BORAX-TARA GUM HYDROGEL MATRIX TABLET FOR GASTROPROTECTIVE DRUG DELIVERY

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CERTIFICATE OF APPROVAL

This is to certify that **RIYA HAZRA** (Class Roll No.: 002211402051 and Reg. No.: 163691 of 2022-2023, Examination Roll No.: M4PIP24001) has carried out the research work on the subject entitled "***BORAX-TARA GUM HYDROGEL MATRIX TABLET FOR GASTROPROTECTIVE DRUG DELIVERY***" under our supervision in the Pharmaceutical Biotechnology and Pharmaceutics Research Laboratory in the Department of Pharmaceutical Technology of this university. She has incorporated her findings into this thesis of the same title, being submitted by her, in partial fulfilment of the requirements for the degree of **Master of Pharmacy** of Jadavpur University. She has carried out this research work independently and with proper care and attention to our 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 the undersigned candidate, as part of her Master of Pharmaceutical Technology studies. All informationin this document has 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 materials and results that are not original to this work.

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Chapter – 1
Introduction

1.1. Drug Delivery System

The primary goal of drug administration is disease or disorder therapy. According to the FDA, a drug is a substance officially recognized in pharmacopoeia and designed for diagnosis, cure, mitigation, treatment, or prevention of disease. Drugs are never given in their pure form; instead, they are transformed into dosage forms that are appropriate for the patient and allow for the monitoring of the start, severity, and duration of the drug's effects. Drug delivery is the process of giving a patient medication in a way that enhances the concentration of the drug in some areas of the body relative to other areas. This procedure involves administering the medicinal product, allowing the substance to release the active chemicals, and then allowing the active ingredients to pass through biological membranes and reach the site of action. Any delivery system's ultimate objective is to target, restrict, and extend the medication in the diseased tissue while maintaining a safe interaction. A drug delivery system serves as a link between the medication and the patient. It could be a medication formulation intended for therapeutic use or a drug-delivery system [1-4].

1.1.1. Classification of Drug Delivery System

Depending on the target site, length of therapy, and physicochemical characteristics of the medication, different routes can be used to provide different dosage forms as shown in Table 1.1. The most widely used dosage forms are injections, ointments, syrups, tablets, capsules, and pills. The area of the body being treated, the drug's mode of action inside the body, and the drug's solubility and permeability all influence the best approach to administering a medication [5].

Table 1.1: Various Routes of Administration Available with Various Dosage Forms

Route of Administration	Dosage form
Oral	Tablet, granules, capsules
	Suspension, emulsion, syrup
Nasal	Drop, spray
Otic	Topical, intracocheal
Topical	Ointment, Cream
Parenteral	Injection
Ocular	Eye drops, eye spray
Rectal	Suppositories
Vaginal	Pessaries

1.1.1.1. Conventional Drug Delivery System

Conventional drug delivery systems are the traditional ones that administer drugs or medication to patients. These systems have been used widely for centuries to this date. Their main objective is to achieve therapeutic levels by releasing the drug in a controlled and predictable manner. The main characteristic features of this drug delivery system are to release the drug immediately after administration and follow a predictable pharmacokinetic profile. The advantages of such kind of drug delivery system are that easy to administer, cost-effective, and well-established processes. But this drug delivery system has various limitations like poor bioavailability, frequent dosing, high dose dumping, etc in Fig. 1.1 [6].

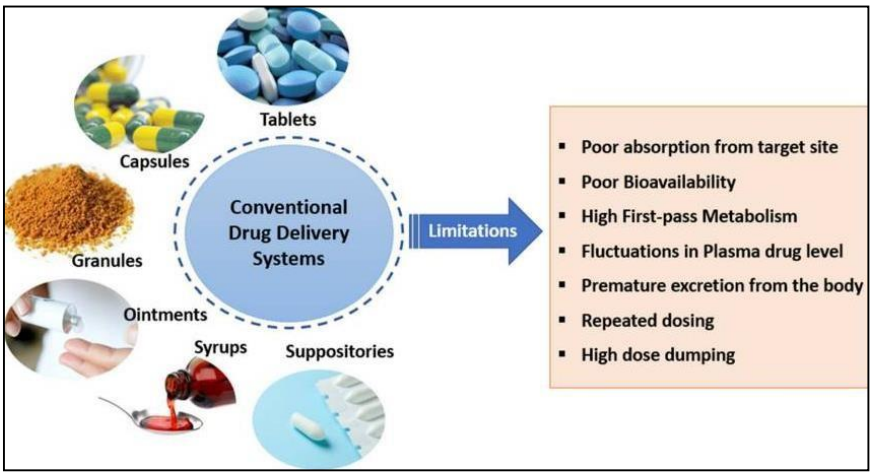


Fig. 1.1: Limitations of Conventional Drug Delivery Systems

1.1.2. Tablets as Conventional Drug Delivery System

Pharmaceutical tablets are unit, solid, flat dishes dosage forms developed by compressing a drug or combination of drugs using or without diluents as per Indian Pharmacopoeia. Tablets have different sizes, shapes, and weights depending on the amount of medication introduced in the tablet and the deliberate administration system. Tablets are the most common dosage form and almost 70% of the medicaments are available in tablet form [7-9].

1.1.2.1. Advantages of Tablets

Tablet provides various advantages [7-9]:

- ❖ Tablets are unit dosage forms while maintaining the exact dose of drugs.
- ❖ Manufacturing methods are easier than other dosage forms.

- ❖ They are compact and have a lighter dosage form.
- ❖ Easy to swallow.
- ❖ Tablets can sustain drug release, which is achieved by enteric coating.
- ❖ They are suitable for production on a large scale.
- ❖ Cost-effective.
- ❖ Packaging is most easiest and cheapest.
- ❖ In the process of coating technique unpleasant odor and bitter taste of the drug can be masked.
- ❖ Amongst all the dosage forms tablets have the highest microbial and chemical stability.
- ❖ Easy to use.

1.1.3. Conventional Drug Delivery System v/s Controlled Drug Delivery System

Controlled-release drug delivery has just emerged as the norm in contemporary pharmaceutical design, and extensive research has been conducted to improve the efficacy, safety, and reliability of therapeutic products. Conventional drug delivery systems, such as tablets, capsules, and syrups are rapidly excreted from the body and their dosage is not adequately regulated during the therapeutic window. The drug metabolizes swiftly after a single typical dose, increasing the drug level for a brief period before experiencing an exponential decline. It's possible that the duration won't last long enough to have a meaningful therapeutic impact, leading to a sub-therapeutic reaction [6].

1.1.3.1. Advantages of Controlled Drug Delivery System

When compared to alternative administration methods, these controlled drug delivery systems offered the following benefits [10-12]:

- ❖ The ability to maintain therapeutically desirable plasma drug levels.
- ❖ The potential to eliminate or reduce harmful side effects from systemic administration by local administration from a controlled release system.
- ❖ Drug administration may be improved and facilitated in underprivileged areas where good medical supervision is not available.
- ❖ The potential to greatly facilitate the administration of drugs with a short in vivo half-life.
- ❖ Continuous small amounts of drug may be less painful than several large doses.
- ❖ Improvement of patient compliance.
- ❖ The potential for the use of drug delivery systems to produce a relatively less expensive product and less waste of the drug.

1.2. Sustained Release Tablets as a Drug Delivery System

The term "sustained release" is used to explain a pharmaceutical dosage form prepared to decrease the release rate of a drug that showed delayed or prolonged release of the drug in the systemic circulation. Sustained drug-release tablets are beneficial for the treatment of chronic diseases. Sustained-release tablet showed their pharmacological action by keeping the plasma drug concentration constant, sustaining the drug release rate over time, and generating therapeutic action for an extended period. The formulation which showed extended release plays a crucial role in making the half-life shorter and the dosing frequency becomes high. In this way of sustained release side effects are reduced by prevention of fluctuation the therapeutic concentration of the drug in the body. In a Novel Drug Delivery System sustained release tablet became most popular worldwide [13- 15].

1.2.1. Advantages of Sustained Release Tablet as Drug Delivery System

Sustained release tablets offer various advantages are as follows [13-16]:

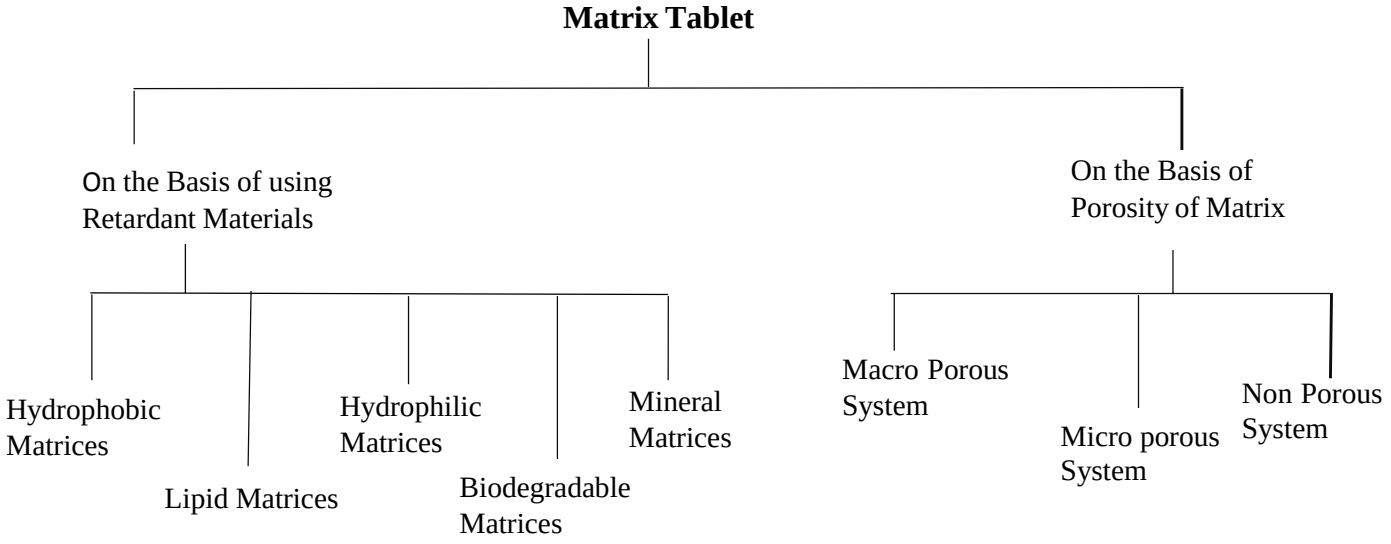
- **Patient Compliance:** Sustained release tablets can increase patient compliance by decreasing the number of doses which leads to improvement in therapeutic plans.
- **Decreased 'see-saw' Fluctuation:** The concentration of the drug frequently exhibits a 'see-saw' pattern in the systemic circulation and tissue chamber when the drug is administered in the conventional dosage form. Sustained release tablet decreases drug dosing frequency and also balanced drug concentration is maintained in the blood circulation.
- **Dose Reduction:** In a sustained release drug delivery system, a very small amount of aggregated drug is used for the treatment of ailing conditions. Local or systemic side effects have been reduced by decreasing the dose of a drug which leads to economic growth.
- **Improvement of Treatment Deficiency:** Drugs can be effectively moved to the tissues, and organs can be an ideal way for the treatment of any disease. Cells that require a very low amount of the drug have been administered which can obtain an effective dose of the drug therapeutically. This effective drug concentration sometimes showed undesirable, immunological, and toxicological effects in non-targeted tissue. Acute or chronic disease can be controlled by a sustained release tablet.

1.3. Matrix Tablets as Sustained Release Drug Delivery System

A matrix tablet is defined as an oral solid dosage form in which the drug and inactive materials are homogeneously dispersed in hydrophilic or hydrophobic matrices that can decrease the drug release rate and produce sustained release effects. Matrix tablets are an effective strategy for the development of sustained release drug therapy as they provide lower costs for preparing sustained release tablets. The drug release from matrix tablets is regulated by Fick's first law of diffusion. Matrix systems are mainly used to obtain sustained release which can regulate prolonged release of dissolved or dispersed drugs. Matrix is a good mixture of drugs or a combination of drugs and a gelling agent. In the sustained release method, therapeutically efficient drug concentration can be achieved in systemic circulation for a prolonged period, resulting in better patient compliance [15, 17-19].

1.3.1. Classification of Matrix Tablet

Matrix tablet can classified on the basis of two factors as shown below [13, 15, 17, 18]:



I. Based on using Retardant Materials

- **Hydrophobic Matrices:** In 1959 the idea of hydrophobic substances as matrix materials was first established. The oral dosage form becomes a sustained release tablet by mixing the drug with a hydrophobic polymer and then compressing it into a tablet. The dissolving drug has been diffused through the channel's network that can remain between the polymer particles in a compact form. In contact with gastrointestinal fluid and water hydrophpbic matrix becomes inert include ethylcellulose, polyethylene, polyvinyl chloride, etc.

- **Lipid Matrices:** Lipid waxes and their related substance have been incorporated for the preparation of the lipid matrix. The drug has been released from this matrix through both erosion and pore diffusion mechanisms. Lipid matrix including Carnauba wax with stearic acid or stearyl alcohol has been used as a base material for the preparation of sustained release tablets.

- **Hydrophilic Matrices:** In oral controlled release drug delivery hydrophilic matrices have been widely used because of their lower cost, ability to target drug release, and wide regulatory acceptance. This matrix is also called a swellable control drug release matrix. Polymers are divided into their groups for the preparation of these matrices including :

    1. **Cellulose Derivatives:** Hydroxypropylmethylcellulose (HPMC), Sodium carboxymethylcellulose, Hydroxyethylcellulose, Methylcellulose.
    2. **Non-cellulose Polymer:** Alginate, Agar-Agar, Chitosan, Carob gum, Molasses, Modified starches.
    3. **Acrylic Acid Polymers:** Carbopol-934

- **Biodegradable Matrices:** This matrix is prepared by polymers which consist of monomers linked with each other through functional groups that have unstable linkage in their backbone. This matrix can be biologically degraded by an enzyme that is excreted through living cells or a nonenzymatic process into a polymer that becomes metabolized or excreted. Examples include a natural polymer (Protein and polysaccharide), modification of natural polymer, and synthetic polymers like polyesters and polyanhydrides.

- **Mineral Matrices:** Mineral matrices are composed of polymers that can be found in seaweed species. Examples include Alginic acid (hydrophilic carbohydrate) found in brown seaweed species using dilute alkali.

II. Based on the Porosity of the Matrix

Drug diffusion through the matrix is shown in Fig. 1.2.

- **Macro Porous System:** In this system, the pore size of the matrix is between 0.1 to 1μm through which drug diffusion takes place.
- **Micro Porous System:** Drug diffusion occurred from the pore sizes between 50 – 200 A° of the matrix.
- **Non Porous System:** Molecule diffusion occurs through network meshes as no pores are present in this system. Only the polymeric phase takes place and the pore phase is not present.

