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Design& In Vitro Evaluation Of Matrix Tablets Of Naproxen Using Natural Gum.

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Abstract:-

Over the past thirty years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled- drug delivery, greater attention has been focused on development of sustained or controlled-release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exists. The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting. The goal in designing sustained- or controlled- delivery systems is to reduce the frequency of dosing or to increase effectiveness of drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery.[1] Today the conventional drug delivery system is the primary pharmaceutical products commonly seen in the prescription and over the counter drug market place. This type of drug delivery system is known to provide a prompt release of drug. It is often necessary to take this type of drug delivery system several times a day for maintaining the drug concentration within the therapeutically effective range. This results in a significant fluctuation in drug plasma levels and dumping of excess excipients in the body.

Keywords:- Design, medication, Drug, Matrix tablet

The major Drawbacks Associated with Conventional Dosage Forms are

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over
- medication.
- A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.
- Recently, several advancements in drug delivery system have been made to overcome the drawback of conventional drug delivery system. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and/ or targeting the delivery of drug to a tissue.
- Increased exposure of physiological system to the drug as well as excipients.[2]

Drug candidates like Naproxen are useful to formulate as matrix dosage form. Naproxen, (S)-2-(6-methoxynaphth-2-yl) propionic acid, is one of the most potent nonsteroidal anti-inflammatory agents; it also presents analgesic and antipyretic properties. Propionic acid derivatives are approved for use in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and acute gouty arthritis; they also used as analgesics, for acute tendinitis and bursitis, and for primary dysmenorrhea.[3] The anti-inflammatory effects of Naproxen, and most of its other pharmacological effects, are generally thought to be related to its inhibition of cyclooxygenase and consequent decrease in prostaglandin concentrations. Naproxen is extensively bound to plasma albumin, so it may be more efficient to deliver this drug in its sustained-release dosage form. For many drugs, the optimal therapeutic response is observed only when adequate blood levels are achieved and maintained with minimal variations. Sustained-release products have become important for the oral administration of many drugs because they give more consistent blood levels. One of the most commonly used methods of modulating tablet drug release is to include it in a matrix system. The classification of matrix systems is based on matrix structure, release kinetics, controlled release properties (diffusion, erosion, swelling), and the chemical nature and properties of employed materials. Matrix systems are usually classified in 3 main groups: hydrophilic, inert, and lipidic.[4]

Diseased conditions for which Naproxen is applicable:

- NSAIDs are particularly effective when inflammation has caused sensitization of pain receptors to normally painless mechanical or chemical stimuli. Pain that accompanies inflammation and tissue injury probably results from local stimulation of pain fibres and enhanced pain sensitivity. NSAIDs are considered as mild analgesics[3].
- Ankylosing Spondylitis is an inflammatory disease of unknown origin that affects joints between vertebrae and between the sacrum and hip bone. It is characterized by pain and stiffness in the hips and lower back that progress upward along the backbone.

- Osteoarthritis (OA) is a degenerative joint disease in which joint cartilage is gradually lost; causing exposure of the bone and where new osseous tissue deposits which is termed as spurs. These spurs decrease the space of the cavity and restrict joint movement.

- Rheumatoid Arthritis (RA) is an autoimmune disease in which the immune system of the body attacks its own tissues. In RA synovial membrane gets inflamed, if untreated, membrane thickens and synovial fluid accumulates. The resulting pressure causes pain and tenderness.

- Juvenile Arthritis is found in adolescent patients less than 16 years of age that is characterised by acute onset of fever and predominant involvement of knees and ankles.

- Gouty Arthritis: In Gouty Arthritis, sodium urate salts are deposited in the soft.

tissues of the joints. The crystals irritate and erode the cartilage, causing inflammation, swelling and acute pain. Eventually, the crystals destroy all joint tissues.[5]The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the pharmaceutical industry for some time. The desire to maintain a near constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained or controlled release drug delivery systems. Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. The goal of an extended releasedosage form is to maintain therapeutic drug level in plasma for extended period of time.[6]

By the sustained release method therapeutically effective concentration can be achieved over a prolonged period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.[7]

1.1 ADVANTAGES OF MATRIX TABLET:

- Versatile, effective, reduced dosage and dosing frequency and low cost, so, improved patient compliance.
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration which reduces the toxicity by slowing drug absorption. Hence, minimum the local and systemic side effects.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- Minimize drug accumulation with chronic dosing.
- Usage of less total drug.
- Improvement of the ability to provide special effects. Ex: Morning relief of arthritis through bed time dosing.[7]

1.2 OBJECTIVES:

Recently, controlled release drug delivery has become the standards in the modern pharmaceutical design and intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. Oral sustain release drug delivery medication will continue to account for the largest share of drug delivery systems. Hence in this work, an attempt was made to formulate sustained release system for Naproxen in order to achieve even plasma concentration profile up to 24 h.

1.3 Potential advantages of API to formulate as Sustained Release (SR):

- Being BCS class II drug it is low soluble in water and highly permeable. And it is necessary to sustain the drug release.Less risk of dose dumping.
- High degree of dispersion in the digestive tract thus minimizing the risk of high local drug concentrations.
- Drug may reach the site of optimum absorption in a reproducible fashion so reproducible bioavailability.
- Transport of drug is independent of gastric emptying. [6,7]

4. CLASSIFICATION OF SR FORMULATION:

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

Diffusion systems :- Diffusion systems are characterized by the release rate of drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. In general, two types or subclasses of diffusional systems are recognized reservoir devices and matrix devices.

A] Reservoir Devices

Reservoir devices, as the name implies, are characterized by a core of drug, the reservoir surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system. It is also possible to use polymer coatings to achieve sustained release. For this purpose the polymer itself should not dissolve, but rather should allow the drug to diffusion through the polymer membrane to the outside, in the case of oral drug delivery, into the gastrointestinal tract.

B] Matrix Devices

A matrix device, as the name implies, consist of drug dispersed homogeneously throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface betweenthe bathing solution and the solid drug moving towards the interior, obviously, for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix.

Dissolution systems :- It seems inherently obvious that a drug with a slow dissolution rate will demonstrate sustaining properties, since the release of drug will be limited by the rate of dissolution. This being true, sustained-release preparation of drugs could be made by decreasing their rate of dissolution. The

approaches to achieve this include preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier.

Osmotic system :- Osmotic pressure is employed as the driving force to generate a constant release of drug. Consider semipermeable membrane that is permeable to water, but not to drug. When this device is exposed to water or any body fluid, Water will flow into the tablet owing to the osmotic pressure difference.

Ion-exchange resins :- Ion-exchange systems generally use resins composed of water-insoluble cross- linked polymers. These polymers contain salt-forming functional groups inrepeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion-exchange groups. The free drug diffuses out of the resin. The drug-resin complex is prepared either by repeated exposure of the resin to the drug in a chromatography column, or by prolonged contact in solution.

Swelling and expansion systems :- Conventional hydrogels swell slowly upon contact with water due to their small pore size, which usually ranges in the nanometers and low-micrometer scale. However if the hydrogel has a pore size of more than 100 µm, swelling is much faster and may lead to a large increase in size. These swollen systems become too large to pass through the pylorus and thus may be retained in the stomach.

