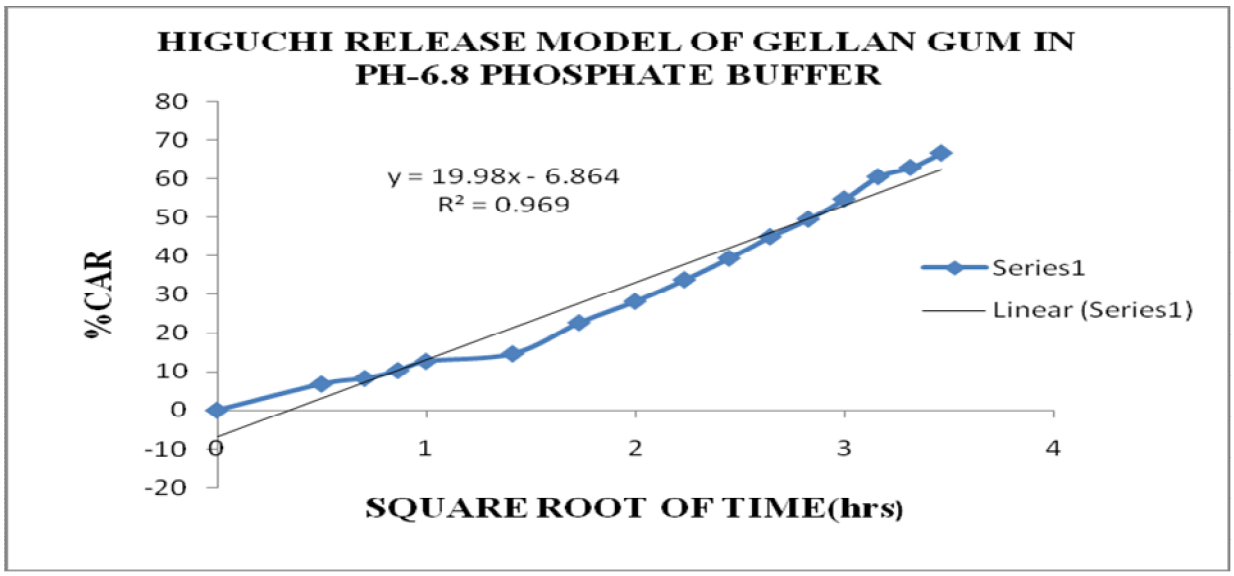


Figure 1:



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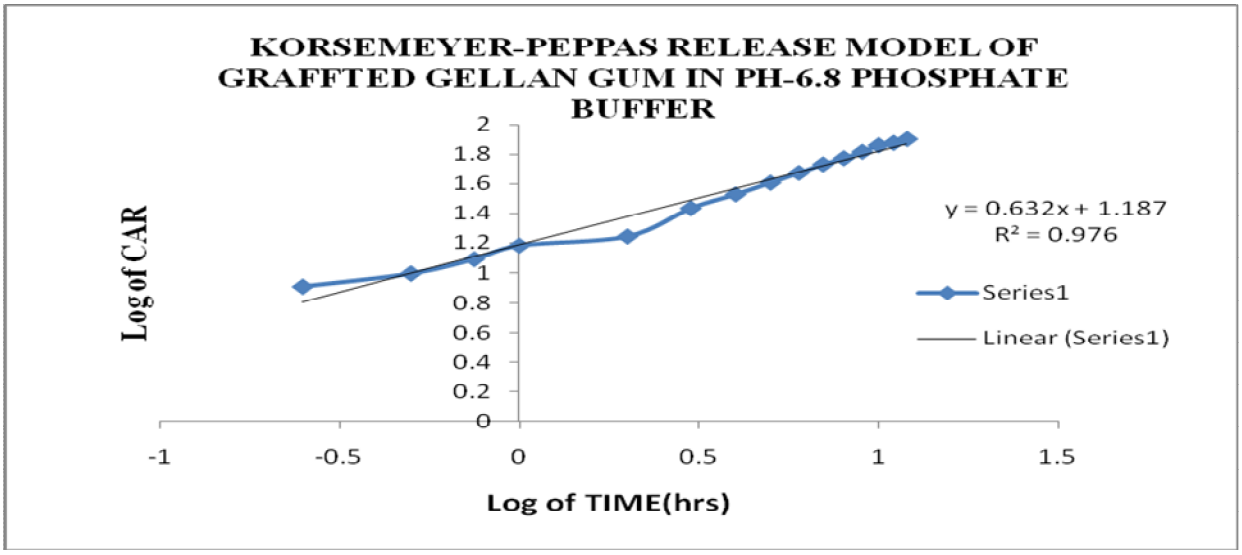
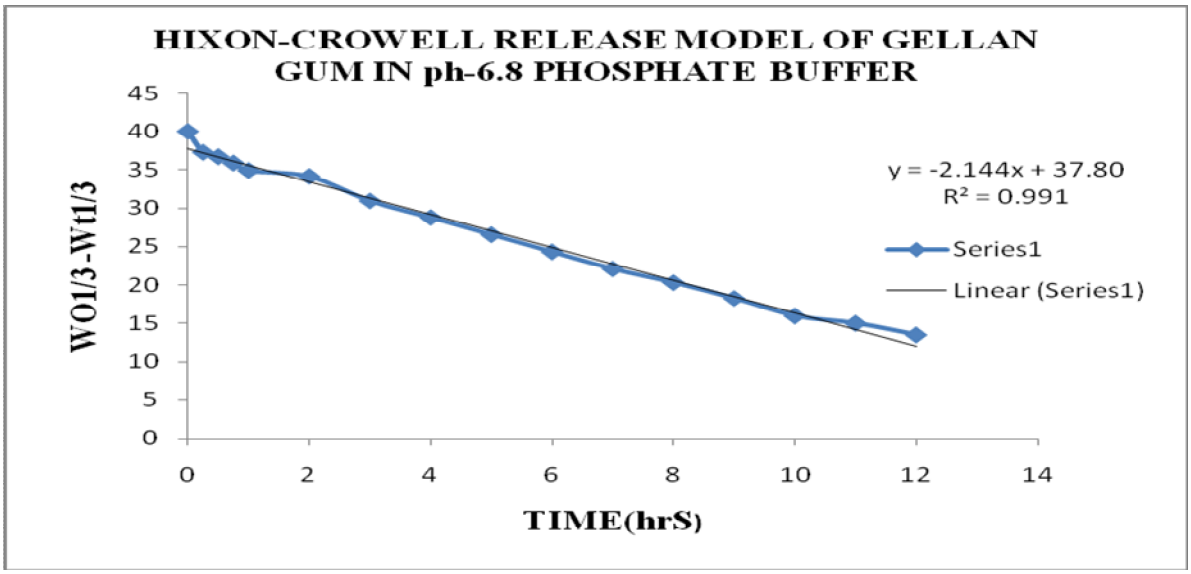


Figure 3:



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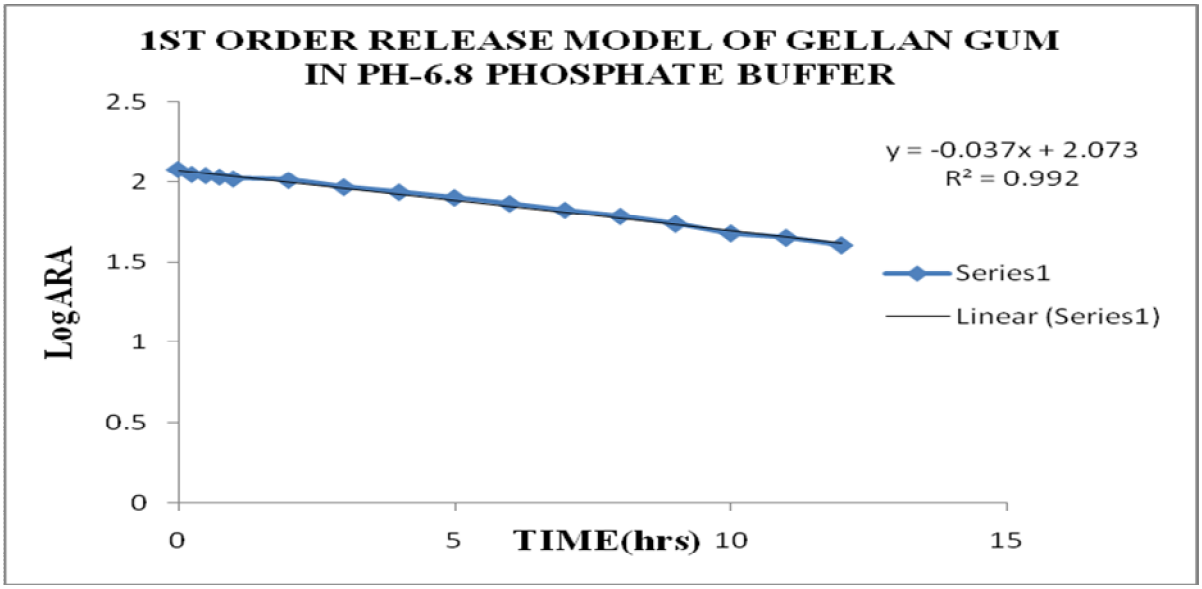