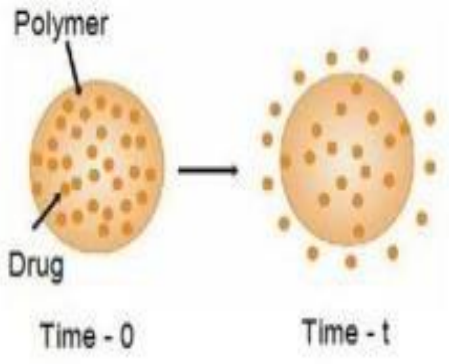


Fig. 1.2: Drug Diffusion through The Matrix

1.3.2. Drug Release Mechanism from Matrix System

The drug is released from the matrix system by several mechanisms [17, 20-22]:

- Diffusion controlled system
- Dissolution controlled system
- Erosion controlled system

- **Diffusion Controlled System:** In this system, the drug is dispersed in a porous matrix like solid particles to produce water-insoluble polymer like polyvinyl chloride. At the exterior of the release section, the drug particles are present initially which will dissolve leading to rapid drug release. After that drug particles rise to space from the exterior of the release section which will be dissolved and the drug is released through the pores of the surface of

the release section by diffusion. The mechanism of the drug released through diffusion controlled system is shown in Fig. 1.3.

Diffusion-controlled systems are two types-

1. Matrix diffusion-controlled system
2. Reservoir devices

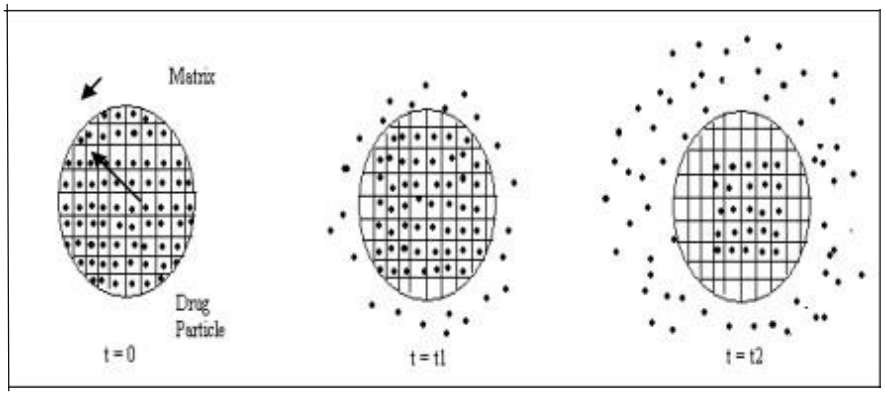


Fig. 1.3: Mechanism of Drug Release from Diffusion Controlled System

- **Dissolution Controlled System:** Sustaining characteristics will be observed when the drug shows a slow dissolution rate since the drug release rate will be restricted by the dissolution rate. Drug release from a dissolution controlled system is shown in Fig. 1.4. Sustained release tablets prepared by decreasing the drug dissolution rate which are highly soluble in water. This is done by-

  1. Producing suitable salts or their derivatives.

  2. The drug is coated with a material that can slowly be dissolved.

  3. Introducing a carrier that can slowly be dissolved when the drug is incorporated into a tablet.

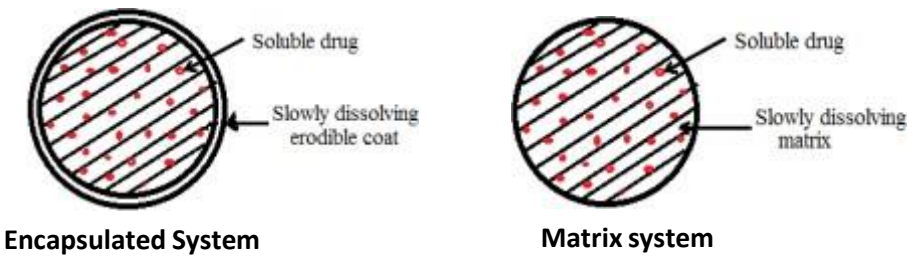


Fig. 1.4: Dissolution Controlled Release System

- **Erosion Controlled System:** In this system, the drug is dispersed in a matrix and the drug release rate is controlled by the erosion of the matrix. The erosion technique is the easiest way to control the drug release in which matrix material is continuously liberated from the exterior of the tablet. This is called surface erosion. The mechanism of drug release from erosion controlled system is shown in Fig. 1.5.

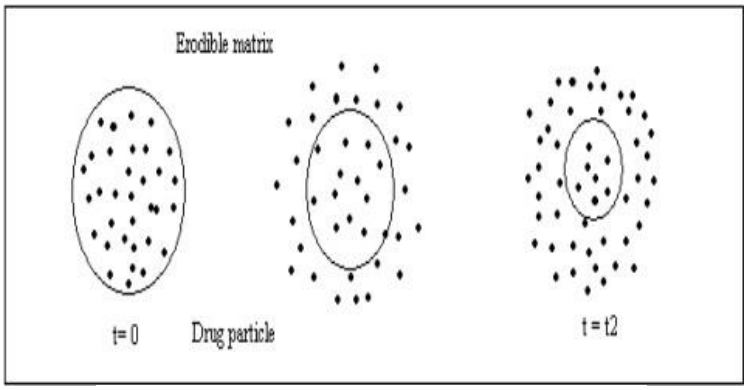


Fig. 1.5: Erosion Controlled System

1.4. Cross-linked Matrix Tablets as Sustained Release Drug Delivery System

Sustained release matrix tablets can be prepared by crosslinking the hydrophilic polymer causing the structures known as hydrogel. Hydrogels are cross-linked hydrophilic polymer structures that absorb huge volumes of water or biological fluids. Hydrogels are one of the emerging categories of polymer-based systems with diverse biological and pharmacological uses. Their intrinsic biocompatibility makes them ideal for protein delivery systems [23].

1.4.1. Significance of Crosslinking

Adding cross-links between polymer chains affects the polymer's physical properties, including crystallinity [24]:

Crosslinking effects on-

- **Elasticity-** Elastomers are elastic polymers produced through restricted crosslinking. Increasing the number of cross-links causes the polymer to become stiffer and less elastic, perhaps leading to brittleness. Vulcanization, also known as sulfur curing, occurs when short chains of sulfur atoms are introduced between the polymer chains of natural rubber. Short chains of sulfur atoms form bridges between polyisoprene strands, eventually joining them into a single supermolecule. Vulcanization is a chemical process that strengthens rubber by crosslinking it.

- **Decrease in Viscosity**- Crosslinking stops polymer chains from flowing past each other. Restricting flow results in improved creep behavior.

- **Decrease in Solubility of Polymer**- Crosslinking creates insoluble chains due to strong covalent connections between them. Cross-linked materials cannot dissolve in solvents, but can absorb them. Gels are cross-linked materials that have absorbed a large amount of solvent. For example, cross-linked polyacrylamide gel. Uncross-linked polyacrylamide is soluble in water, but cross-linked polyacrylamide absorbs water but is insoluble. Water-logged gels of cross-linked polyacrylamides are used to create soft contact lenses.

- **Increase in Strength, Toughness, and Glass Transition Temperature**- Crosslinking alters local molecule packing, decreasing free volume and increasing glass transition temperature. PVA crosslinking with boric acid resulted in higher glass transition temperatures. Cross-links in PVA can slow down molecular mobility and should not be present in crystalline domains.

- **Decrease in Melting point- C**rosslinking in crystalline polymers reduces their crystalline behavior, resulting in softer, elastic polymers with lower melting points.

1.4.2. Method of Crosslinking

Crosslinking processes vary depending on the polymer type. Crosslinking can occur through the polymerization of monomers with more than two functionalities (by condensation), or through covalent bonding between polymeric chains via irradiation, sulfur vulcanization, or chemical reactions involving the addition of various chemicals in conjunction with heating and, in some cases, pressure. The crosslinking procedure invariably alters the chemical structure of the polymer. Irradiation crosslinking uses high-energy ionizing radiation such as electron beam (e-beam), gamma, or x-rays. Gamma irradiation is most cost-effective at low doses (<80 kGy) and for large, high-density items. Fig. 1.6 represents polymer crosslinking [24].

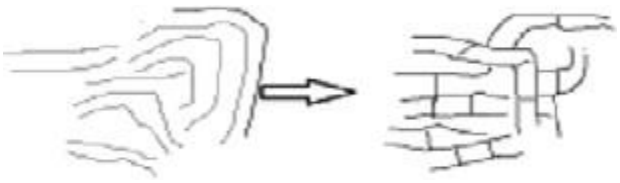


Fig. 1.6: Crosslinking in Polymer

1.4.3. Types of Crosslinking

Hydrogel can be classified into two categories based on its mechanism- physical and chemical crosslinking.

1.4.3.1. Physical Cross-linked Hydrogel

Physical crosslinks involve entangled chains, hydrogen bonding, hydrophobic interactions, and crystallite formation. Hydrogels are insoluble in aqueous fluids due to physical crosslinks, which may not be permanent. Physical crosslinking produces reversible hydrogels. Although physical hydrogels can absorb water, they may have inhomogeneities or network faults caused by free chain ends or loops. Ionic contact, crystallization, stereo-complex formation, hydrophobized polysaccharides, protein interaction, and hydrogen bonding all contribute to the creation of physically cross-linked hydrogels. Hydrogels can crosslink at mild settings, such as room temperature and physiological pH, through ionic interactions. This crosslinking mechanism does not need the presence of ionic groups in polymers. Metallic ions enhance the strength of hydrogels. To generate a stereo-complex, lactic acid oligomers with opposing chirality are cross-linked to form ahydrogel. Hydrophobic interactions cause the polymer to swell and absorb water, creating the hydrogel. Research suggests that hydrophobic alteration of polysaccharides such as chitosan, dextran, pullulan, and carboxymethyl curdlan can result in physically cross-linked hydrogels [25].

1.4.3.2. Chemical Cross-linked Hydrogel

Chemical cross-linked hydrogels involve the covalent crosslinking of polymers which is created by polymerizing end-functionalized macromers. The covalent networks involve a net like structure which consists of voids which enhances the ability of hydrogel to absorb water. The chemical hydrogels are generally prepared by methods: electron and gamma beam polymerization, condensation and addition polymerization, chain growth polymerization. As compared to other processes, chemical linking are considered as flexible and advantageous because this process provides permanent crosslinking to hydrogel which prevents loss of structure integrity, greater mechanical strength and longer durability of hydrogels. Chemical crosslinking process enhance the mechanical properties and viscoelasticity of hydrogels. This kind of hydrogel have much application in pharmaceutical and biomedical areas and becomes a promising drug delivery system through colon. [26-29].

1.5. Borax as a Crosslinking Agent

Borax, or sodium tetraborate decahydrate, a chemical formula $Na_2B_4O_7$, $10H_2O$ (as shown in Fig 1.7) is a member of the monoclinic system which has a space group of C2/c. Every sodium ion in the borax structure has a deformed octahedral geometry and is positioned in the inversion symmetry position in the crystallographic spatial structure. The structure of borax is shown in Fig. 1.7.

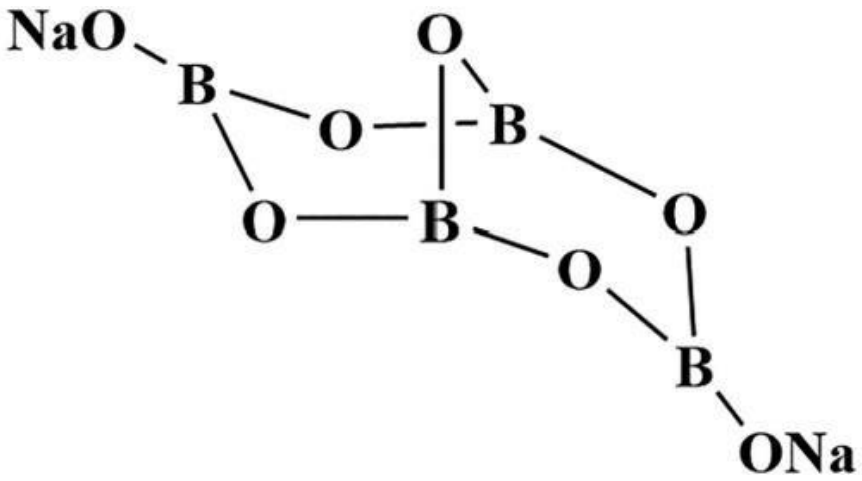


Fig. 1.7: Structure of Borax

Borax is a well-known effective crosslinker that may quickly generate hydrogels out of materials containing active hydroxyl groups. Moreover, borax can react with up to four hydroxyl groups and exists as $B(OH)_4^-$ in an aqueous solution, enabling crosslinking reactions to happen even at lower concentrations. As a result, a borax crosslinker is required for the production of affordable, biodegradable, and environmentally friendly products. Fig. 1.8 illustrates how borax acts as a crosslinking agent. Borax dissolves readily in water and has a slightly alkaline aqueous solution. It generates conjugated acid-base pairs ($B(OH)_4^-$ and H_3BO_3) when dissolved in water. Furthermore, in order to create stable complexes, boric acid ions can cross-link with materials that include cis hydroxyl groups of polysaccharides like sodium alginate, fenugreek galactomannan, konjac glucomannan, and Portulaca oleracea, etc.

It is possible to increase borax's solubility by applying the principles of reaction equilibrium found in Fig. 1.8a. In other words, as pH rises, the balance shifts in favor of boric acid ion production. OH− of borate hydrolysis is one of the fundamental requirements for the crosslinking agent [30-31].