Matrix systems :- One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blends of drug, retardant materials and additives to form a tablet in which drug is embedded in matrix core of the retardant. Alternately, retardant drug blends may be granulated prior to compression.

1.5 Types of Matrix Hydrophobic Matrices

In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers.

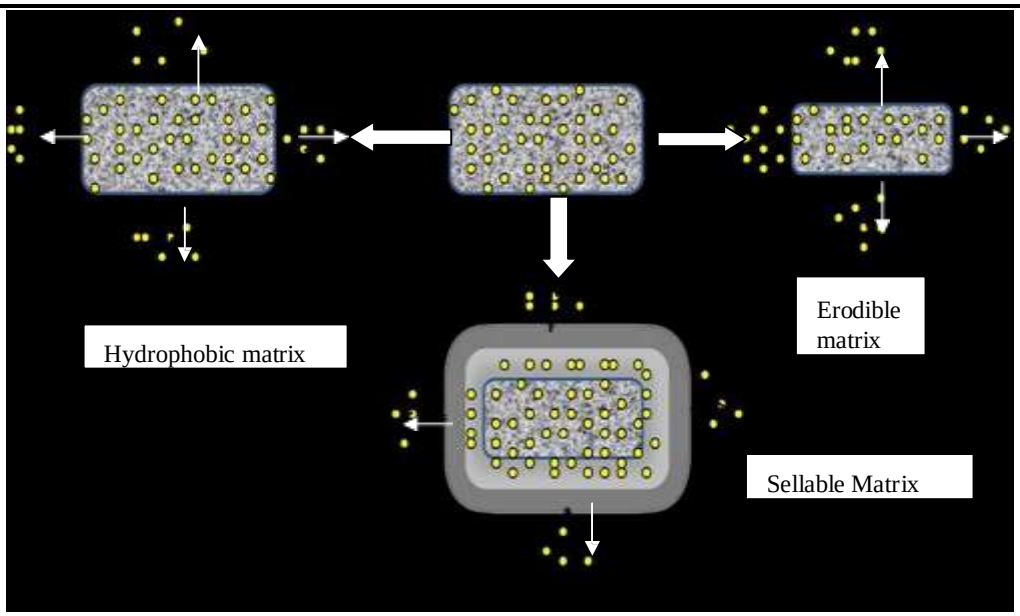


Fig. No. 01: Diagram showing drug release patterns from various matrix systems namely Hydrophobic matrix, Erodible matrix and sellable matrix.[8]

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

Mineral Matrices

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

1.6 Classification On the Basis of Porosity of Matrix:

Matrix tablets can be divided in to 3 types.

- *Macro porous systems* :- In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 µm. This pore size is larger than diffusant molecule size.
- *Micro porous system* :- Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.
- *Non-porous system.*

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.[9]

1.7] Polymers used in matrix tablets:

There are number of polymers which may be used to formulate matrix tablets depending on the physicochemical properties of the drug substance to be incorporated into matrix system and type of drug release required. Polymers used for matrix tablets may be classified as:

a) Hydrogels: Poly-hydroxyethylemethylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked Polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA)
b) Soluble polymers: Polyethylene glycol (PEG), Polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC)
c) Biodegradable polymers: Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters.
d) Non-biodegradable polymers: Polyethylene vinyl acetate (PVA),

Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).

I. Mucoadhesive polymers: Polycarbophil, Sodium Carboxymethyl cellulose, Polyacrylic acid, Tragacant, Methyl cellulose, Pectin.
II. Natural gums: Xanthan gum, Guar gum, Karaya gum, Gum Arabic, Locust bean gum.[10]

1.8] Method of Preparation of Matrix Tablet

1] Wet Granulation Technique

- Milling and gravitational mixing of drug, polymer and excipients.
- Preparation of binder solution
- Wet massing by addition of binder solution or granulating solvent
- Screening of wet mass.
- Drying of the wet granules.
- Screening of dry granules
- Blending with lubricant and disintegrants to produce “running powder”.
- Compression of tablet.

2] Dry Granulation Technique

- Milling and gravitational mixing of drug, polymer and excipients.
- Compression into slugs or roll compaction
- Milling and screening of slugs and compacted powder
- Mixing with lubricant and disintegrants.
- Compression of tablet.

3] Sintering Technique

- Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat.
- Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure.

- The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as a result of sintering.
- The sintering process has been used for the fabrication of sustained releasematrix tablets for the stabilization and retardation of the drug release.[6]

1.9 Grafting of Natural Polysaccharides:

Polymers are inexpensive, have wide availability, wide structural variations and with a variety of properties. They can be easily modified and are highly stable, safe, nontoxic, hydrophillic, gel forming and biodegradable. Problem encountered with the use of polysaccharides is their high water solubility. An ideal approach is to modify the solubility while still retaining their biodegradability[11]. The modification of polymers has received much attention recently. 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 polymer 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 monomer 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. Among these methods grafting is one of the promising methods. In principle, graft copolymerization is an attractive method to impart a variety of functional groups to the polymers. Two major types of grafting may be considered: (i) Grafting with a single monomer and (ii) Grafting with a mixture of (two or more) monomers.

Techniques of grafting:

1] Grafting initiated by chemical means:

- Free radical grafting.
- Grafting through living polymerization.
- Ionic grafting.

2] Grafting initiated by radiation technique:

- Free radical grafting.
- Ionic grafting.

3] Photochemical grafting.

4] Plasma radiation induced grafting.

5] Enzymatic grafting[12].

Graft copolymerization by use of free radical initiators has been the default method of synthesis for decades, but the complicated nature of the synthesis procedures had actually been instrumental in preventing full commercial exploitation of graft copolymers. Comparatively, grafting with the help of microwave radiation is cleaner, simpler, straight forward, highly reproducible and eco-friendly technology. It conforms to all the accepted norms of green chemistry. The best method of graft copolymer synthesis is by use of microwave radiation to generate the free radical sites on the natural polymer backbone. Grafted carbohydrate polymers have different applications in different fields of science and technology i.e. flocculant for waste water treatment, medium for controlled drug release and sizing and finishing agents for cotton textiles. The field of drug delivery revolves around the development of intelligent matrices, which releases

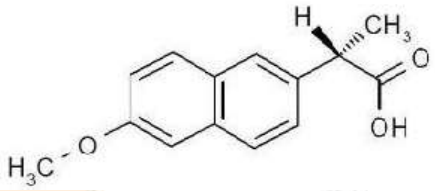
the enclosed drug at rate and place and under predetermined conditions. In the field of drug delivery, polysaccharides (such as Starch, Chitosan, Alginate, and Cellulose) and modified polysaccharides (e.g., Cellulose derivatives viz. HPMC, HPC) have earned special attention due to their high biocompatibility and hydrophilicity. guar gum) was studied. Ammonium Cross linked CMG can retard drug release to a larger extent hence found to be better than Guar Gum[39]. Rajyalaxmi *et al*., designed and evaluated Naproxen tablets using guar gum and crosslinked guar gum. It was found that the cross linking polymer reduces the drug release by enhancing the viscosity and reducing the swelling index; when compared with guar gum matrix tablets[40]

2.1 Drug Profile

NAPROXEN

Physicochemical Properties:

Molecular Structure:



Chemical name: Naproxen is (2S)-2-(6-methoxynaphthalen-2-yl) propionic acid.