Figure 5:

Drug release patter of Graffted Gellan gum in phosphate Buffer PH-6.8

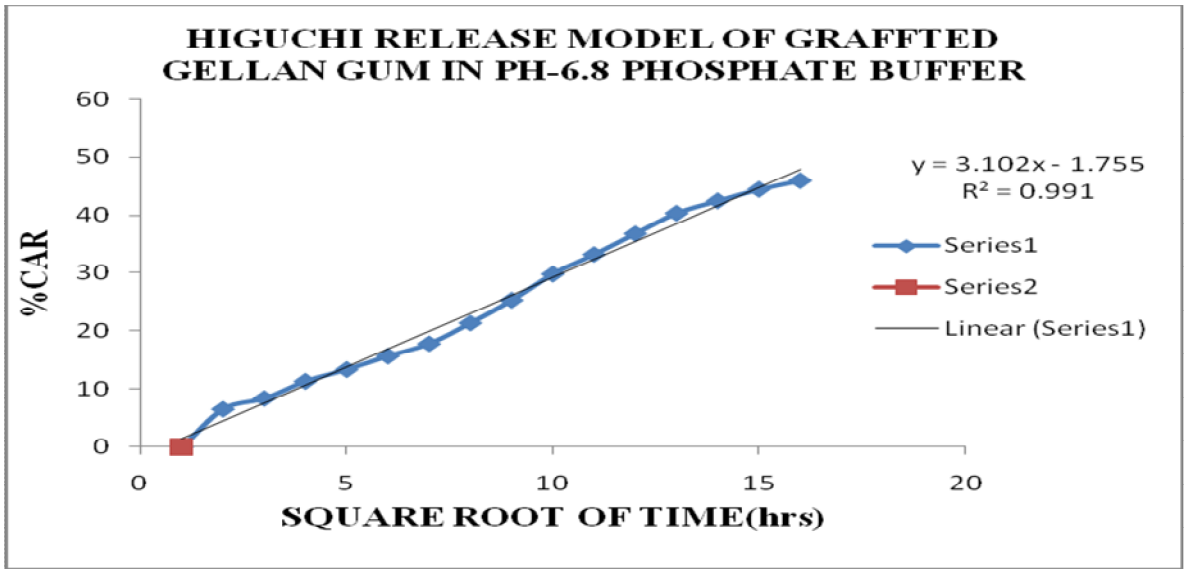

Figure 1:

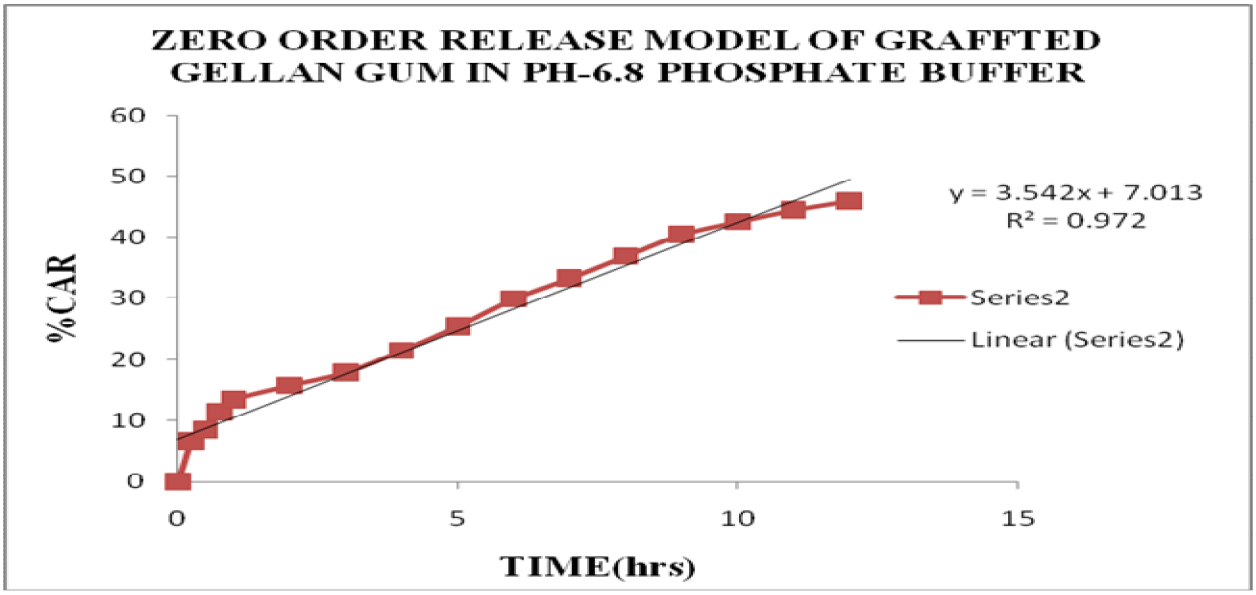

Figure 2:

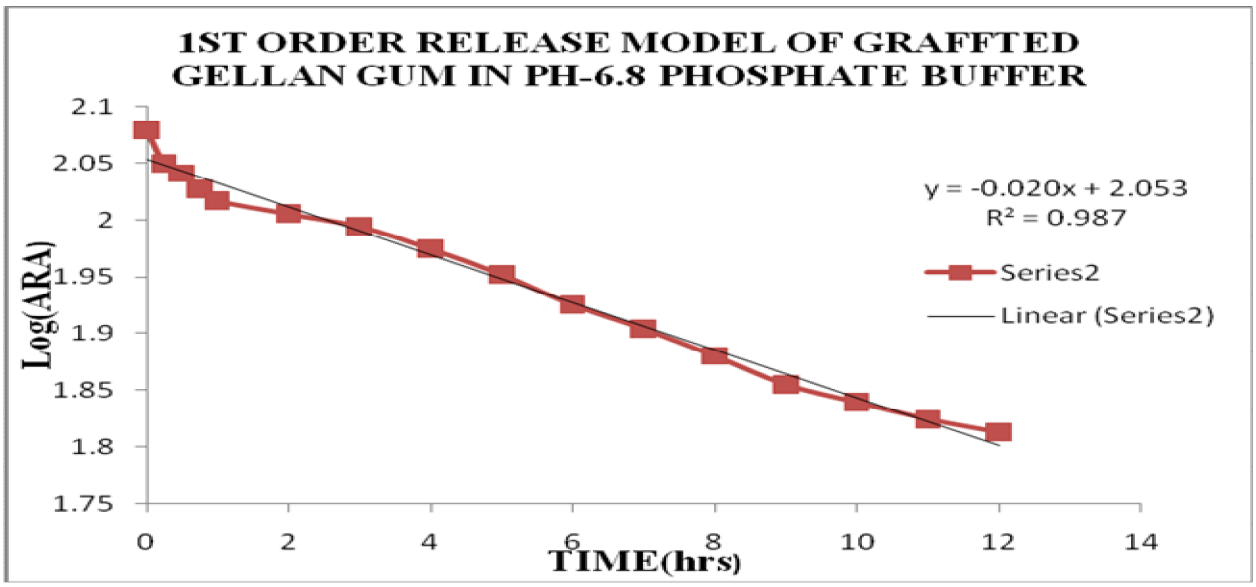

Figure 3:

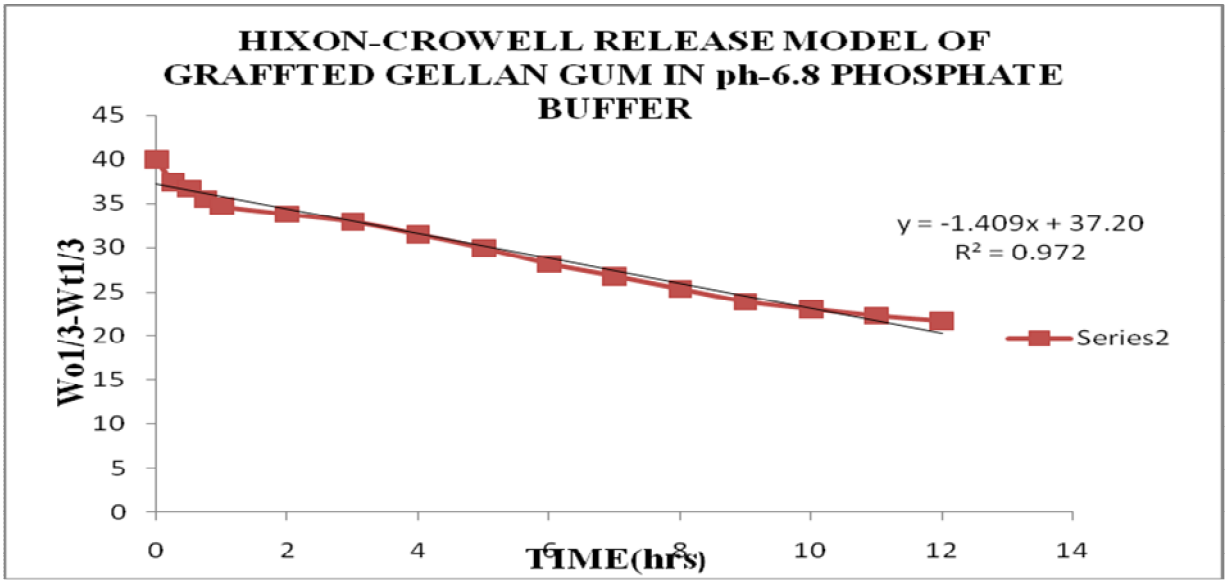

Figure 4:

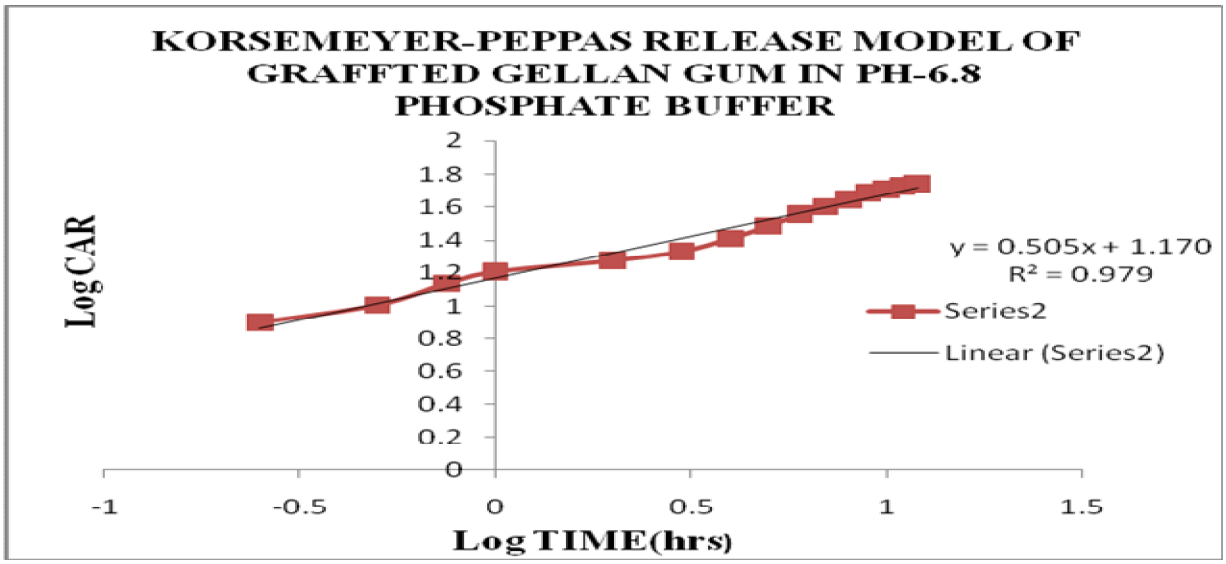

Figure 5:

CHAPTER 10: SUMMARY & CONCLUSION

1.Summary & Conclusion:

The grafting of methacrylic acid (MA) on gellan gum (GG) was achieved under microwave irradiation using catalytic amount of cerric ammonium nitrate (CAN). The use of microwave when the reaction mixture containing 400 mg CAN,10.14 mg MA and one minite microwave. Polymethacrylic acid grafted gellan gum (Pma-g-GG) was synthesized by microwave irradiation using ceric ammonium nitrate as a redox initiator. The MS6 batch was found to be the optimized batch. The grafting of methacrylic acid onto gellan gum was evidenced by FTIR,NMR and elemental analysis.FTIR analysis shows that in gellan gum peaks and grafting gellan gum peaks are completely different.Gellan gum gives peaks at 745.43 per cm but grafting gellan gum give peaks at 1998.82 per cm.In DSC analysis the gellan melting temperature shows near 250^0C but grafting gellan gum shows below 250^0C.The X-ray Result shows gellan angle of degree almost 20^0 where as grafting gellan shows near to 18^0.Finally the NMR result shows that the gellan gives peaks at 75.580 ppm,102.760ppm and 61.92ppm where grafting gellan gives peak at 45.690ppm,55.392ppm,16.937ppm.The NMR result shows the difference between gellan and grafting gellan.

According to the DSC result as well as temperature evolution of dynamic moduli, gellan had a transition temperature 0f 36.5^0C, such temperature corresponds to the change of molecular conformation from random coil to rigid helices in the grafting gellan. There for it can be assumed that below 42^0C, where moduli began to reach their equilibrium value, the system is formed by rigid helices associated through interaction with the methacrylic acid molecules that forms a gel or structured network the compactness of which depends on polymer content and ionic strength.T is simply emphasized the fact that rheological data, which are obtained at 25^0C, describe the behavior of ordered and rigid gellan molecules. At a higher gellan content,0.01% the extent of gellan association increased yield a less tenuous but homogenous network, although great pores or zones devoid of polymer were also observed.

The gellan concentrations studied here allowed us to distinguish different levels of structure organization well consistent with their rheological behaviors. From the log G versus gellan concentration relationships, it can be seen that the low polysaccharide concentrations used here are close to the critical gel concentration.

The thermal data show that the synthesized graft copolymer is thermally more stable than pure gellan gum. The synthesized graft copolymer polymethacrylic acid shows better results for swelling, and flocculating properties in comparison to gellan gum, this could be interpreted that graft copolymer shows the enhancement in these properties.The thermal analysis data show that graft copolymer, a hybrid material in which properties of monomer is added by grafting, could be exploited very well industrially.

CHAPTER 10: SUMMARY & CONCLUSION

The combined use of high-field and low-field solid-state NMR techniques provided good insight into the chemical composition and structural aspects of the gellan samples, showing variations in their molecular structure and chemical composition. The samples showed differences with respect to the ratios of their main components, reflecting changes in the dynamic molecular behaviour. Differences in sample homogeneity were also observed.The results clearly identified the samples' characteristics and differences, helping to make inferences on the best uses of these different varieties with regard to industrial and household uses.

The experimental studies and the kinetic modelling based on Peppas, Higuchi, first-order and zero-order equations revealed that the release of the coriander essential oil followed a swelling-diffusion controlled process.Considering the swelling process, the water penetrated the polymeric matrix and the release rate was determined by the glass-to-rubbery process.

This optimized grafted gum was further used to formulate controlled-release matrix tablet of vinpocetine hydrochloride (VH). The release pattern was compared with HPMC matrix tablet of VH. The release of drug from both the matrix tablets followed non-Fickian diffusion controlled drug release process. Hence, it can be concluded that Pma-g-gG can be used as a rate controlling hydrophilic polymer for controlled-release application.