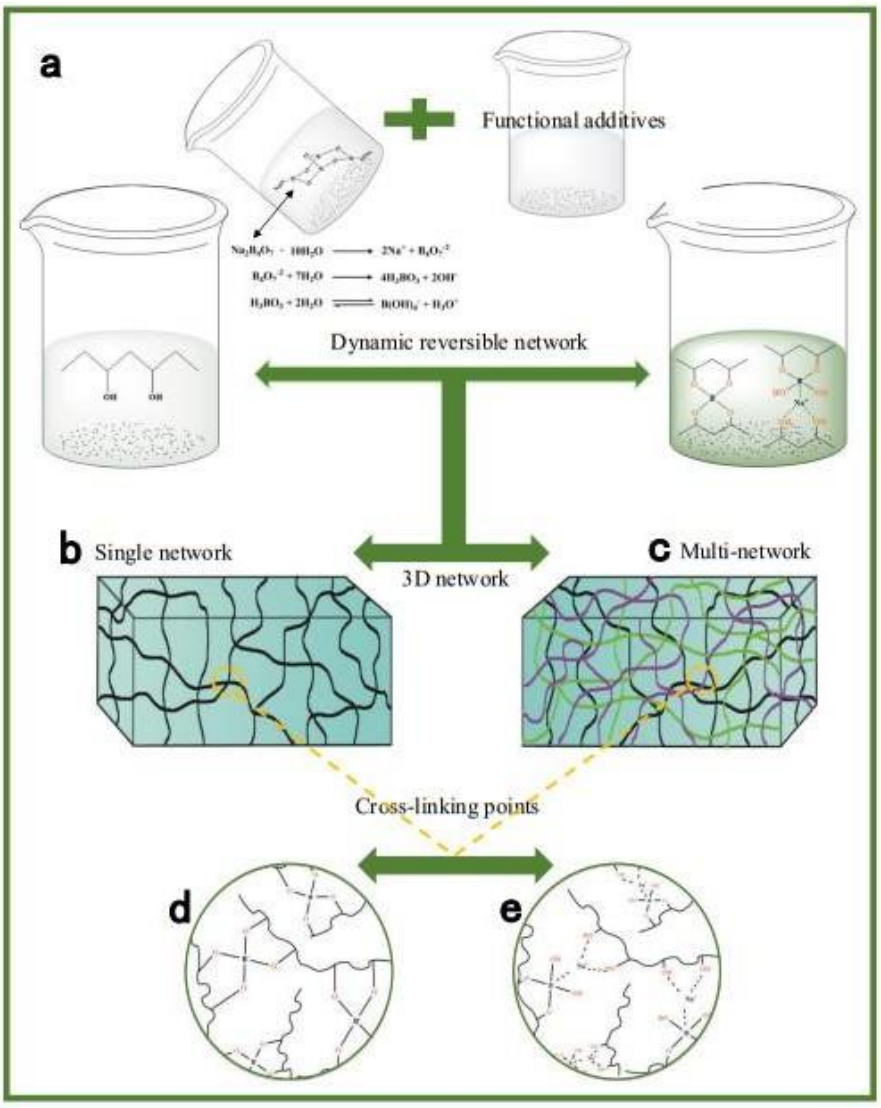


Fig. 1.8 Crosslinking Mechanism of Borax

Borax is a crosslinking agent that improves swelling properties, self-healing properties, and drug release. Mate et al. prepared Jhingan gum hydrogel cross-linked with borax and found a maximum swelling index of 2400%. Ding et al. prepared hydrogels based on cellulose nanofibers-polypyrrole, borax, and polyvinyl alcohol. The self-healing efficiency of the hydrogel was found to be 97% in air for 20 s and 87% underwater for 90 s, which indicated the excellent underwater self-healing ability of the hydrogel. Asnani et al. developed Portulaca

oleracea polysaccharide-alginate-borax hydrogel beads for targeted colon-specific delivery. Different concentrations of beads are prepared by the single and dual crosslinking method. Portulaca-Alginate single cross-linked beads and dual cross-linked beads are prepared by adding borax. Beads are loaded with 5-fluorouracil drug. In vivo drug release study they showed when the concentration of borax increases, drug release decreases and the drug release was about 32.0% - 89.9%.

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Chapter - 2
Literature Review

Thombare et al. prepared guar gum hydrogel using borax as a crosslinker for water purification [1]. Different concentrations of hydrogel are prepared by altering theconcentration of borax. In the swelling study, they showed 20% borax containing hydrogel showed maximum swelling according to increasing pH whereas 5% borax containing hydrogelshowed minimum swelling but when the borax concentration increases by 25%, swelling capacity decreases due to impermeable crosslinking, rise in osmotic pressure in the external solution due to abundance of unreacted borax. In SEM analysis borax cross-linked hydrogel showed a raptured and porous structure but the guar gum surface showed flakes. The porous structure can diffuse aqueous fluid in a polymer matrix leading to increased swelling capacity.Cross-linked gum exhibits better flocculation efficiency than raw guar gum. In a dye removal study with aniline blue, up to 94.30% decolorization was observed within 50-60 minutes in borax cross-linked hydrogel, so this formulation is effective as an adsorbent for water purification.

Matricardi et al. prepared scleroglucan-alginate–borax matrices for drug delivery [2]. This semi–IPN is loaded with myoglobin and different tablet formulations were prepared for targeted protein delivery. These tablets were characterized by drug release efficiency, swelling capacity, and SEM analysis. They performed drug release studies in different media i.e. water, SGF, and SIF. The drug release study showed 70% of drug release from scleroglucan/borax matrices in 24h while the alginate-borax matrix released the drug completely in 24h in both water and SGF media. In SIF media, the alginate-borax matrix shows a slower release rate than the scleroglucan-borax matrix because borax can prompt connectivity between the scleroglucan chain in matrices which creates a network that slowly leads to drug release. In the swelling study, they showed water uptake capacity decreases in the presence of borax. SEM analysis observed that the tablet surface rapidly swelled after immersion in water for 5 minutes but when immersed in an acidic medium reduced swelling, therefore intact surface. This study concluded that borax meets the requirement for sustained release tablets.

Asnani et al. developed Portulaca oleracea polysaccharide-alginate-borax hydrogel beads for targeted colon-specific delivery [3]. Different concentrations of beads are prepared by the single and dual crosslinking method. Portulaca-Alginate single cross-linked beads and dual cross- linked beads are prepared by adding borax. Beads are loaded with 5-fluorouracil. The beads were characterized using various techniques including drug entrapment efficiency, drug release study in vitro and in vivo, swelling study, FTIR analysis, and SEM study. The drug

entrapment efficiency was found to be 53–88% w/w in all formulations. In vivo drug release study they showed when the concentration of borax increases, drug release decreases. The optimum concentration of this formulation contains1% w/v borax which showed a drug release of about 89.9%. When the formulation contains 3% w/v borax, the drug releases about 32%. In the SEM study, they observed the surface of the beads was more wrinkled and rough with increasing the concentration of crosslinking. In the swelling study, they showed when the pH of the media increases the swelling also increases and dual cross-linked beads reduce swelling due to the presence of borax than single cross- linked beads. The in vitro drug release study was performed using rat caecal content media. They observed that 5% of the drug is released in the first 5h and the addition of rat caecal content media drug release increases due to the presence of microflora in this media which deteriorates the polysaccharide and raises the drug release. 80% of the drug was released at the end of 16h. This study concluded that dual cross-linked borax beads are efficiently used for the sustained release of drugs in the colon.

Liu et al. prepared fenugreek galactomannan-borax hydrogel as a retaining agent of water in agriculture [4]. Different hydrogel formulations are prepared by altering the concentration of polymer and borax. These hydrogels were characterized using various techniques including swelling index (hydrogel & mixture of hydrogel and soil), self-repairing ability, FTIR, XRD, SEM, and TGA. They found that hydrogels have self-repairing properties. In XRD analysis the peak intensity is lower in hydrogel than in polymer due to crosslinking with borax, hydroxyl groups of gum are consumed by borate ions. They showed that hydrogels have thermal stability in TGA analysis. In fenugreek galactomannan-borax hydrogel the absorption capacity decreases due to high concentration of ions present in the solution which decreases osmotic pressure between two phases (internal& external) which prevents the penetrating of water in matrices. When fenugreek galactomannan-borax hydrogel was introduced in soil they observed increased porosity and water-retaining capacity. They can conclude that this hydrogel is beneficial for plant growth and a significant water-retaining agent in agriculture.

Ch. Jamkhokai Mate et al. synthesized jhingan gum hydrogel cross-linked with borax for water purification by removal of the dye Remazol Brilliant Blue R (RBBR) [5]. Hydrogels are prepared by grafting the gum with acrylamide by microwave-assisted technique and then crosslinking with borax. These hydrogels are characterized by various techniques including

elemental analysis, FTIR, XRD, swelling capacity in different pH and temperature, dye removal efficiency, reusability capacity, and biodegradation study. Elemental analysis proved that grafting of the polymer due to nitrogen present in hydrogel which was not present in crude gum. In the XRD study, they showed that crosslinking with borax reduced crystallinity. When temperature increases swelling also increases due to bonds present between the monomer chain and cross-linked are breaking down leading to more penetrating water. They optimized that these hydrogels have excellent adsorption efficiency and that Freundlich isotherms are best for explaining the adsorption process. They revealed that these hydrogels have good reusability capacity. The dye removal efficiency was found to be 92.18% in the first cycle. In a biodegradation study, they observed these hydrogels are biodegradable and half-life was observed at 53.3 days. They conclude that this hydrogel was implemented for the removal of anionic RBBR dye for water purification.

Rezvan et al. synthesized curcumin-loaded polyvinyl alcohol-borax hydrogel for use as a wound dressing substance [6]. Different concentrations of hydrogels are prepared by altering the concentration of borax. The drug entrapment efficiency of hydrogels was found to be 89±1%. In a drug release study, they observed that when borax concentration decreases, drug release is increased. They conclude that this hydrogel was employed as wound dressing material.

Palungan et al. prepared (S-Nitrosoglutathione) loaded with borax cross-linked PVA- based carboxymethyl chitosan hydrogel for wound healing [7]. They prepared different concentrations of hydrogels by altering the concentration of borax, carboxymethyl chitosan, and S-Nitrosoglutathione, and PVA concentration remained the same in all formulations. These hydrogels were characterized using various techniques including FTIR, SEM, self-healing behavior of with or without drug loading hydrogel, pH, swelling index, drug loading efficiency & drug loading capacity, in vitro drug release study, stability study, etc. The SEM images showed that hydrogels have a more irregular porous structure. When the concentration of borax increases, the difference between molecular structures decreases, resulting in a more compact polymer network structure. In the self-healing study, the self-healing time increases according to increasing the concentration of borax because higher concentrations of borax have a more compact structure which requires more time for rejoining. For the identification of the mechanical properties of hydrogels, they observed that the tensile strain increases as the

concentration of borax increases. A higher concentration of borax produces more flexible hydrogel which is easily applied to the skin. They found the pH value of hydrogels was neutral, which increases the healing rate for wound healing. Borax leads to increasing both drug loading efficiency and drug loading capacity. The drug loading efficiency and drug loading capacity were found to be 90.61- 97.34% and 36.24%-38.94% respectively. In the drug release study, 25% of drugs were released first 12h, and within 24h, 30% of drugs were released. When more borax was added as a crosslinking agent the drug release tended to be reduced. They concluded that these hydrogels were used as wound dressing material.

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Chapter - 3
Polymer Profile

3.1. Tara Gum

Tara gum, also known as Peruvian carob, is a white or beige powder produced by milling the seed endosperm of the *Caesalpinia spinosa* tree, a species native to Peru and widely cultivated in China's Yunnan and Sichuan provinces, shown in Fig. 3.1. Its primary component is galactomannan polysaccharides, which feature a linear backbone of (1-4)-β-D-mannopyranose units linked by (1–6) bonds to α-D-galactopyranose units. Structurally and functionally, tara gum resembles guar and locust bean gums. It has a mannose-to-galactose ratio of 3:1[1-2].

3.1.1. Family: Leguminosae

3.1.2. Common Name: Peruvian Carob, Guaranga.

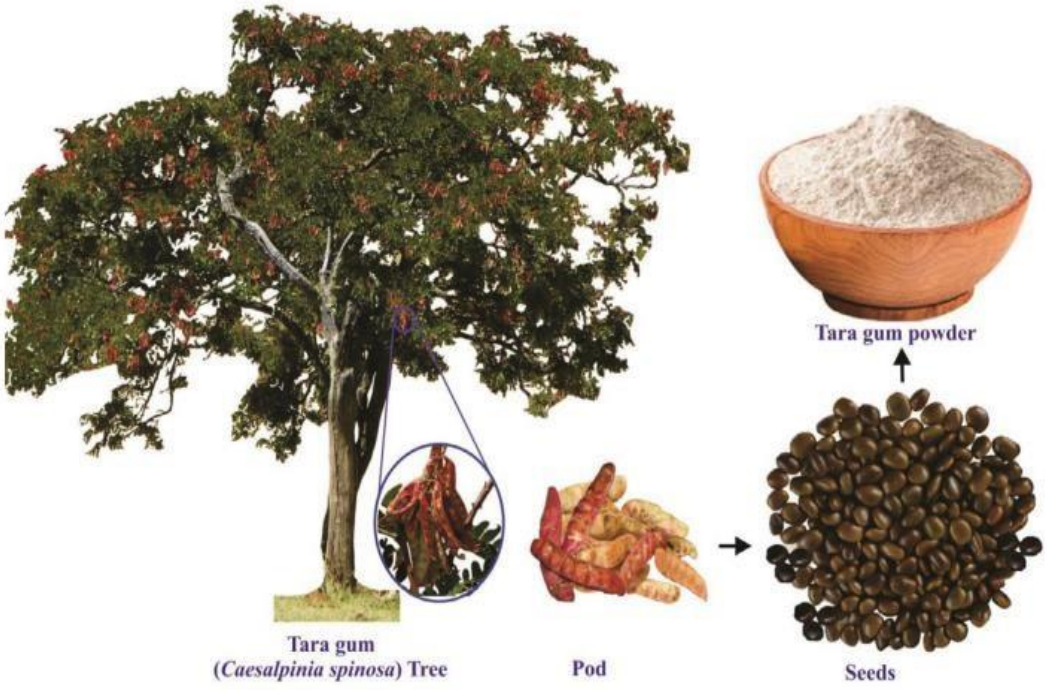

Fig. 3.1: Tara Gum Tree with Seeds (Reproduced from [3])

3.1.3. Structure

The chemical structure of borax shown in Fig. 3.2.