Molecular Formula: $C_{14}H_{14}O_3$

Molecular Weight: 230.3

Category: Anti-inflammatory, analgesic.

Description: White or almost white, crystalline powder.

Solubility: Practically insoluble in water, soluble in alcohol and in methanol, sparingly soluble in ether.

Melting point: 154˚C to 158˚C.

pKa[41]**:** 4.15

Identification: Dissolve 40.0mg in methanol R and dilute to 100.0 ml with the same solvent.Dilute to 10.0 ml of the solution to 100.0 ml with methanol R. Examined between 230 nm and 350 nm, the solution shows four absorption maxima, at 262 nm, 271 nm, 316 nm and 331 nm[41].

Assay: Dissolve 0.200 g in amixture of 25 ml water R and 75 ml of methanol R. Titrate with 0.1M sodium hydroxide, using 1 ml of phenolphthalein solution R as indicator. 1 ml of 0.1 M sodium hydroxide is equivalent to 23.03 mg of $C_{14}H_{14}O_3$.

Storage :- Store protected from light.

5. MATERIALS AND METHODOLOGY

Materials and Equipments

The presented work was planned to prepare sustained release tablets of Naproxen.

Materials used and their sources

Table 5.1 Materials used and their sources

Sr.No	Name Of Chemical	Supplier/ Manufacturer
1	Naproxen	RPG Life Sciences, Mumbai.
2	Guar gum	Loba chemicals, Mumbai
3	Acrylamide	Loba chemicals, Mumbai
4	Lactose	Loba chemicals, Mumbai
5	Magnessium stearate	Loba chemicals, Mumbai
6	Methanol UV spectroscopy grade	Loba chemicals, Mumbai
7	Potassium dihydrogen orthophosphate	Loba chemicals, Mumbai
8	Concentrated Hydrochloric acid	Loba chemicals, Mumbai
9	Hydroquinone	Loba chemicals, Mumbai
10	Acetone	Loba chemicals, Mumbai
11	Formamide	Loba chemicals, Mumbai
12	Acetic acid	Loba chemicals, Mumbai
13	Sodium hydroxide pellets	Loba chemicals, Mumbai
14	Tween 80	Loba chemicals, Mumbai

1] Preformulation studies of Naproxen

- **Identification :-** Naproxen was initially dissolved in methanol and the volume was made up with PBS pH 7.2. The UV spectrum of Naproxen was obtained using a 1cm cell and by scanning from 300 nm to 250 nm at a scan rate of 1 nm/min. The resulting spectrum was qualitatively compared to the spectrum obtained from Naproxen reference standard. The drug substance spectrum was characterized by maxima at 273 nm[41].
- **Solubility studies:-** Naproxen solubility was determined by preparing saturated Naproxen solutions in phosphate buffer solution pH 7.2, that were maintained at 37.0°C ± 0.5°C and continually shaken, on a rotary shaker until saturated. Withdrawn samples were filtered through Whatman filter paper and assayed spectrophotometrically at 273 nm against blank

5.2.2 Melting point:

Melting point was determined by taking small quantity of Naproxen in a capillary tube closed at one end. It was placed in Thiele's melting point apparatus and the melting point was noted. Average of three readings was taken.

Calibration curve of Naproxen :- Spectrophotometric method based on the measurement of absorbance at 273nm of UV region in phosphate buffer solution pH 7.2 was used for the estimation of Naproxen.

Preparation of Hydrochloric Acid Buffer (HCl):- Solution pH 1.2

Preparation of 0.1 N HCl pH 1.2:

- Solution of 0.1 N HCl prepared by diluting 8.5 ml of Hydrochloric acid with 1000 ml of water[46].

Preparation of Phosphate Buffer Solution (PBS) pH 7.2:

Preparation of 0.2 M Sodium Hydroxide:

- Sodium Hydroxide (8.00 g) was dissolved in sufficient quantity of distilled water and volume was made up to 1000ml with water in volumetric flask **Preparation of 0.2 M Potassium Dihydrogen Orthophosphate:** Potassium Dihydrogen Orthophosphate (27.218 g) was dissolved in sufficient quantity of distilled water and water was added to make the volume 1000ml in volumetric flask.

Preparation of Phosphate Buffer Solution of pH 7.2:

It was prepared by placing 50 ml of 0.2 M Potassium Dihydrogen Orthophosphate solution and 34.7 ml of 0.2 M Sodium Hydroxide solution and volume was made up to 200 ml with distilled water. The pH of the buffer solution was found to be 7.2.

Calibration curve of Naproxen in Hydrochloric acid buffer pH 1.2 and/ Phosphate buffer pH 7.2

1[**Preparation of stock solution no. I**

Naproxen (50 mg) was dissolved in 5ml of methanol in a 50 ml volumetric flask and volume was adjusted further with acid buffer pH 1.2/ phosphate buffer pH 7.2. From this solution, 2 ml was withdrawn and diluted with acid buffer pH 1.2/ phosphate buffer pH 7.2 up to 100 ml to get a concentration of 20 µg/ml, which was labelled as stock-I. After preparation of stock solution no. I, 1, 2, 3, 4, 5 and 6 ml aliquots were withdrawn from this and diluted up to 10 ml with hydrochloric acid buffer pH 1.2/ phosphate buffer pH 7.2 to get subsequent concentrations of 2, 4, 6, 8, 10 and 12 mg/ml solutions respectively. Absorbance was recorded at 271 nm and 273 nm, respectively using UV spectrophotometer (Lab India 3200) for Naproxen per ml versus absorbance. The linear regression analysis was carried on absorbance data points. A straight line equation (Y= mx + C) was generated to facilitate the calculation of amount of drug[47].

Absorbance= Slope x concentration + intercept.

5.4 Compatibility Study between Drug and Excipients by FTIR spectroscopy :- FTIR spectroscopy is a qualitative analytical technique, which offers the possibilities of detecting chemical interaction between drug and excipients in the formulation. Infrared spectra of the samples were recorded on Fourier transform Infrared Spectrometer (Bruker Alpha). The spectra of pure Naproxen and the physical mixtureof Naproxen

with polymers (ratio 1:1) were recorded on FTIR spectrophotometer and evaluated for the compatibility between the various formulation excipients.

5.5 Microwave initiated synthesis of polyacrylamide grafted guar gum (GG-g- PAM)

In this method, microwave irradiation alone was used to generate the free radical sites on the guar gum backbone. No free radical initiator was used in the process. For the synthesis of Guar gum-g-Polyacrylamide copolymer, 1 g of Guar gum was dissolved in 40 ml of distilled water. 5 g of Acrylamide was dissolved in 10 ml water separately. After ensuring complete mixing of solutions of Guar gum and acrylamide, content was transferred into reaction vessel (1000 ml borosil beaker) and placed on the turntable of a microwave oven (LG Microwave oven). The reaction vessel was irradiated at 600Wof power for desired amount of time (7 minutes). A saturated solution of Hydroquinone was prepared and added to the reaction vessel in order to quench the reaction. It was allowed to cool to room temperature. After cooling, the resultant gel was poured into excess of acetone. The precipitate of the grafted polymer was collected and dried in hot air oven at 60˚C for 3 h. Subsequently, it was pulverized and sieved through 60 #. Product was stored in desiccator until further use. The percentage grafting (% G) was calculated by using following formula:

$$\%G = \frac{\text{wt of the grafted product} - \text{wt of polysaccharide taken X } 100}{\text{Wt of polysaccharide taken}}$$

Purification of the graft copolymer (Guar gum-g-Polyacrylamide) by solvent extraction method- Any occluded polyacrylamide (PAM) formed by competing homopolymer formation reaction was removed from the grafted polymers synthesized as above, by solvent extraction using a solvent mixture of formamide: acetic acid (1:1)[13].