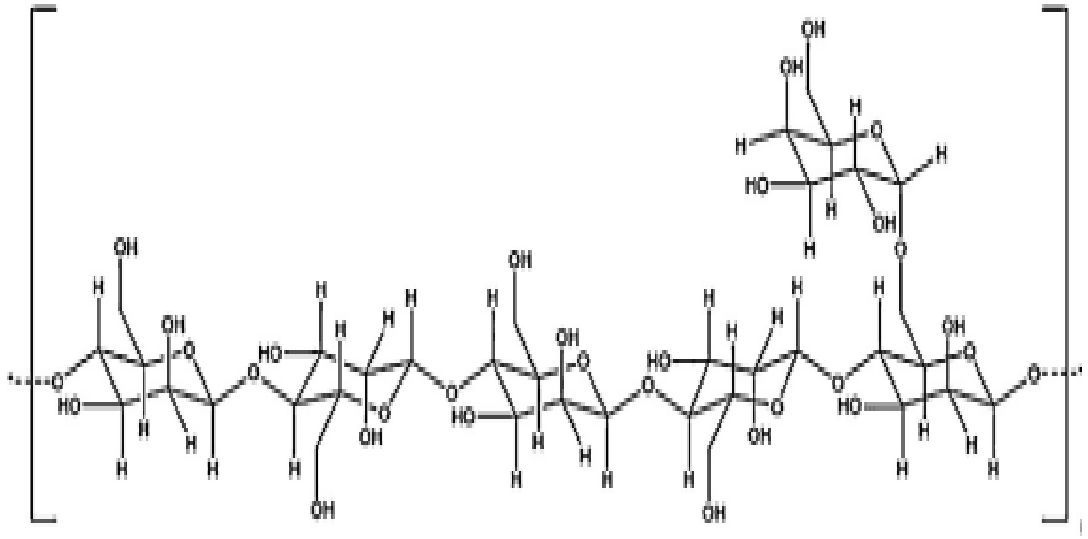

Fig. 3.2: Structure of Tara Gum (Reproduced from [4])

3.1.4. Physicochemical Properties

TG is almost soluble in water at room temperature and reaches about 75% of its maximum viscosity potential. When heated to 95°C and then cooled to 25°C, it forms opaque, tan-colored sols. These solutions (1% w/v) have viscosities ranging from 300 to 400 cps, depending on the quality of gum extraction. The viscosities remain stable across a wide pH range at any given shear rate. Tara sols exhibit pseudoplastic rheology. TG solutions quickly gel when cross-linked with specific metal ions. Borax, a well-known cross-linker for galactomannans, binds to cis-hydroxyl groups of either D-galactosyl or D-mannosyl moieties on different chains when the solution pH exceeds 9. Other cross-linkers include multivalent cations such as Chromium and Antimony (III). Gelation in TG solutions can also be induced by intermolecular association, which can be achieved by adding an excess of ethylene glycol or sucrose, or by the freeze-thaw process, as both methods reduce or remove available free water, increasing gum concentration and promoting interaction [3].

3.1.5. Toxicological Profile

The toxicological aspects of tara gum have been thoroughly investigated. It is free of acute and chronic toxic effects and is classified as Generally Recognized As Safe (GRAS). In a 90-day study, rats were fed diets containing 0%, 1%, 2%, or 5% tara gum. At the highest concentration (5%), both male and female rats exhibited reducedbody weight, while only males showed this effect at the 2% concentration. Additionally, there was an increase in blood urea nitrogen levels in rats given the 5% solution, although these levels remained within normal ranges. Other parameters such as hematology, urinalysis, and tissue examinations did not show significant differences from the control groups. Reproductive and teratogenicity studies were also conducted with various concentrations of the gum. The fetuses were examined and showed no signs of embryonic or teratogenic effects from tara gum consumption [3].

3.1.6. Application

- ❖ The gum is widely utilized as a thickener and stabilizer in the food industry.
- ❖ It also has wide applications in the food packaging industry as edible films.
- ❖ TG has also been used in the synthesis of superabsorbent hydrogels by grafting them with polyacrylic acid [3].

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Chapter – 4
Drug Profile

4.1. Introduction

Aceclofenac is a non-steroidal anti-inflammatory drug widely used torelieve pain and inflammation. Aceclofenac is a water-insoluble drug with greater permeability (log ¼ 2.170) and belongs to the family biopharmaceutics classification system (BCS) class II category. Aceclofenac is a non-selective potent inhibitor of both cyclooxygenase (COX)I and cyclooxygenase (COX)II but specific in COX-II inhibitor. COX-II enzymes are involved in prostaglandin production, which is responsible for inflammation and pain. Aceclofenac have a small "therapeutic window" that can manage the symptomatic condition of both types of arthritis (i.e osteo arthritis, rheumatoid arthritis), spondylitis, and another acute pain condition [1].

4.2. General Information of Aceclofenac

The basic information of aceclofenac shown in 4.1 [3].

Table 4.1: General Information of Aceclofenac

Name	Aceclofenac
Chemical Formula	$C_{16}H_{13}Cl_2NO_4$
Chemical Name (IUPAC)	2-[[2-[2-[(2,6-dichlorophenyl)amino] phenyl] acetyl] oxy] acetic acid.
Description	White to slightly yellowish crystalline powder
Category	Analgesic; anti-inflammatory
Molecular Weight	354.2
Melting point	149-153^{0}C
Plasma elimination half life	4h
Solubility	Insoluble in water, Soluble in pH 1.2, in pH 7.4
Storage	Store in well-closed, light-resistant containers

4.3. Chemical Structure [3]

The chemical structure of aceclofenac shown in Fig. 4.2.

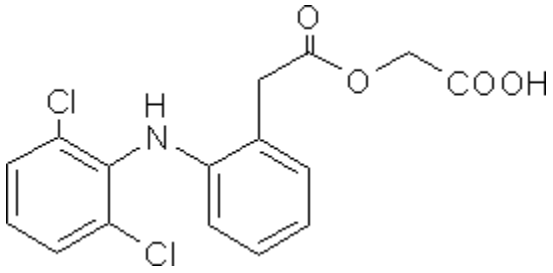

Fig. 4.2: Structure of Aceclofenac

4.4. Identification

A. Dissolve 50.0 mg in *methanol R* and dilute to 100.0 ml with the same solvent. Dilute 2.0ml of the solution to 50.0 ml with *methanol R*. Examined between 220 nm and 370 nm, the solution shows an absorption maximum at 275 nm. The specific absorbance at the absorption maximum is 320 to 350.

B. Infrared absorption spectrophotometry.

C. Dissolve about 10 mg in 10 ml of *alcohol R*. To 1 ml of the solution, add 0.2 ml of a mixture, prepared immediately before use, of equal volumes of a 6 g/l solution of *potassium ferricyanide R* and a 9 g/l solution of *ferric chloride R*. Allow to stand protected from light for 5 min. Add 3 ml of a 10.0 g/l solution of *hydrochloric acid R*. Allow to stand protected from light for 15 min. A blue colour develops and a precipitate is formed.

4.5. Mode of Action

The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins. The drugs inhibits synthesis of the inflammatory cytokines interleukin (IL)-1 and tumor necrosis factor and prostaglandin E_2 (PGE2) production. Effects on cell adhesion molecular from neurophils have also been noted. In vitro data indicate inhibition of cyclooxygenase (Cox)-1 and 2 by aceclofenac in whole blood assays, with selectivity for Cox-2 being evident [2-4].

4.6. Pharmacokinetics

Aceclofenac is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3h after an oral dose. The drug is highly protein bound (7.99%). The presence of food does alter the extent of absorption of aceclofenac but the absorption rate is reduced. Aceclofenac is metabolized to a major metabolite, 4'-hydroxyaceclofenac and to a number of other metabolites including 5-hydroxyaceclofenac, 4'-hydroxydiclofenac, diclofenac and 5- hydroxydiclofenac. Renal excretion is the main route of elimination of aceclofenac with70 to 80% of an administered dose found in the urine, mainly as the glucuronides of aceclofenac and its metabolites of each dose of aceclofenac, 20% is excreted in the feces [3].

4.7. Adverse Effects

Dyspepsia, Nausea, Vomiting, Diarrhea, Headache, Gastrointestinal irritation, GIT bleeding, Epigastric pain, Constipation, Dizziness, Vertigo [2-4].

4.8. Dosage and Administration

The usual dose of aceclofenac is 100 mg given twice daily by mouth, one tablet in the morning and one in the evening. There is no evidence that the dosage of aceclofenac needs to be modified in patients with mild renal impairment, but as with other NSAIDS caution should be exercised. Dose of aceclofenac is 200 mg once daily for sustained release formulation [3].

4.9. Co-administration with Other Drugs

Aceclofenac is co-administered with other drugs [3]:

- Aceclofenac+Paracetamol: This type of combination drug is used for antipyretic effects and to control inflammation and pain in conditions like rheumatoid arthritis, and osteoarthritis.
- Aceclofenac+Thiocolchicoside: This combination drug is used for muscle relaxation and pain relief.
- Aceclofenac+Rabeprazole: This combination drug is used for the treatment of gastrointestinal ulcers.

4.10. Uses

Aceclofenac has been used in the following areas of treatment widely [2-4].

- ❖ Osteoarthritis and rheumatoid arthritis
- ❖ Ankylosing spondylitis
- ❖ Dental pain
- ❖ Postoperative pain
- ❖ Gonalgia (knee pain)

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Chapter – 5
Aims and Objectives

Aim and Objectives

The objective of this project work is to develop and evaluate borax cross-linked tara gum hydrogel matrix tablets loaded with aceclofenac for extending its release for a prolonged period. The aim is to reduce the dosing frequency of aceclofenac by preparing a sustained release formulation by using natural polymer, as the biological half-life of aceclofenac is very short.

The specific objectives of the research work are-

- Preparation of the standard curve of aceclofenac in different mediums (pH 1.2 and pH 7.4 buffer system).
- Synthesis of borax cross-linked tara gum hydrogel.
- Determining the swelling study and flow properties of the hydrogel powder.
- Performing FTIR of the hydrogel powder to confirm the crosslinking reaction betweenTG and borax.
- Preparation of matrix tablets using the hydrogel powder in different concentration loading with aceclofenac.
- Determination of the hardness, thickness, diameter, and weight variation of tablets.
- Performing FTIR, XRD, and DSC for the compatibility of the drug (AFN) in the matrix.
- Determination of the morphological evaluation of the matrices.
- Determination of the drug content of the prepared tablets.
- Performing the *in-vitro* drug release study of the tablets.
- Performing drug release kinetics study.

Chapter – 6
Analytical Monitoring of Drug

6.1. UV Spectrophotometric Method Development and Validation for the Estimation of Aceclofenac

6.1.1 Preparation of 0.1 (N) HCl Solution (Acid Solution of pH 1.2)

A total volume of 8.5 ml HCl was carefully measured and added to a volumetric flask initially containing 200 ml of distilled water. Further distilled water was added to reach a total volume of 1000 ml. pH meter (Orion 2-Star, Thermo Scientific, US) was used to adjust the pH of the resulting solution at pH 1.2.

6.1.2 Preparation of 0.2 (M) Tri Sodium Phosphate Dodecahydrate (TSP)

76 grams of TSP were measured and placed into a volumetric flask already containing 500 ml of distilled water. Additional distilled water was added to reach a total volume of 1000 ml in the flask.

6.1.3 Preparation of Modified Phosphate Buffer (MPB) Solution of pH 7.4

A solution consisting of 200 ml of 0.2 molarity tri-sodium orthophosphate dodecahydrate was introduced into a 700 ml acid solution with a pH of 1.2 to get 900 ml solution with pH 7.4.

6.1.4. Determination of λ_{max} of Aceclofenac in Acid Solution of pH 1.2

10 mg of Aceclofenac were dissolved in 10 milliliters of pH 1.2 solution, and the volume was increased to 100 milliliters using an acid solution with a pH of 1.2. From this solution, 2 milliliters were taken and diluted to 25 milliliters using an acid solution with a pH of 1.2. The resulting solution was then scanned from 200 to 400 nanometers using a UV Spectrophotometer (UV 2450, Shimadzu, Japan). UV-spectrum of aceclofenac in acid solutionof pH 1.2 shown in Fig. 6.1.

6.1.5. Determination of λ_{max} of Aceclofenac in Phosphate Buffer (PB) Solution of pH 7.4

10 mg of Aceclofenac were dissolved in 10 milliliters of pH 7.4 solution, and the volume was increased to 100 milliliters using a phosphate solution with a pH of 7.4. From this solution, 2 milliliters were taken and diluted to 25 milliliters using an phosphate buffer solution with a pH of 7.4. The resulting solution was then scanned from 200 to 400 nanometers using a UV Spectrophotometer (UV 2450, Shimadzu, Japan). UV-spectrum of aceclofenac in PB solution of pH 1.2 shown in Fig. 6.2.

6.1.6. Method Development for the Estimation of Aceclofenac in Acid Solution of pH 1.2

Precisely, 3 milligrams of Aceclofenac were dissolved in 300 milliliters of pH 1.2 solution in a 250 milliliter volumetric flask. Subsequently, aliquots of 1, 2, 3, 4, 5, milliliters were withdrawn from this stock solution and diluted up to 10 milliliters with acid solution. Absorbance measurements were conducted at 243 nanometers for each dilution. The observations were recorded three times (Table 6.1). Fig. 6.1 shows the calibration curve of aceclofenac in pH 1.2 solution.

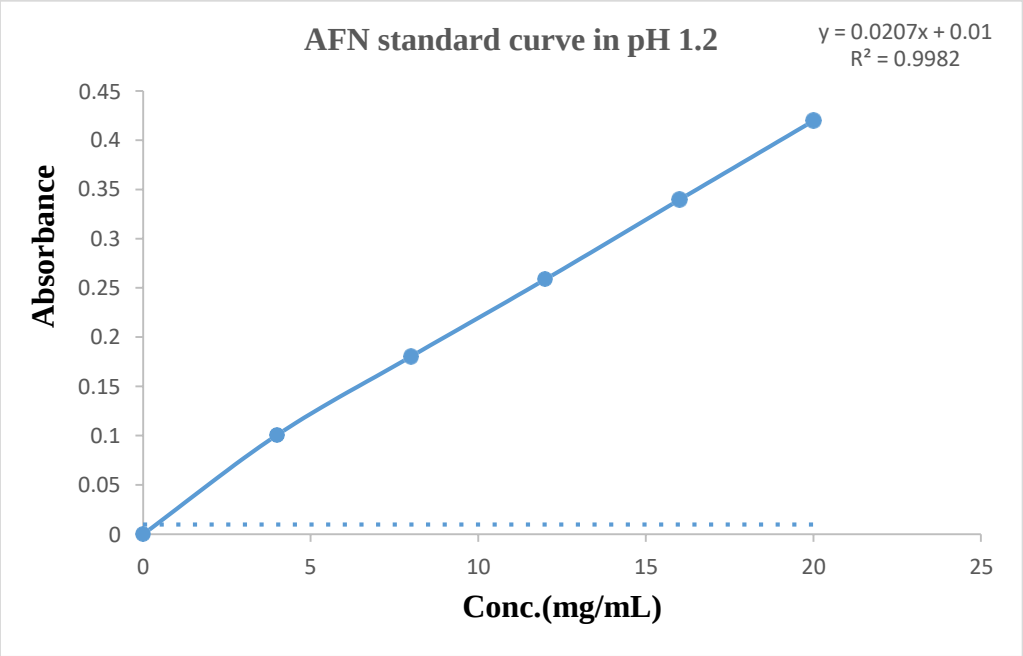

Fig. 6.1: Aceclofenac Standard Curve in pH 1.2

Table 6.1: Absorbance of Aceclofenac in pH 1.2

Conc.(mg /mL)	Abs.1	Abs.2	Abs.3	Abs.4	Abs.5	Abs.6	Abs.7	Abs.8	Average Abs.
0	0	0	0	0	0	0	0	0	0
4	0.112	0.109	0.107	0.108	0.093	0.095	0.094	0.09	0.101
8	0.182	0.179	0.182	0.185	0.174	0.184	0.184	0.176	0.180
12	0.244	0.249	0.247	0.25	0.272	0.28	0.266	0.264	0.259
16	0.33	0.34	0.314	0.314	0.35	0.352	0.357	0.362	0.339
20	0.381	0.384	0.388	0.383	0.453	0.463	0.451	0.458	0.420

6.1.7. Method Development for the Estimation of Aceclofenac in PB Solution of pH 7.4

Precisely, 3 milligrams of Aceclofenac were dissolved in 300 milliliters of pH 7.4 solution in a 250 milliliter volumetric flask. Subsequently, aliquots of 1, 2, 3, 4, and 5 milliliters were withdrawn from this stock solution and diluted up to 10 milliliters with acid solution. Absorbance measurements were conducted at 243 nanometers for each dilution. The observations were recorded three times (Table 6.2). Fig. 6.2 shows the calibration curve of aceclofenac in pH 7.4 solution.

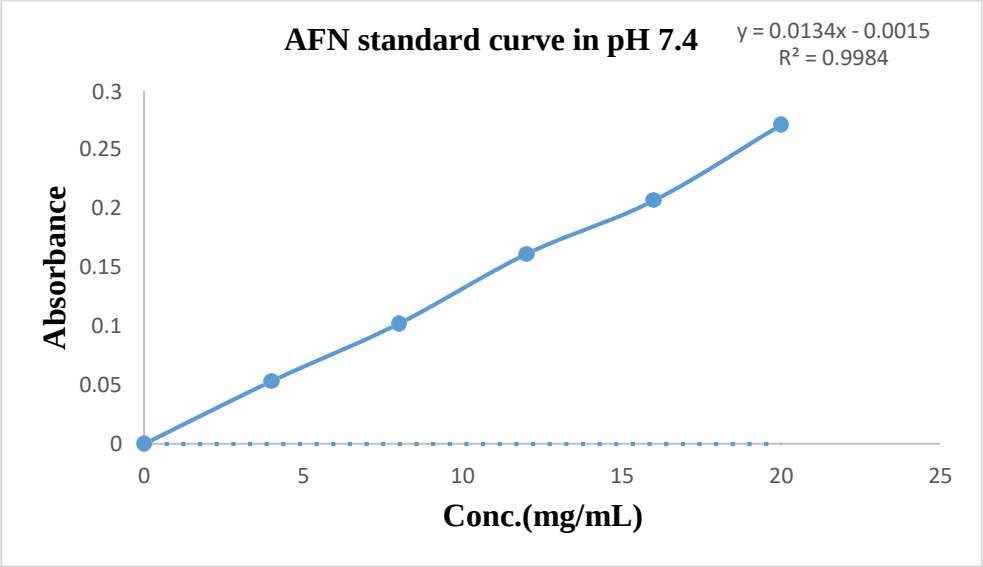

Fig. 6.2: Aceclofenac Standard Curve in pH 7.4

Table 6.2: Absorbance of Aceclofenac in pH 7.4

Conc. (mg /ml)	Abs. 1	Abs. 2	Abs. 3	Abs. 4	Abs. 5	Abs. 6	Abs. 7	Abs. 8	Average Abs.
0	0	0	0	0	0	0	0	0	0
4	0.065	0.055	0.057	0.062	0.048	0.047	0.045	0.047	0.053
8	0.121	0.129	0.127	0.121	0.08	0.081	0.078	0.08	0.102
12	0.207	0.203	0.207	0.197	0.121	0.118	0.118	0.119	0.161
16	0.26	0.251	0.259	0.253	0.161	0.155	0.159	0.155	0.206
20	0.324	0.33	0.333	0.331	0.215	0.21	0.213	0.211	0.270

Chapter – 7
Materials and Methods

7.1. Materials

Aceclofenac was purchased from SARAL CHEMTECH LLP, India, and Tara gum was purchased from IAMPURE Ingredients (Chennai, India). Analytical grade Tri Sodium orthophosphate dodecahydrate and talc were obtained from Loba Chemie Pvt. Ltd. India. Analytical grade Borax was purchased from Sisco Research Laboratories Pvt. Ltd. (Mumbai, India). Analytical grade HCl and methanol were purchased from Merck Life Science Private Limited and in-house distilled water was used.

Methods

7.2. Preparation of Hydrogel

At first required quantity of TG powder (Table 7.1) was sprinkled in ice-cold deionized water and kept overnight in a magnetic stirrer at 840 rpm to prepare a homogenous solution of the gum. A clear solution of borax was prepared by mixing the required amount of borax (Table 7.1) into deionized water using a magnetic stirrer at 640 rpm. The borax solution was then slowly added to the TG dispersion under constant stirring at 1000 rpm and kept there for 1h to effect a complete cross-link reaction. The formed hydrogel was then washed with distilled water to remove excess unreacted borax. Then the hydrogel was dried at 40-45℃ in a dryer overnight, following which it was ground to # 250 mesh and kept for further studies. The composition of hydrogel powder is shown in Table 7.1 and the preparation method of hydrogel powder is shown in Fig 7.1[1,2].

Table 7.1: - Composition of Hydrogel Powder

Formulation Code	Concentration of TG (% w/v)	Concentration of Borax (% w/v)
H1	1%	3%
H2	1%	6%
H3	1%	9%
H4	1%	12%
H5	1%	15%
H6	1%	18%
H7	0.5%	18%
H8	0.75%	18%
H9	1.25%	18%
H10	1.5%	18%

Fig. 7.1: - Preparation of Hydrogel Powder

Characterization of Hydrogel

7.3. Swelling Study: The swelling study of hydrogel powders was performed in the USP type II dissolution apparatus. Exactly 0.1 gm of hydrogel powders (Wo, initial weight) were poured into a tea bag and then dipped in a dissolution solution. The swelling study was performed in a buffer solution (pH 1.2) for initial 2h and then performed in a buffer solution (pH 7.4) for the next 6h. The hydrogel powder containing tea bag was taken out at proper time intervals (same as dissolution sampling time), gently blotted them with tissue paper to remove excess surface water and weighed accurately (Wt, swelling weight during sampling intervals) in an electronic balance (SPT 200, Prime, India). The percentage of the swelling index can be determined by the following Eq. (1) [1,2].

$$\%\text{Swelling} = \frac{(W_t - W_0)}{W_0} \times 100 \quad \text{.....(1)}$$

where, Wt= Swelling weight during sampling intervals

Wo= Initial weight

Flow Properties

7.4. Bulk Density- 1gm of hydrogel powder was weighed properly from each formulation and transferred in a measuring cylinder (100 ml). Powder must be free from accumulation. Powder volume is noted without compacting. Bulk density was calculated in gm/ml by using the following Eq. (2) [3].

$$\text{Bulk Density} = Powder\ weight/Bulk\ volume \quad \text{.....(2)}$$

7.5.Tapped Density- 1gm of hydrogel powder was weighed properly from each formulation and was transferred in a measuring cylinder (100 ml). Then measuring cylinder was tapped from a height of approximately 2.5 cm onto a hard surface 100 times. The volumeof the powder is noted. Tapped density was determined in gm/ml by using the following Eq. (3) [3].

$$\text{Tapped Density} = Powder\ weight/Tapped\ volume \quad \text{.....(3)}$$

7.6. Carr's Index- The compressibility index of the hydrogel powder is determined by using Carr's index which was developed by Aulton and Wells in 1988. Carr's index is used to obtain the rate of packed down. Carr's index was calculated by using the following Eq.(4) [4].

$$\text{Carr's Index (\%)} = \frac{(TD - BD)}{TD} \times 100 \quad \text{.....(4)}$$

where, TD = Tapped Density, BD = Bulk Density

7.7. Hausner Ratio- The Hausner's ratio of the hydrogel powder is used to determine the powder material's flowability and it was calculated by using the following Eq. (5) [4].

$$\text{Hausner's ratio} = TD/BD \quad \text{.....(5)}$$

Where, TD = Tapped Density, BD = Bulk Density

7.8.Angle of Repose- The funnel method was employed for the determination of the angle of repose of the powder [4]. 1gm of hydrogel powder was weighed and poured into a funnel. The funnel's height was set up in a way that the funnel's tip just touched the powder's apex. Hydrogel powder should be freely flowing through the surface of the funnel. The angle of repose was measured by the following Eq. (6).

$$\tan\theta = {}^{h}/_{r} \ldots\ldots\ldots (6)$$

Where, h = Height of the powder, r = Radius of the powder

7.9. Preparation of Hydrogel Tablet

The composition of hydrogel tablets is shown in Table 7.2. At first required quantities of hydrogel powder (Table 7.2) and aceclofenac (previously pass-through #250 mesh) were taken and blended manually. Distilled water was added to the mixture and triturate verywell until a cohesive, moist mass was formed. The moist mass was then passed through #18 mesh and dried in a hot air oven at 45-50ºC for 15 minutes. The dried granules then were passed through #22 mesh and were dried in a hot air oven at 45-50ºC for 20 minutes. The completely dried granules were mixed with talc as a lubricant, blended, and then compressed using a 6 mmflat-faced punch in a 10-station rotary tablet machine (RIMEK, Karnavai Engineering Ltd., India).

Table 7.2: Composition of Tablets

Formulation Code	**Amount of TG (mg)**	**Batches of Hydrogel (TG-B)**	**Amount of Hydrogel (TG-B) (mg)**	**Amount of Drug (AFN) (mg)**	**Talc (mg)**	**Total Weight of Matrix (mg) (TG-B/TG+AFC +Talc)**	**Hardness (Kg/cm^2)**
Pure TG matrix	197	_	_	100	3	300	4
F1	_	H1	197	100	3	300	4
F2	_	H2	197	100	3	300	4
F3	_	H3	197	100	3	300	4
F4	_	H4	197	100	3	300	4
F5	_	H5	197	100	3	300	4
F6	_	H6	197	100	3	300	4
F7	_	H7	197	100	3	300	4
F8	_	H8	197	100	3	300	4
F9	_	H9	197	100	3	300	4
F10	_	H10	197	100	3	300	4

Characterization Study

7.10. Fourier Transform Infrared (FTIR) Study- FTIR spectra of AFN and AFN-loaded matrix tablet, TG, and TG-Borax hydrogel powder were carried out in an FTIR spectrophotometer (RX 1, Perkin Elmer, UK) at wavelength 4000–400 cm^{-1}. Samples were prepared by mixing with potassium bromide and changing them into pellets by a hydraulic press [1, 2].

7.11. X-ray Diffraction (XRD) Analysis- The X-ray diffraction of AFN and AFN-loaded matrix tablets was determined by using an X-ray diffractometer (D8, Bruker, Germany). This study was done by maintaining the following parameters: Diffraction angle (2θ) 10– 80° at scan speed 5°/min, current 30 mA, and voltage 45Kv [1, 2].

7.12. Differential Scanning Colorimetry (DSC) Analysis- The DSC thermograms of AFN and AFN-loaded matrix tablets were performed in a differential scanning calorimeter (Pyris Diamond TG/ DTA, Perkin Elmer, Singapore), calibrated regarding indium. Samples were prepared by heating over the range of 30–400°C with a constant nitrogen atmosphere at 10°C/min in an air-tight container of aluminium [1, 2].

7.13. Morphological Evaluation of Tablets- The morphological evaluation of tablets was performed at pH 1.2 for 2h and then at pH 7.4 for 6h in a petri dish. At first pH 1.2 buffer solution was added in a petri dish and a tablet is immersed in the media. After 2h, the pH 1.2 buffer solution was pipetted out and removed from the petri dish. Then pH 7.4 buffer solution was added to that petri dish and the morphological evaluation was continued for 6h. The images of tablets were taken at an interval of every 1h [2].

7.14. Drug Content- One tablet was finely powdered using a pestle and mortar. The amount of the tablet powder equivalent to 10 mg aceclofenac was weighed accurately and taken in a 250 ml volumetric flask. Then, 10 ml methanol was added in a volumetric flask and shaken well, until tablet powder was dissolved. 250 ml volume was to be made up with buffer solution (pH 7.4). Then, this volumetric flask was kept in a shaker overnight. The solution was then filtered and 2 ml of this solution was taken and diluted to 10 ml with buffer solution pH 7.4. Drug content was obtained by UV spectrophotometer (UV-1700, Shimadzu, Japan) at 272 nm using a calibration curve of standard solutions [5].

7.15. In-Vitro Drug Release Study- The *in-vitro* release of drug from the matrix of tablet was carried out in a USP type II dissolution apparatus (TDT-06P, Electrolab, India) at 37˚C, 75 rpm as per Indian Pharmacopoeia, 2010. A hydrogel matrix tablet was immersed in a vessel containing 700 ml of an acidic buffer solution (pH 1.2) and it was continued for 2h. In between, 0.2(M), 200 ml tri-sodium orthophosphate dodecahydrate solution was prepared and mixed in a vessel to increase the pH to 7.4 and dissolution was run in 900 ml of this buffer solution for the next 10h. 10 ml aliquots were pipetted out from this dissolution media at proper time intervals and refilled the dissolution media with the same amount of fresh respective buffer solution during the entire dissolution study. The absorbance was done by using a UV–Vis spectrophotometer (UV 2450, Shimadzu, Japan) at 272 nm. The amount of AFN release at various time intervals was measured from the standard curve plotted at the respective dissolution medium. The *in-vitro* drug release study of each formulation (F1-F10) was conducted in triplicate [1, 2].

7.16. AFN Release Mechanism- The kinetics and mechanism of AFN release from the matrices can be determined by power law Eq. (7) [1, 2].

$$M_t / M_\alpha = kt^n \qquad \text{…….(7)}$$

Where, $\frac{M^t}{M^\alpha}$ = percentage of AFN dissolution, k = Constant release rate, n = Diffusional exponent which indicates that mechanism of transport.

For a matrix tablet, n = 0.5 indicates Fickian diffusion, 1.0 > n > 0.5 shows non-Fickian transport or anamolous transport, n = 1.0 indicates case II transport and n >1.0 shows the mechanism of super case II transport.

References:

1. Mukherjee K, Dutta P, Giri TK, Al3+/Ca2+ cross-linked hydrogel matrix tablet of etherified tara gum for sustained delivery of tramadol hydrochloride in gastrointestinal milieu, International Journal of Biological Macromolecules, 232 (2023) 123448.
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5. Dinda SC, Mukherjee B, Samanta A, Gum odina: a novel matrix forming material for sustained drug delivery, Oriental Pharmacy and Experimental Medicine, 11 (2011) 131-136.