5.5.1 Characterization of Guar gum-g-Polyacrylamide copolymer:

A. **Viscosity measurement**

Viscosity measurements of the polymer solutions were carried out with the Brookfield Digital viscometer (Brookfield LV DV-E Viscometer) at 25ºC. The viscosities were measured in dilute aqueous solution. The pH of the aqueous solution was neutral. The time of flow for solutions was measured at four different concentrations, i.e., 0.5%, 1%, 2% and 3% w/v. Analysis was carried out by using Spindle no. 64, at a shear stress of 50 rpm and 100 rpm for all the samples. Viscosity and resultant torque was noted for respective shear stress[40].

b) **Swelling study:** Swelling study of Guar gum and Guar gum-g-Polyacrylamide copolymer was carried out in acid buffer pH 1.2 and phosphate buffer pH 7.2. For this 1 g of each polymer was placed in 100 ml of respective solvent in beakers and kept at room temperature

for 24 h. At the end of 24 h, the contents of the beaker were carefully filtered to remove unabsorbed excessive solvent; residue on filter paper was weighed[40].

c) **FTIR spectroscopy**

The FTIR spectra of guar gum and GG-g-PAM were recorded in solid state, using Fourier transform Infrared Spectrometer (Bruker Alpha) between 400cm^{-1} and 4000cm^{-1}.[36]

d) **TGA studies** :- The thermogravimetric analysis (TGA) of guar gum and that of the Guar gum-g-Polyacrylamide copolymer was carried out with TGA instrument (Model: NETZSCH STA 449 F3 Jupiter). The study was performed up to 800ºC, starting from 32ºC, in an inert atmosphere (of nitrogen). The heating rate was uniform at 5ºC/min[13].

5.6 Preparation of Naproxen matrix tablets:

Naproxen tablets were prepared by wet granulation method. Accurately weighed quantity of Naproxen, Guar gum-g-Polyacrylamide copolymer, Guar gum and lactose were individually passed through sieve no. 60 #. Guar gum and Guar gum-g- Polyacrylamide copolymer were soaked in sufficient quantity of distilled water respectively. Then Naproxen was uniformly mixed within this polymeric solution, this drug- polymer blend solution was introduced into lactose to form a damp mass. This damp mass was passed through sieve no. 16 # to obtain granules of definite shape. Naproxen granules were dried at 45˚C for 1 h, in hot air oven; the dried granules were passed through sieve no. 18#. Lubricant Magnesium stearate was added to above shifted granules and mixed in polythene bag. Naproxen matrix

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1. Naproxen	250	250	250	250	250	250	250	250
2. Guar gum-g-polyacrylamide	62.5	125	187.5	250	---	---	---	---
3. Guar gum	---	---	---	---	62.5	125	187.5	250
4. Lactose	232	169.5	107	44.5	232	169.5	107	44.5
5. Magnessium stearate	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5

*All weights are in mg and each tablet weight is 550 mg.

5.6.1 Precompression studies of Naproxen matrix granules[49, 50, 51]:

a. Bulk density:

Bulk density was determined by pouring a known quantity of granules into a graduated cylinder and volume was measured. Bulk density was calculated from the formula.

Bulk density = W /V

Where,

W= Weight, V= Volume

B.Tapped density:

It was determined by placing a graduated cylinder containing a known mass of granules on mechanical tapping apparatus, which was subjected to 100 tappings at (25 taps/min), and the study was carried out for 4 minutes for all the formulation granules. The volumes of granules before tapping and after tapping were noted and the tapped density was calculated from the formula:

Tapped density = W /V

Where,

W= Weight, V= Volume

C .Angle of repose:

Angle of repose was determined by using static funnel of fixed height method. A funnel was fixed at a particular height 'h' (2cm) on a burette stand. A graph paper was placed below the funnel on the table. Granules were poured from a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of heap (r) and height (h) was measured. The angle of repose (θ) was calculated by formula

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

D.**Carr's index:**

Carr's index for Naproxen granules was calculated by using following formula:

Tapped density – Bulk density

$$\% \text{ Carr's Index} = \frac{\text{Tapped Density – Bulk Dsensity}}{\text{Tapped Density}} \times 100$$

 # Haussler's ratio:

Hauser's ratio for Naproxen granules was calculated by using following formula:

$$\text{Haussler's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \times 100$$

1] Evaluation of Naproxen matrix tablets[50, 51, 52]:

The important parameters in the evaluation of tablets can be divided in to physical and chemical parameters.

Physical parameters:-

a. Thickness.

b. Weight variation.

c. Hardness.

d. Friability.

A] Thickness:

Thickness is essential for tablet uniformity. The thickness of the tablet was measured using Electronic micrometer.

B] Weight variation:

Twenty tablets were weighed individually and the average weight was calculated. The individual weights were then compared with the average weight. A tablet passes the test; if not more than two tablets fall the percentage limit and none of the tablets differ by more than double the percentage limit given below.

C] **Hardness:**

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw, the body of the Monsanto hardness tester carries an adjustable scale which was set to zero against an index mark fixed at the compression end, when the tablet was held between the jaws. The load was gradually increased until the tablet breaks. The value of the load at the point gave a measure of the tablet hardness value.

D] Friability:

Friability was evaluated by Roche Friabilator. Twenty tablets were randomly selected and weighed (initial weight) and placed in the friabilator. The revolving cylinder of the friabilator was allowed to rotate at 25 rpm for four minutes. After dedusting of tablets final weight was recorded.

The difference in the two weights is used to calculate Friability (F).

$$F = [1 - W/ W_o]$$

Where,

W_o – Initial weight

W – Final weight.

Drug content: :- Naproxen content in the matrix tablets was determined by randomly selecting six tablets and they were crushed in glass mortar with the help of pestle. Powder sample equivalent to 100 mg was accurately weighed and placed in 100 ml volumetric flask; containing 3:7 methanol: Phosphate buffer solution pH 7.2 solvent blend. The flask was shaken on rotary shaker for 1 h. The solution was filtered through Whatman filter paper. After appropriate dilution, filtrate was subjected for estimation of Naproxen by UV- Vis Spectrophotometer (LabIndia 3200), at λ_{max} 273 nm against blank. Average of three determinations was taken [4].