Chapter – 8
Results and Discussions

8.1. Synthesis and Characterization of Hydrogel

Tara gum is a neutral galactomannan polysaccharide [1, 2]. The chemical structure of TG consists of many OH groups which can take part in different crosslinking reactions. Borax is an effective crosslinker that can cross-link with the active hydroxyl groups of TG and quickly form hydrogels [3]. The TG-B hydrogels can enhance the physical properties of the polymer. Borax reacts with water to produce boric acid and sodium hydroxide which then dissociates to release borate ions [4]. The borate ion ($B(OH)_4^-$) can react with the mannose chain of TG by creating bonds between units of two diols and one borate ion to produce TG-B hydrogel [5]. This crosslinking mechanism is known as borate/di-diol complexation as shown in Fig. 8.1.

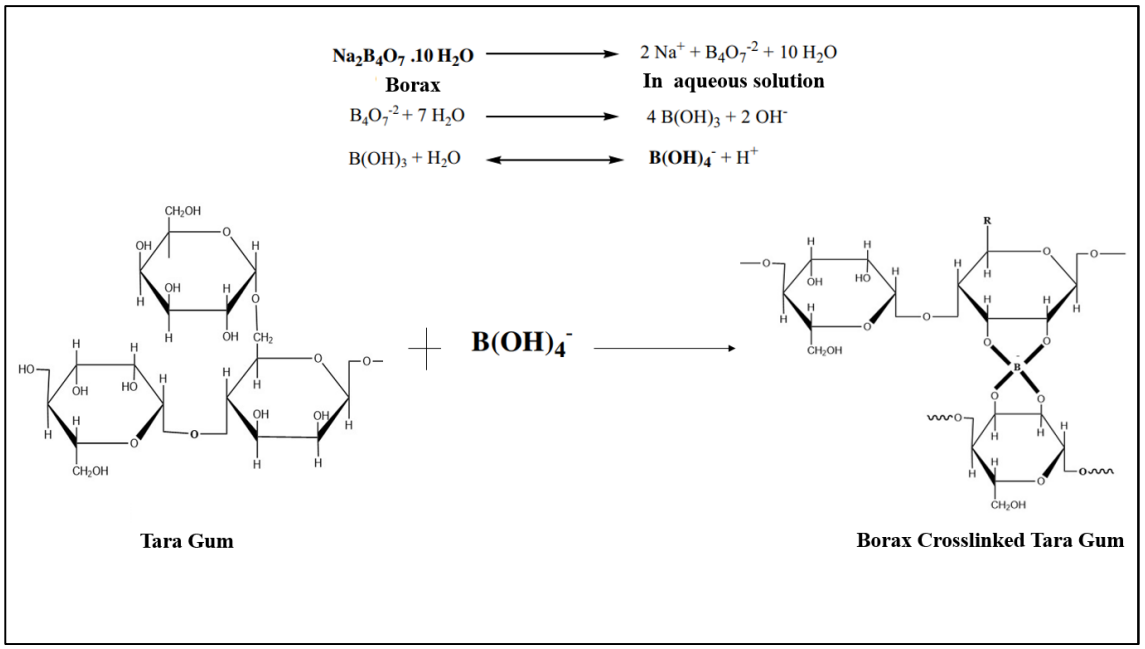

Fig. 8.1: Schematic Diagram of Borate/Di-Diol Complexation

The FTIR study confirmed the crosslinking reaction between TG and borax. The FTIRspectrum of TG and hydrogel (TG-B) are shown in Fig. 8.2. A broad peak was observed at 3300 cm^{-1} in the spectrum of TG which represents the –OH stretching vibration that occurred in the hydroxyl group of TG. An absorption band due to the symmetrical stretching of CH is displayed at 2918 cm^{-1} in the spectrum of TG. The peak appeared at 1643 cm^{-1} because of thebending vibration of OH in water. A peak observed at 1022 cm^{-1} due to bending occurred in the CH_2-O-CH_2 bond. The peak at 812 cm^{-1} and 870 cm^{-1} represents the presence of the units of α-D-galactopyranose and β-D-galactopyranose. In previous literature, similar IR spectrumsof TG have also been reported [1]. The IR spectrum of TG-B hydrogels also had almost similar spectrums to that of

the TG spectrum. However, the FTIR spectra of TG at 3300 cm^{-1} were slightly shifted towards a large wavelength in the spectrum of hydrogel (TG-B), being displayed at 3363 cm^{-1} due to the -OH stretching vibration of the hydrogel's molecule. Additionally, a new peak was observed at 780 cm^{-1} which is due to the addition of borax (symmetrical stretching of tetrahedral borax) [3, 5]. A similar range of 750-900 cm^{-1} was also stated by other researchers [3]. The upward shift of the spectrum due to the –OH stretching vibration and the appearance of additional peaks at 780 cm^{-1} indicated the successful cross-link of the borax with TG.

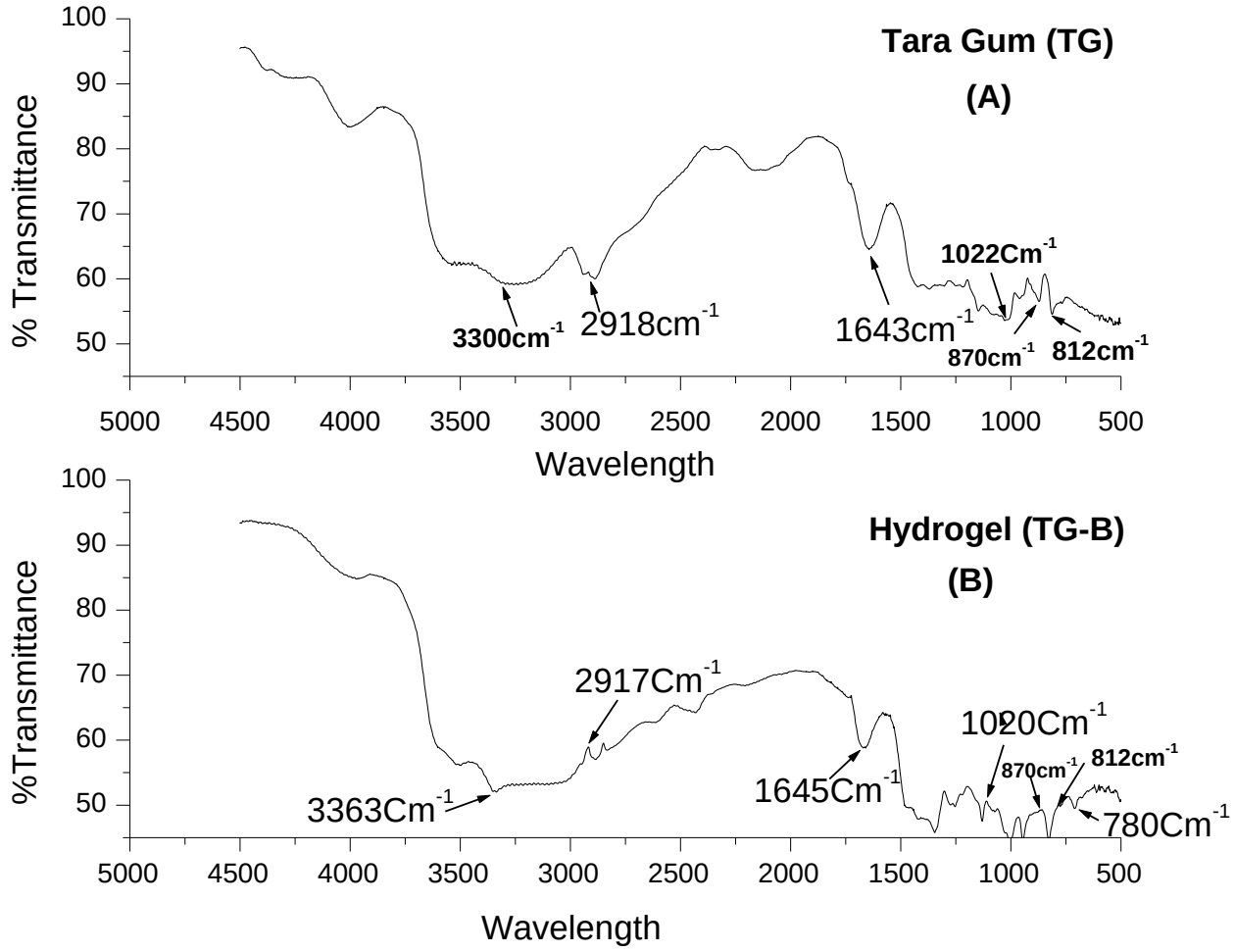

Fig. 8.2: FTIR Spectra of (A) TG and (B) TG-B Hydrogel

The TG-B hydrogel was characterized by its flow properties. The Hausner's ratio, Carr's index, and angle of repose of the TG-B hydrogel were determined. The results are shown in Table 8.1. Friction or cohesion between particles (internally) is determined by the value of the angle of repose (θ). If the values show a high angle of repose, the powder nature is cohesive and if the

value is low, the powder nature is noncohesive [6, 7]. All hydrogel powders except H6, H7, and H10 show the angle of repose (11.17-20.55) indicating excellent flow properties. H6 has good flow properties as they show the value of the angle of repose is 26.56. The angle of repose of H7 and H10 shows (31.52- 34.59) indicates passable flow properties. Carr's index of all hydrogel powder (H1-H10) shows excellent to good flow properties as the value indicates (5.26-13.63). All hydrogel powder (H1-H10) show Hausner's ratio (1.05- 1.15) indicating lower friction (interparticle) and excellent to good flowability.

Table 8.1: Flow Properties of Hydrogel Powder (n=3, mean ± SD).

Formulation	Carr's Index	Hausner's Ratio	Angle of Repose
H1	6.25 ± 0.5	1.06 ± 0.3	13.24 ± 0.7
H2	11.11 ± 0.7	1.12 ± 1.2	11.17 ± 0.3
H3	10 ± 1.2	1.11 ± 1.6	17.28 ± 0.5
H4	10 ± 1.2	1.11 ± 1.4	15.29 ± 2.1
H5	11.11 ± 0.8	1.12 ± 2.1	18.90 ± 1.0
H6	6.25 ± 0.4	1.06 ± 0.6	26.56 ± 0.5
H7	5.26 ± 2.2	1.05 ± 1.3	34.59 ± 2.3
H8	11.11 ± 1.4	1.12 ± 1.2	18.09 ± 1.8
H9	10 ± 1.3	1.11 ± 0.4	20.55 ± 1.3
H10	13.63 ± 0.6	1.57 ± 0.4	31.52 ± 1.2

The swelling study of TG-B hydrogel powder (H1-H6) and pure TG was performed at pH 1.2 for 2h and then at pH 7.4 for 6h and the results of the study are given in Fig. 8.3 and Table 8.2. The swelling ratio of TG powder was 1223.8% at 0.5h, 1456.15% at 2h, 1874.55% at 4h, and 2102.55% at 6h. The swelling index of TG-B hydrogel powder declined significantly with the increase in the concentration of borax in the TG-B hydrogel powder composition. The swelling ratio of TG-B hydrogel powder declined in the following manner: after 0.5h- H1 (1160.5%)> H2 (983.8%)> H3 (891.5%)> H4 (662.55%)> H5 (540.02%)> H6 (363.3%), after 2h- H1 (1186%)> H2 (998.45%)> H3 (946.5%)> H4 (706.05%)> H5 (567.53%)> H6 (406.7%), after 4h- H1 (1283%)> H2 (1159.55%)> H3 (1034.5%)> H4 (659.05)> H5 (584.45%)> H6 (449.5%), after 6h- H1 (1451.5%)> H2 (1300.6%)> H3 (1190%)> H4 (644.05%)> H5 (632.6%)> H6 (506.4%).

TG is a hydrophilic polymer network that contains a lot of number of hydroxyl groups in its polymer chains. These hydroxyl groups produce hydrogen bonding with the hydroxyl groups of the dissolution media and have great affinity with each other. When borax is cross-linked with polymer reduces the OH group of the polymer which is responsible for water absorption. Borax produces covalent bonds between TG molecules which create a more rigid and dense network. This decreases the ability of water to absorb and swell. Polymer chains become more compact and entangled which reduces the space available for penetrating water molecules and swelling of the gum. Augmentation of the concentration of borax in the TG-B hydrogel composition decreases the ability of gum to absorb water and decreases the swelling ratio. H6 shows the lowest swelling ratio as it contains 18% of the borax in the TG-B hydrogel composition and the pure TG shows the highest swelling ratio as it does not contain borax as a crosslinking agent. Zhou et al. reported similar results from 1-ethyl-(3-3-dimethylaminopropyl) carbodiimide (EDC) cross-linked Gelatin/Hyaluronic Acid Complexed hydrogels [8]. The author observed that the swelling ratio decreased with the increase in the concentration of EDC as a chemical crosslinker due to the decrease in the hydrophilic group.

TG-B hydrogel powder (H7-H10) was prepared by keeping the concentration of borax constant and the TG concentration was altered (0.5%-1.5%). The swelling ratio of TG-B hydrogel powder increased significantly with the increase in the concentration of TG in the TG-B hydrogel powder composition shown in Fig. 8.4 and Table 8.2. The swelling ratio of TG-B hydrogel powder increased in the following way: after 0.5h- H7 (82.2%) < H8 (250.2%) < H9 (550.5%) < H10 (720.65%), after2h- H7 (134.35%) < H8 (299.45%) < H9 (592%) < H10 (742.65%), after 4h- H7 (190.25%) <H8 (362.25%) < H9 (651.85%) < H10 (799.25%), after 6h- H7 (254%) < H8 (430.25%) < H9(720.3%) < H10 (851%).

With an increase in the concentration of TG in the TG-B hydrogel composition, the swelling index of this hydrogel powder becomes greater. The OH group of the TG increases with increasing the concentration of TG resulting in increasing hydrophilicity of the hydrogel, allowing it to absorb more water and leading to increased swelling. When TG concentration rises, the hydrophilicity of the TG-B powder increases, which increases the water absorption and consequently the swelling of the hydrogel powder. H7 shows the lowest swelling ratio as it contains 0.5% of the TG in the TG-B hydrogel composition and H10 shows the highest swelling ratio as it contains 1.5% of the TG in the composition of TG-B hydrogel. Similar results have been reported by Mukherjee et al. [2]. They reported that the augmentation of TG concentration increases the swelling percentage of the semi-IPN hydrogel matrices.

Table 8.2: Percentage Swelling of TG-B Hydrogel Powder (n=3, mean ± SD).

Hydrogel Code	Percentage Swelling			
	0.5h	**2h**	**4h**	**6h**
Pure TG	1223.8 ± 0.7	1456.15 ± 2.05	1874.55 ± 1.25	2102.55 ± 4.45
H1	1160.5 ± 0.5	1186 ± 6	1283 ± 3	1451.5 ± 6.5
H2	983.8 ± 0.7	998.45 ± 0.35	1159.55 ± 1.45	1300.6 ± 0.5
H3	891.5 ± 3.5	946.5 ± 1.5	1034.5 ± 3.5	1190 ± 2
H4	662.55 ± 3	706.05 ± 3.05	659.05 ± 1.05	644.05 ± 2.05
H5	540.02 ± 4.7	567.53 ± 0.2	584.45 ± 1.8	632.6 ± 0.8
H6	363.3 ± 0.5	406.7 ± 2	449.5 ± 3	506.4 ± 1
H7	82.2 ± 0.2	134.35 ± 0.15	190.25 ± 0.25	254 ± 2
H8	250.2 ± 0.1	299.45 ± 0.15	362.25 ± 0.25	430.25 ± 0.25
H9	550.5 ± 0.1	592 ± 2	651.85 ± 0.65	720.3 ± 0.2
H10	720.65 ± 0.15	742.65 ± 0.15	799.25 ± 0.25	851 ± 2

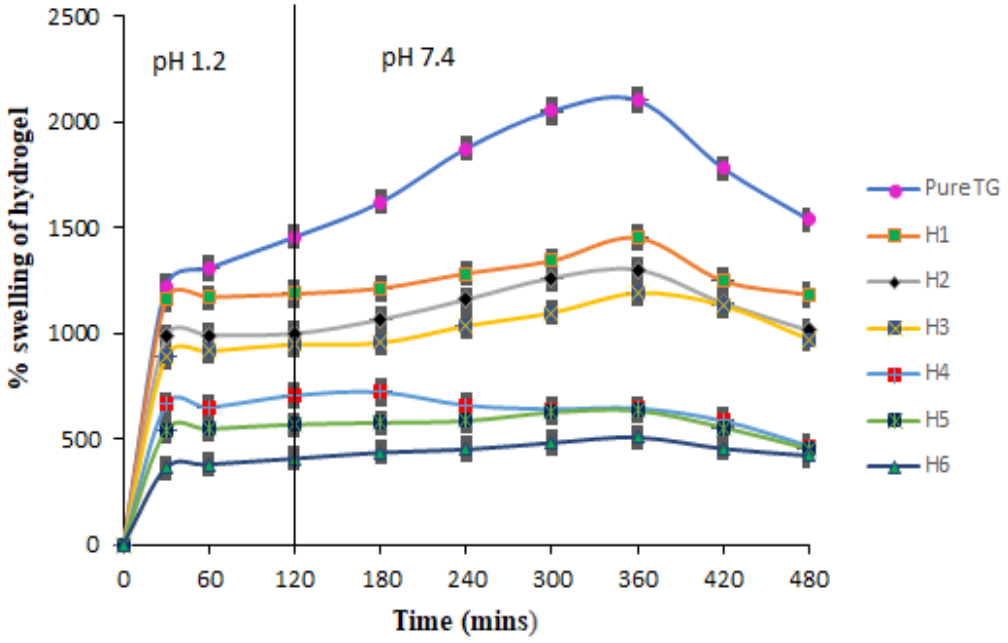

Fig. 8.3: Dynamic Swelling Profiles of Pure TG and Hydrogel Powder (H1-H6) in pH 1.2 for 2h Followed by pH 7.4 upto 8h.

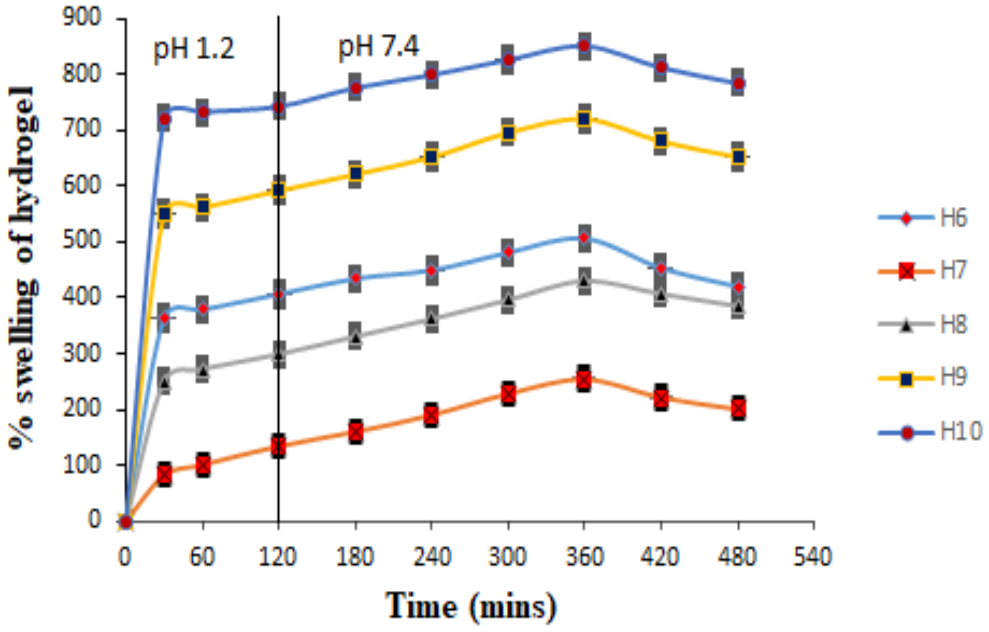

Fig. 8.4: Dynamic Swelling Profiles of Hydrogel Powder (H6-H10) in pH 1.2 for 2h Followed by pH 7.4 upto 8h.

8.2. Compatibility of AFN in Matrix

FTIR, XRD, and DSC studies assessed the compatibility of drug excipients. The FTIR spectrum of AFN and AFN-loaded matrix tablet are shown in Fig. 8.5. The IR spectrum of AFN showed a principle peak due to aromatic C-H stretching at 3029 cm^{-1} and a peak due to aliphatic C-H stretching at 2937 cm^{-1}. Subsequently, a band was observed at 1718 cm^{-1} due to C-O stretching. In 1772 cm^{-1} a sharp band was shown due to carboxylic acid C-O stretching. A band at 3320 cm^{-1} owing to N-H rocking (secondary) vibration. Jana et al. reported the same absorption peaks are present in AFN in their project work [9]. The IR spectrum of the AFN-loaded hydrogel tablet showed peaks at almost similar wave numbers that the pure AFN showed. This result confirmed the compatibility of AFN in hydrogel tablets.

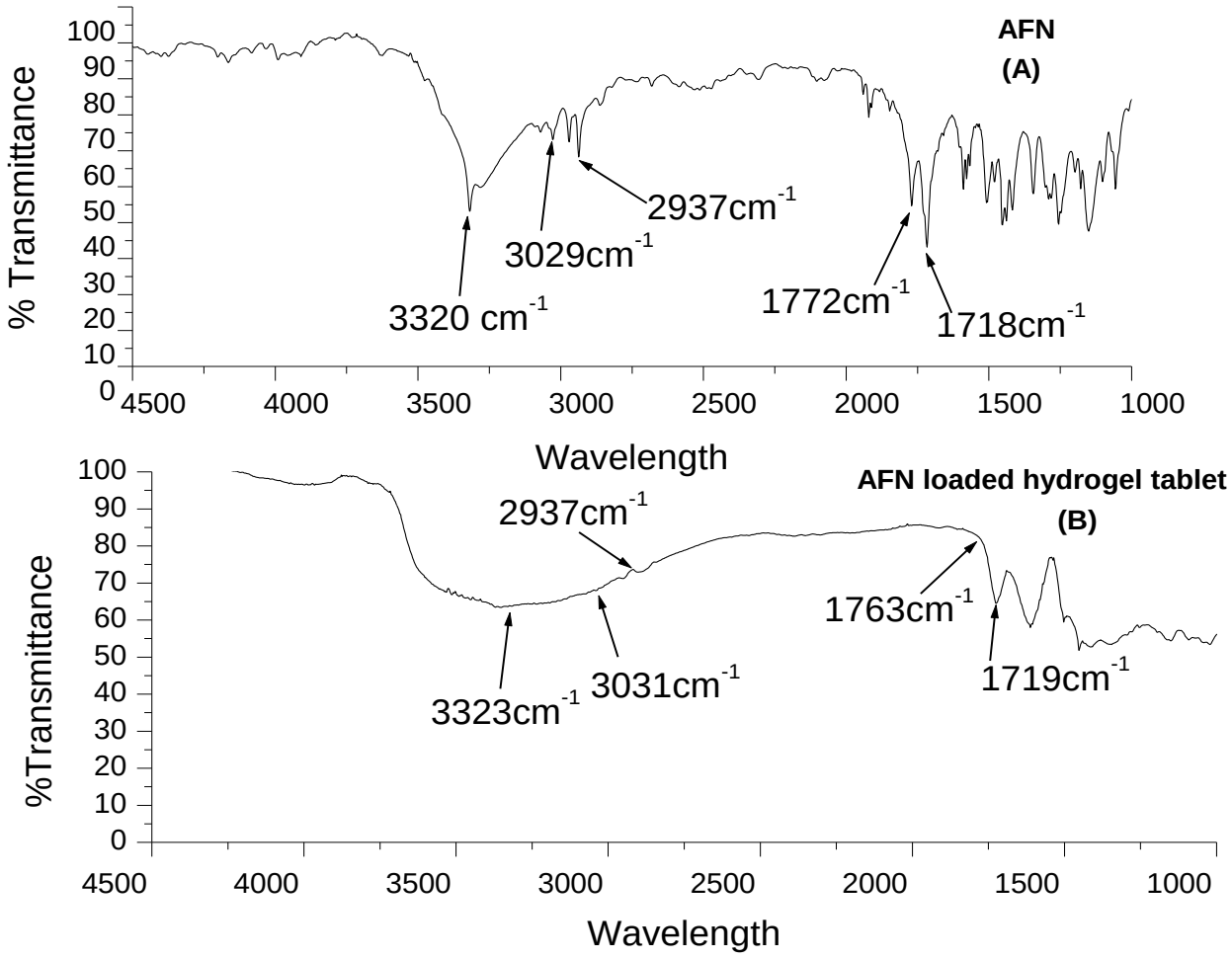

Fig. 8.5 FTIR Spectra of (A) AFN and (B) AFN-loaded Hydrogel Tablet

XRD studies were done to precisely know the state of AFN in the hydrogel matrix. The X-ray diffraction of AFN and AFN-loaded hydrogel tablet powdered are shown in Fig. 8.6. The XRD pattern of AFN showed reflections at 18.52^0, 19.34^0, 22.10^0, 23.58^0, 24.54^0 2θ indicating crystalline characteristics of pure AFN. The intensities of peaks are completely absent at 2θ values in AFN-loaded hydrogel tablets which can indicate drug was present in an amorphous state [9].

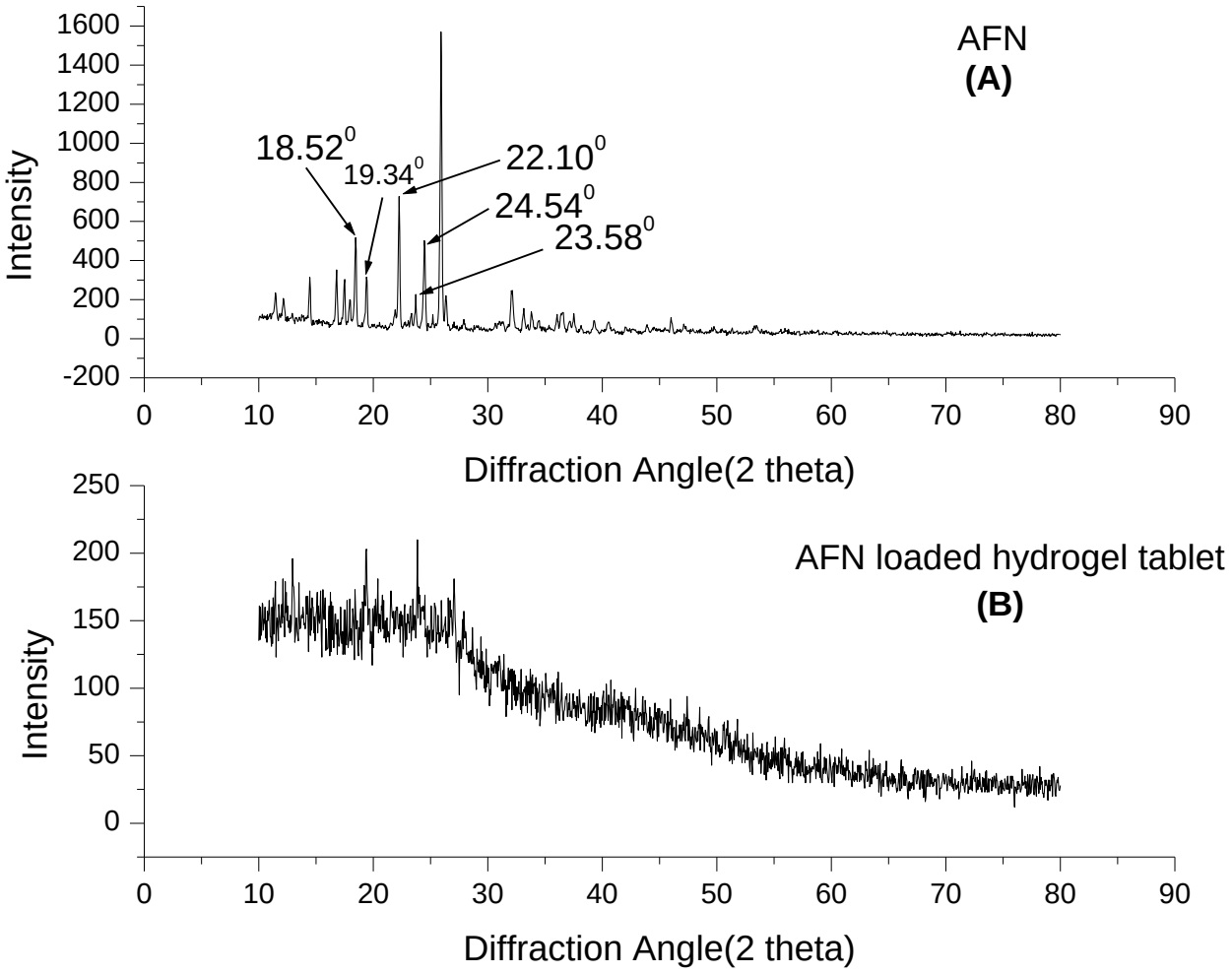

Fig. 8.6: XRD Patterns of (A) AFN and (B) AFN loaded Hydrogel Tablet

DSC study was done to know the physical state of the AFN in the matrix of hydrogel tablet. The DSC thermogram of AFN (pure) and AFN-loaded hydrogel tablets is shown in Fig. 8.7. A sharp endothermic peak was observed at 152.77 ^{0}C which represents the melting transition point of the drug (AFN). The DSC thermogram of the AFN-loaded hydrogel tablet did not show any peak. The absence of a peak represents the drug (AFN) transformation to an amorphous state during the preparation of the matrix tablet [9].