***In- vitro* dissolution studies**: - The *in- vitro* dissolution profile of each formulation was determined on USP XXIV dissolution apparatus type II. Dissolution of Naproxen matrix tablets was carried out in 900 ml of dissolution medium to which 0.5% v/v Tween 80 was added to facilitate drug dissolution in alkaline medium[4]. The paddle rotation was adjusted to 50 rpm and the temperature of the media was maintained at 37˚C± 1˚C. *In vitro* dissolution study was conducted for 24 h, in which 2 h in acid buffer pH 1.2 followed by, Phosphate buffer solution pH 7.2. Aliquotes of 1 ml were withdrawn at predetermined time intervals of, 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 h and 1 ml of drug free buffer was replaced to maintain sink condition. After appropriate dilution, the aliquots were analysed spectrophotometrically at 273 nm against blank.

Scanning Electron Microscopy :- Morphological characteristics of Naproxen matrix tablets were examined by Scanning Electron Microscopy**.** The study was performed using SEM instrument (JEOL 5400, Japan); particles were coated with Gold ions for 5 to 6 minutes. Optimized formulations were subjected to the release kinetics study. The drug release profile of formulations were fitted to Zero order kinetic (Eq-1), first order kinetic (Eq-2), Higuchi equation (Eq-3) and Korsmeyer-Peppas equation (Eq-4) to ascertain the kinetic modelling of drug release and the model with the higher correlation coefficient was considered to be the best fit model.

1) $Q = k_o t$ *2)* $In\ (100 - Q) = In\ Q_o - k_1 t$

3) $Q = k_H t^{1/}$ *4})* $Q = kp\ t^n$

In equations Q is the percent of drug released at time t and k_o, k_1 *and* k_H *are the coefficients of the equations, kp is constant incorporating structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of release. When n approximates to 0.5, a Fickian/ diffusion controlled release is implied, where 0.5<n< 1.0 non-Fickian transport and n =1 for zero order (case II transport). When the value of n approaches 1.0, phenomenologically one may conclude that, the release is approaching zero order. The statistical analysis was performed by calculating the correlation (r) existing between the in vitro release and the model proposed at different n values[53,54].*

6. RESULTS:-

6.1 Preformulation study

Table 6.1 Preformulation Study of Naproxen

Parameter	Description	Identification	Solubility (mg/ml)	Melting point (^{0}C)
Observed value	White powder	λ_{max} at 273 nm; Absorbance 0.476	5.76	154˚C
Reported value	White	λ_{max} at 271 nm	6	154˚C-158˚C

6.2 Spectrum Scan of Naproxen pure drug

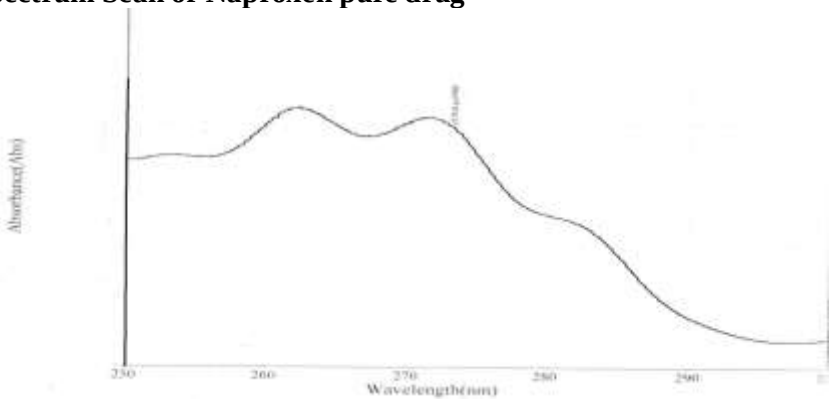


Fig.no. 6.1 Spectrum scan of Naproxen pure drug.

Calibration curve of Naproxen in pH 1

Table no. 6.2 Calibration curve of Naproxen in pH 1.2

Sr. No.	Absorbance*	Concentration (µg/ml)	Regression Analysis
1	0	0	
2	0.0068	2	
3	0.0127	4	
4	0.0181	6	
5	0.0249	8	
6	0.0301	10	
7	0.0365	12	

Regression Analysis
Slope = 0.003
Intercept = 0.009
Regression Coefficient
R = 0.99

6.5.1 Composition of Guar gum-g-Polyacrylamide Copolymer

Table no. 6.4 Composition of Guar gum-g-Polyacrylamide Copolymer

Fig.no. 6.4 FTIR spectrum showing compatibility of drug and excipients.

(A- FTIR of Naproxen, **B**- FTIR of Naproxen- Guar gum physical mixture, **C**- FTIR of Naproxen- Guar gum-g-PAM copolymer, **D**- FTIR of Formulation F2.)

6.5.2 Characterization of Guar gum-g-Polyacrylamide copolymer:

a) Viscosity measurement

Table no. 6.5 Viscosity measurement of Guar gum-g-Polyacrylamide copolymer Sr.

Sample name			Viscosity at 50 rpm	Viscosity at 100 rpm	
Sr. no.	Guar gum (g)	Acrylamide (g)	Description	% Grafting	% GE
1	1	5	White powder	40	8

b) Swelling study

Table no. 6.6 Swelling study in acid buffer pH 1.2 and PBS pH 7.2

Sr. no.	Guar gum		GG-g-PAM	
no.	cp	Torque	cp	Torque
1 Guar gum-g-Polyacrylamide solution (0.5% w/v)	190	1.6	317	2.5
2 Guar gum-g-Polyacrylamide solution (1% w/v)	416	3.5	593	4.7
3 Guar gum-g-Polyacrylamide solution (2% w/v)	725	5.7	896	6.2
4 Guar gum-g-Polyacrylamide solution (3% w/v)	1063	6.9	1293	7.4

c) FTIR spectrum of polymers

	Acid buffer pH 1.2	PBS pH 7.2	Acid buffer pH 1.2	PBS pH 7.2
Initial weight (g)	1.0	1.0	1.0	1.0
Final weight (g)	46.26	57.16	33.82	37.1

d) Thermal Analysis

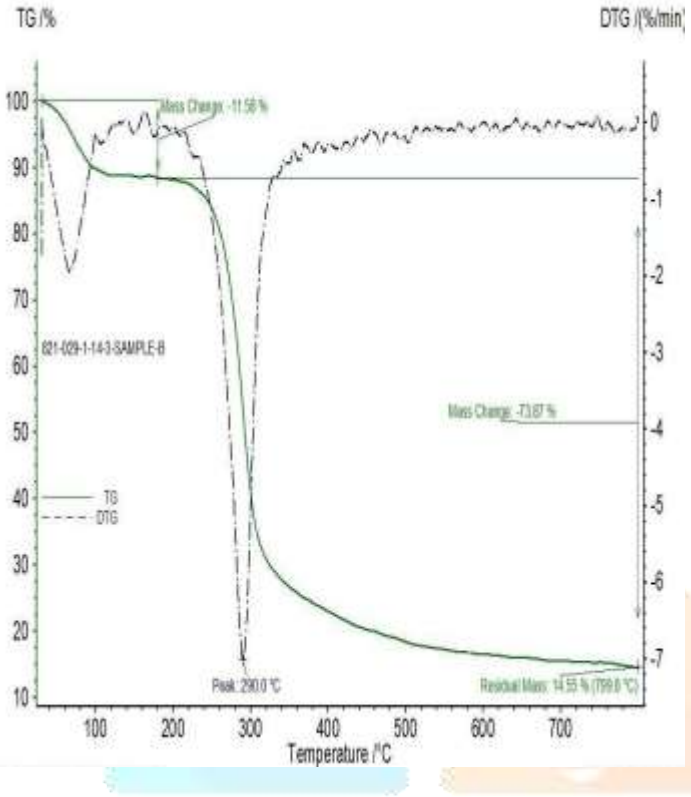


Fig. no. 6.6 Thermal analysis result of Guar gum.

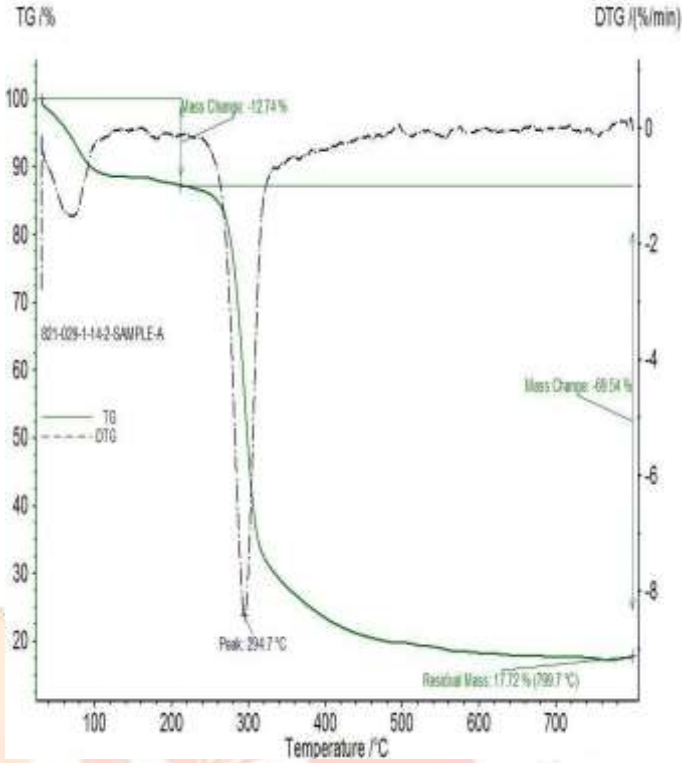


Fig. no. 6.7 Thermal analysis result of Guar gum-g-PAM

6.5.2 Post compression studies of Naproxen matrix tablets:

Table no. 6.8 Post compression study of Naproxen matrix granules

*** Average of 3 determinations. ± -Standard deviation**

	F1	F2	F3	F4	F5	F6	F7	F8
Bulk density	0.392±0.01	0.39±0.02	0.388±0.04	0.389±0.01	0.391±0.03	0.39±0.02	0.392±0.01	0.391±0.04
(g/cc)*								
Tapped density	0.423±0.03	0.422±0.02	0.42±0.01	0.421±0.03	0.421±0.01	0.421±0.02	0.423±0.03	0.422±0.01
(g/cc)*	20.18±0.01	20.32±0.03	20.67±0.02	21.72±0.03	19.98±0.01	19.78±0.03	19.14±0.04	19.01±0.01
Angle of repose								

(θº)* **Carr's index %**	7.3	7.5	7.6	7.6	7.1	7.3	7.3	7.3
Hausner's ratio	1.07	1.08	1.08	1.08	1.08	1.07	1.07	1.07

***In vitro* drug release of Naproxen through Guar gum-g-Polyacrylamide matrix:**

Table No. 6.9 *In vitro* release profile of formulation F1

Table No. 6.10 *In vitro* release profile of formulation F2

Scanning Electron Microscopy

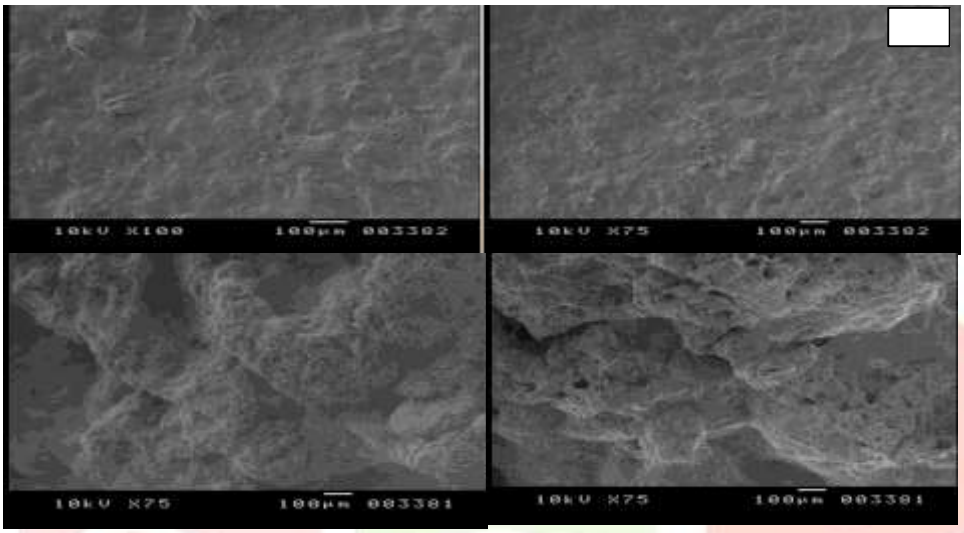


Fig. no. 6.16 Scanning Electron Microscopy results of F2 and F6

.

A, B- SEM of F6 and C, D- SEM of F2.

Evaluation of Formulation Parameters:

7. DISCUSSION

7.1. Preformulation study:

Preformulation study has vital importance in the development of dosage form. Preformulation study, by considering physicochemical properties of drug entity like, identification, melting point of drug always emphases on formulation.

1. **Identification** :- The pure drug Naproxen used in the study was obtained as a gift sample from RPG Life Sciences, Mumbai. The drug was identified by UV-specrophotometry (Lab India 3200); the wavelength scan of sample was performed at 200-400 nm according to British Pharmacopeia. The absorption of drug shows maxima at 273 nm with an absorbance value of 0.476. The results are given in Table no. 6.1 and Fig. no. 6.1.

2. **Description** :- The drug is received in white powder form which complies with description of British Pharmacopoeia.

3. **Solubility** :- Aqueous solubility is a useful pre-formulation parameter mainly for poorly water- soluble drugs such as naproxen. Bioavailability problems are often present when the aqueous solubility of a drug is less than 10 mg/ml over the pH range 1-8[4]. The naproxen equilibrium solubility in pH 7.2 phosphate buffer solution determined at 37°C was 5.76 mg/ml. Thus, sink conditions existed for naproxen release at this pH. Results are depicted in Table 6.1.

4. **Melting point** :- The melting point of Naproxen was found to be 154^0C, which is in accordance with reported value 154^0C of British Pharmacopoeial standards. The melting point study shows purity of obtained drug sample. The results are shown in table no. 6.1.

5. **FTIR** :- FTIR spectrum of Naproxen is mainly characterized by vibrations at 1725 cm^{-1} and 1684 cm^{-1} attributed to non-hydrogen-bonded –C=O stretching and hydrogen- bonded -C=O stretching of the catemer, respectively. As most of the Naproxen molecules are not engaged in hydrogen bonding the intensity of the vibrational band at 1725 cm^{-1} is more dominant. According to FTIR study none of the excipients showed interaction with the pure drug. Results of the study are depicted in Fig. No. 6.4.

GG.g.1 **Synthesis of Guar gum-g-Polyacrylamide copolymer by microwave initiated Method**

GG-g-PAM has been synthesized by microwave initiated method i.e. synthesis based on free radical mechanism, using microwave irradiation to generate free radicals on the Guar Gum backbone. Various grades of the graft copolymer were synthesized by varying the irradiation time, the concentration of Guar gum and Acrylamide were kept constant and also microwave power was set at 600 W. It was seen that the increase in radiation time tends to decrease the percentage grafting[13]. The optimized grade has been determined through its percentage grafting. From Table no. 6.4, it is obvious that the grafting is optimized at an irradiation time of 7 min, when the microwave power is maintained at 600 W. With an increase in exposure time (up to 7 min); the percentage grafting increases, beyond which it decreases. This may be because of the fact that beyond exposure time of 7 min, the prolonged exposure to microwave irradiation may have degraded the polysaccharide backbone and also may have enhanced appreciably the competing side reaction leading to more homopolymer (PAM) synthesis[13]. This results in the decrease of percentage grafting. Inhibitors such as hydroquinone (HQ) react with chain radicals to terminate chain propagation and the resulting hydroquinone radical is stable and cannot initiate further polymerization.

7.2.2 Characterization of Guar gum-g-Polyacrylamide copolymer:

a) Viscosity :- The viscosity of GG-g-PAM polymeric solution form at different concentrations, as stated in Table no. 6.5. It is obvious that the viscosities of all the grades of GG-g- PAM are higher. Viscosities of polymeric solutions were recorded for four different concentrations, at different speeds (50rpm and 100 rpm). 0.5% w/v polymeric solution shows a viscosity of 190 cp and 317 cp and torque values were found to be 1.6 and 2.5, at the speeds of 50 and 100 rpm respectively. 1% w/v polymeric solution shows a viscosity of 416 cp and 593 cp and torque values were found to be 3.5 and 4.7, at the speeds of 50 and 100 rpm respectively. 2% w/v polymeric solution shows a viscosity of 725 cp and 896 cp and torque values were found to be 5.7 and 6.2, at the speeds of 50 and 100 rpm respectively. 3% w/v polymeric solution shows a viscosity of 1063 cp and 1293 cp and torque values were found to be 6.9 and 7.4, at the speeds of 50 and 100 rpm respectively. This can be explained by the high molecular weight of GG-g- PAM, due to the grafting of the PAM branches on the main polymer backbone[13].

b) Swelling Study :- In vitro swelling study of Guar gum and GG-g-PAM copolymer was carried out in acid buffer pH 1.2 and PBS pH 7.2. The results of the study are depicted in Table no. 6.6. After the swelling study the final weights of Guar gum were found to be 46.26 g and 57.16 g in acid buffer pH 1.2 and PBS pH 7.2 respectively. In case of GG-g-PAM copolymer, swelling values were 33.82 g and 37.1 g in respective pH conditions. The swelling behaviour of grafted copolymer was comparatively less than GG in both the media; this might be due to hydrophobicity and increase in molecular weight of GG- g-PAM copolymer[13].

c) FTIR :- From FTIR spectrum of Guar gum, a broad peak at 3298 cm^{-1}attributed to O-H stretching vibration which shows hydrogen bonding with water molecules. Similarly, the absorbance bands at 1008 $cm^{-1}$and 866 cm^{-1}corresponds to C-O-C stretching vibrations from glycosidic linkages as the peaks observed in the spectrum between1200 and 800 cm^{-1}represent the highly coupled C-C-O, C-OH and C-O-C. stretching modes of polymer. For Guar-g-PAM a peak observed at 3757 cm^{-1}showed overlapping of O-H stretching band of OH group of GG and N-H stretching band of amide group. A sharp peak at 2924 cm^{-1} in GG-g-PAM is due to C-H stretching vibrations, where as the appearance of peaks at 1680 cm^{-1}, 1676 cm^{-1}, 1595 cm^{-1} and 1541 $cm^{-1}$of grafted GG has been recognized as C-O and N-H stretching vibration bands, respectively. The appearance of sharp peaks in grafted GG at 1680 $cm^{-1}$and at 1595 $cm^{-1}$are attributed to C-O and N-H stretching, respectively[36]. FTIR studies of polymers were done as a part of pre-formulation study on Bruker Alpha Fourier transform Infrared Spectrometer. As shown in Figure 6.5.

d) Thermo Gravimeric Analysis :- The TGA curves of GG and GG-g-PAM essentially involve three distinct zones of weight loss. The initial weight loss is at 30–120◦C. This is because of the traces of moisture present. The second zone of weight loss (230–335◦C) may be because of the degradation of polymer backbone (secondary alcohol –CHOH) and the third zone of weight loss (335–680◦C) may be because of the degradation of polymer backbone (primary alcohol $–CH_2OH$) [13]. The results of thermal analysis of Guar gum and that of the grafted guar gum are depicted in Fig. no.6.6 and 6.7 respectively.

Evaluation of Naproxen matrix granules

1] Precompression properties

- **Bulk density :-** The ratio of mass of the granules to the volume required to occupy that respective mass is represented as bulk density. The bulk densities of formulations F1 to F8 were found in the range of 0.388±0.04 g/ml to 0.392±0.01 g/ml. Formulations F1 and F7 showed highest bulk density values and Formulations F2, F5, F6 and F8 showed good bulk density values, while Formulations F3 and F4 showed lowest bulk density values. Results are shown in Table no. 6.7.
- **Tapped density :-** The tapped densities of the Formulations F1 to F8 were found in the range of 0.42±0.01 g/ml to 0.423±0.03 g/ml. Formulations F1 and F7 showed highest tappeddensity values, Formulations F2, F4, F5, F6 and F8 showed fair tapped density values while F3 showed lowest tapped density values. The results are shown in Table no. 6.7.
- **Angle of repose: -** As presented in table no.6.7, all formulations show acceptable flowability according to the angle of repose measurement. Angle of repose for Naproxen matrix granules were found to be between 19.01± 0.01 to 21.72±0.03. Formulations F1 to F4 possess excellent flow properties while, Formulations F5 to F8 possess good flow properties. Results have proved that wet

granulation technique can modify the flow properties of poorly flowing materials like Naproxen and Guar gum etc.

- **Carr's Index: -** The Carr's indices of Naproxen matrix granules for F1 to F8 formulations were within the range of 7.1 to 7.6%. All values were found to be within prescribed limits of good flow. The results are given in Table 6.7.
- **Hausner's ratio :-** It is related to the inter particle friction. Values of Hausner's ratio up to 1.25 indicate granules with low inter particle friction indicating good flow while; values higher than 1.25 indicate poor flow properties. Naproxen matrix granules formulations F1 to F8 showed acceptable flow properties. The results are shown in Table no. 6.7.

Evaluation of tablets/ Post compression studies

- **Tablet dimensions: -** Thickness of tablets ranged from 3.67 ± 0.02 to 3.81± 0.03 mm and diameter of 12 mm. The thickness of the tablet depends upon the diameter of die, the amount of fill permitted to enter the die, the compaction characteristic of the fill material and the force applied during compression. Results are shown in Table no. 6.8.
- **Weight variation test: -** Weight variation test revealed that the tablets of all formulations were within thege of Pharmacopoeial specifications. All the formulations passes weight variation test according to I.P. Results are shown in Table no. 6.8.
- **Hardness:** :- The hardness of tablet formulation depends on the granule flow properties. If the granules have higher packability will have the good crushing strength. High bulk and tapped density values indicate better distributions of granules during compression, referring to good consolidation and high hardness. Hardness of all formulations F1 to F8 was found to be in the range of 6±0.1 kg/cm^2 to 6.16±0.11 kg/cm^2. Highest hardness was obtained for Formulation F1 and F7, good values of hardness were obtained for Formulations F2, F4, F5, F6 and F8, while, and lowest hardness was obtained for Formulation F3. Results are shown in Table no. 6.8.
- **Friability:** - To determine the absolute strength of tablet, hardness testing along with friability is necessary and it is one of the early detection methods for capping and lamination. All the Naproxen matrix tablets showed acceptable friability and percentage loss in tablets weight not exceed 1%. Friability of formulations F1 to F8 ranges from 0±0.00 to 0.26±0.04. All formulations showed % friability less than 1%, which indicates good mechanical resistance of tablets. This ensures that tablets could withstand to the pressure, shocks during handling, transportation, shifting processes and free from capping and lamination. Results are shown in Table no. 6.8.
- **Drug content:** - Percentage drug content of Naproxen matrix tablets were estimated in triplicate. Percentage drug content of Naproxen in matrix tablets were determined by UV method and were found to be in the range of 99.2±0.15 to 99.9±0.25. The drug content of all matrix tablets was found to be within the limits of 98.5 to 100.5 according to B.P. Results are shown in Table no. 6.8.
- ***In vitro* drug release studies:** - The results of *in vitro* cumulative percent amount of drug released at different time intervals plotted against time to obtain the release profiles. Percentage cumulative drug release for Formulation F1, F2, F3 and F4 were found to be 99.98, 96.3, 81.8 and 70.2 % at the end of 24 h. Percentage cumulative drug release forFormulation F5, F6, F7 and F8 were found to be 100.1, 99.6, 99.3, 100% at the end of 24 h. Percentage cumulative drug release of F8 was found to be 100% at the end of 13 h; whereas 70.2% for Formulation F4 containing grafted guar gum, at the end of 24 h. This result revealed that even though polymer concentration is same in both the formulations, grafted copolymer showed greater release rate retardation than Guar gum. This project

was aimed to achieve more than 90% of drug release in 24 h and the promising results were obtained from formulation F2 with percent cumulative drug release of 96.3% at the end of 24 h. When Formulation F2 was compared with Formulation F8, which contains Guar gum, showed a percent cumulative drug release of 100% at the end of 13 h, even though polymer concentration was more in F8. This reveals that grafted polymer with lower concentration possesses significant release rate retarding ability. From these drug release profiles, it is evident that due to grafting, the properties of polymer (Guar gum) have changed, i. e. graft chains form effective interlocking and are consequently lower in erosion. Hydrophillicity of Guar gum was more as compared to grafted guar gum due to this. Hence, penetrability of dissolution medium and leaching out of embedded Naproxen from polymer was sustained.

- **SEM study** :- Dissolution tested tablets were subjected for scanning electron microscopy. For this F2 (grafted Guar gum) and F6 (Guar gum) Naproxen matrix tablet formulations were selected. Scanning was performed at a magnification of 75X and 100 µm size. Surface morphology of F2 formulation clearly indicates that formation of channels/ pores and surface was eroded. In case of F6 formulation, surface morphology revealed smooth surface texture than F2 formulation and lacking surface erosion. Results are depicted in Fig. no.6.16.
- **Kinetics of drug release** - In order to elucidate the *in vitro* release mechanism for Guar gum (F8) and Guar gum- g-PAM (F2) matrix tablets, the data was fitted into the models representing Zero- order, First-order, Higuchi's and Korsemeyer's equations.. The kinetic values from different plots are listed in Table no. 6.19. When data was plotted according to zero order kinetics, a linear plot was obtained for Guar gum matrix tablet F8 with its regression coefficient value of 0.993, suggesting the mechanism of release from Formulation F8 followed as per zero-order kinetics. When data was plotted according to zero order kinetics, a linear plot was obtained for Guar gum-g-PAM matrix tablet F2 with its regression coefficient value of 0.995, suggesting the mechanism of release from Formulation F2 followed as per zero-order kinetics. Further the data was plotted as per first-order and Higuchi equation for Guar gum-g-PAM copolymer matrix tablet F2. The plots obtained were linear with their respective regression coefficient values of 0.878 and 0.993, indicating the mechanism of release followed zero-order kinetics. Finally the data of matrix tablet F2 was fitted to Korsemeyer's equation, the plot showed linearity with its regression coefficient value of 0.992 with a slope value of 0.958, as $0.5 < n < 1.0$, indicating the release was followed as per anomalous transport.

8. SUMMARY AND CONCLUSION

8.1 Summary

In the formulation of any matrix drug delivery systems, properties of polymers play an important role. Natural polysaccharides are widely used in such drug delivery systems. Literature survey has proved that Guar gum is a natural polysaccharide which shows a rapid drug release from its matrix, so generally high polymer concentration is preferred to achieve sustained release. If chemical modifications like grafting are attempted for such polymers, it is evident that drug release retarding properties of Guar gum are enhanced. So this was an attempt to formulate a drug delivery system that can release the drug over a period of 24 h. So that dose, dosing frequency, dose dumping and the possible side effects of drugs like Naproxen can be minimized. Also, methods like wet granulation are helpful in order to improve the flow characteristics of the drug and polymer for better tabletting properties.

8.2 Conclusion

The aim of this study was to formulate matrix tablets of Naproxen using natural gum. From the results obtained from executed experiments it can be concluded that: FTIR spectra revealed that, there was no interaction between Naproxen and microwave-synthesized Guar gum-g-Polyacrylamide copolymer and Guar gum. The synthesized grafted coopolymer was found to be viscous, hydrophobic and its flow properties were good as compared to Guar gum. TGA data revealed that there occurred changes on the Guar gum backbone during grafting which yielded a high molecular weight copolymer.Naproxen and Guar gum have poor flow properties, hence wet granulation was employed to yield better flow properties and hence tabletting. *In vitro* drug release study of Naproxen revealed that the drug release through Guar gum matrices was faster and that of Grafted guar gum was sustained. According to kinetic study, the mechanism of drug release is also different for both the polymers. Finally, matrix drug delivery systems can be successfully formulated using, chemically modified form of Guar gum in order to reduce dose, dosing frequency and dose dumping of Naproxen as a model drug which has a high dose and long half life.

RECOMENDATION

Future studies involving their suitability for other dosage form applications, shelf life determination, bioavailability and clinical investigations, they are as follows.

- *In Vivo* Studies
- *In Vivo-In Vitro* correlation.
- Scale up studies of the optimized formulation
- Bioavailability studies [pre-clinical and clinical trials].

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