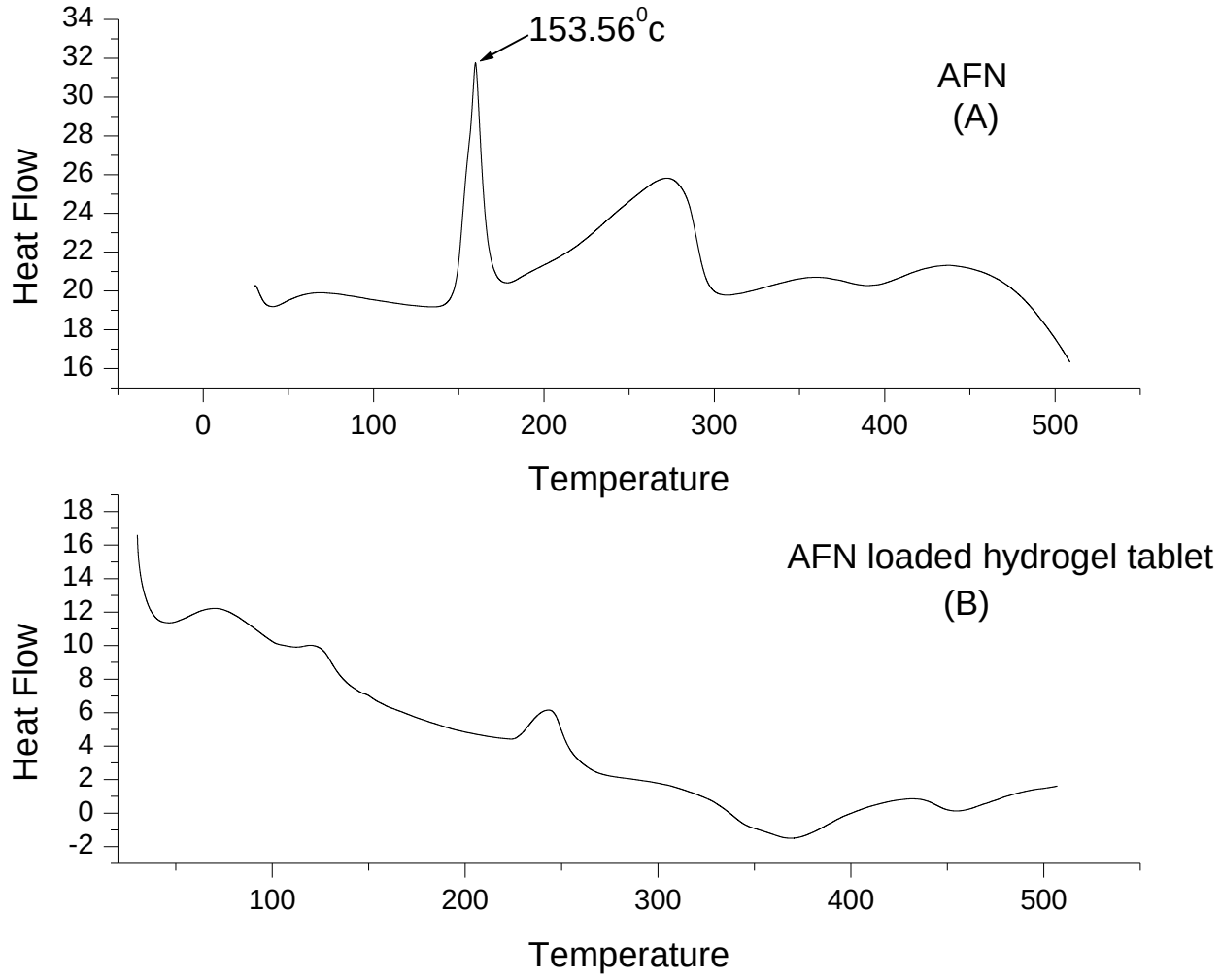

Fig. 8.7: DSC Thermograms of (A) AFN and (B) AFN loaded Hydrogel Tablet

The study of the morphological evaluation of hydrogel tablet (F1-F6) was performed at pH 1.2 for 2h and then at pH 7.4 for 6h. The results of the study of the morphological evaluation of hydrogel tablet (F1-F6) are shown in Fig. 8.8.

From the figure, we can see that increase in the concentration of borax in the TG-B hydrogel composition produces a rigid and stable matrix which swells less and retains its morphological structure for a prolonged period of time. Increase in the concentration of borax increases the cross-linked density and imparts rigidity to the matrix. Thus the matrix remains intact and stable for greater period of time. Matrix F6 is more stable than matrix F1. Similar results have been reported by Liu et al. [10]. They reported that the resistance of chemical or physical crosslinking hindered the dilution of the matrices, resulting in a decrease in the swelling index.

TG-B hydrogel matrix (F7-F10) was prepared by keeping the concentration of borax constant and the TG concentration was changed. The gel strength surrounding the matrix layer decreased with the increase in the concentration of TG in the hydrogel composition. The images of the study are given in Fig 8.8.

From, the figure, we can see that increase in the concentration of TG in the TG-B hydrogel composition increases the swelling of the matrix. Increase in the swelling results in increased erosion of the matrix. This decreases the rigidity, stability and intactness of the matrix. The matrix F10 is less rigid and intact than the matrix F7. Similar results have been reported by Mukherjee et al. [2]. They reported that the augmentation of TG concentration increases the swelling percentageof the semi-IPN hydrogel matrices.

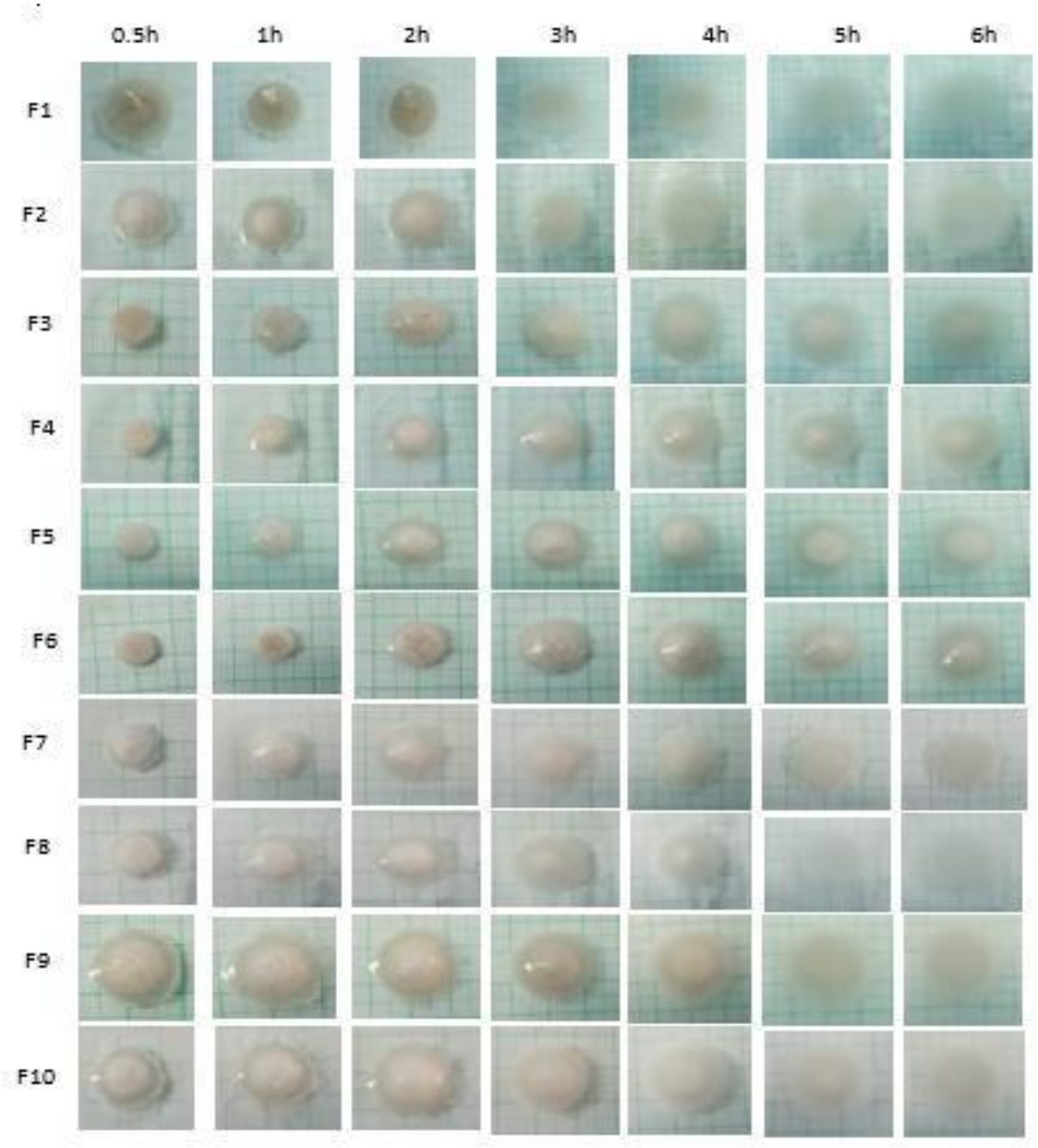

Fig. 8.8: Photo Images of Hydrogel Tablet (F1-F10) Taken at 0.5h, 2h, 4h and 6h Time Interval

The *in-vitro* release of AFN from the matrix tablet was performed at pH 1.2 for 2h and then at pH 7.4 for 6h. The study of AFN dissolution was performed from the tablet matrices prepared with TG only and cross-linked with various percent of borax (F1-F6) and the results of the study are given in Fig 8.9 and Table 8.3. AFN release form TG matrix was 5.62% at 0.5h, 8.62 % at 2h, 63.23% at 4h, and 95.03% at 6h. AFN release from TG-B hydrogel declined significantly with the increase in the concentration of borax in the TG-B hydrogel composition. The AFN release from TG-B hydrogel matrix declined in the following manner:after 0.5h- F1 (4.11%)> F2 (3.26%)> F3 (2.81%)> F4 (2.09%)> F5 (1.20%)> F6 (0.82%), after 2h- F1 (5.60)> F2 (4.16%)> F3 (3.35%)> F4 (2.90%)> F5 (2.04%)> F6 (1.27%), after 4h- F1(60.59%)> F2 (55.28%)> F3 (42.85%)> F4 (38.03%)> F5 (32.34%)> F6 (30.94%), after 6h- F1 (90.61%)> F2 (87.27%)> F3 (72.09%)> F4 (61.66%)> F5 (42.87%)> F6 (38.36%).

TG is a hydrophilic polymer when it contact with water it swells because of the relaxation of the polymer chain and stress generated by infiltrating water. Consequently, it results in the formation of a thick, viscous polymer layer with weak mechanical strength by the entanglement of the polymer chain around the surface of the tablet matrices. Gradually, the dilution of the thick viscous layer occurred and erosion or dissolution of polymer from the surface of the matrix takes place. The AFN present inside the matrix is solubilized and diffused in the dissolution media by the dissolution of the polymer. When borax is cross-linked with the OH group of polymers, the polymer's chain movement is hindered as a result the development of rigid viscous layer around the surface of the matrix tablet. Augmentation of the concentration of borax in the TG-B hydrogel composition increases the cross-link density, which increases the gel strength of the hydrogel and macromolecularly reduces the mesh size, which results in a decrease in diffusion of the drug. Consequently, a reduction in the release of AFN was observed. F6 shows the slowest release of AFN from the matrix as it contains 18% of the borax in the TG-B hydrogel and pure TG matrix shows the fastest release of AFN from the matrix as it does not contain borax as a crosslinker. Mukherjee et al. [1] reported that the resistance of crosslinking hindered the dilution of the matrices, resulting in a decrease in swelling and, thus the drug release was decreased.

TG-B hydrogel matrix (F7-F10) was prepared by keeping the concentration of borax constant and the TG concentration was changed (0.5%-1.5%). The AFN release from hydrogel tablets increased with the increase in the concentration of TG in the hydrogel composition. The results of the study are given in Fig 8.10 and Table 8.3. The AFN release from the matrices increased

in the following manner: after 0.5h- F7 (0.66%)< F8 (0.70)< F9 (4.72)< F10 (24.32), after 2h- F7 (0.95%)< F8 (1.06%)< F9 (6.79%)< F10 (34.04%), after 4h- F7 (20.07%)< F8 (22.62%)< F9 (34.52%)< F10 (64.86%), after 6h- F7 (28.06%)< F8 (30.22%)< F9 (44.33%)< F10 (87.20%).

With an increase in the concentration of TG in the TG-B hydrogel composition, the drug release from the matrices becomes greater. The OH group of the TG makes it more hydrophilic, absorbing more water and promoting swelling and drug release. F7 shows the slowest release of AFN from the matrix as it contains 0.5% of TG in the TG-B hydrogel and F10 shows the fastest release of AFN from the matrix as it contains 1.5% of TG in the TG-B hydrogel composition. Similar results have been reported by Shaikh et al. [11]. They reported that the augmentation of guar gum concentration increases the release of the drug rate.

Table 8.3: Percentage AFN Release of Hydrogel Matrix at 0.5h, 2h, 4h and 6h Time Interval (n=3, mean ± SD).

Formulation Code	**Percentage AFN Release**			
	0.5h	**2h**	**4h**	**6h**
Pure TG Matrix	5.62 ± 1.2	8.62 ± 3.2	63.23 ± 1.2	95.034 ± 2.3
F1	4.11 ± 1.5	5.60 ± 1.2	60.59 ± 3.2	90.61 ± 1.2
F2	3.26 ± 1.2	4.16 ± 1.3	55.28 ± 1.4	87.27 ± 1.5
F3	2.81 ± 1.0	3.35 ± 1.3	42.85 ± 2.2	72.09 ± 2.2
F4	2.09 ± 0.7	2.90 ± 0.5	38.03 ± 2.2	61.66 ± 1.3
F5	1.20 ± 0.4	2.04 ± 0.2	32.34 ± 1.2	42.87 ± 1.1
F6	0.82 ± 0.4	1.27 ± 0.4	30.94 ± 1.1	38.36 ± 1.3
F7	0.66 ± 0.2	0.95 ± 0.1	20.07 ± 0.9	28.06 ± 1.3
F8	0.70 ± 0.2	1.06 ± 0.4	22.62 ± 0.7	30.22 ± 1.1
F9	4.72 ± 0.1	6.79 ± 0.4	34.52 ± 0.8	44.33 ± 1.1
F10	24.32 ± 0.4	34.04 ± 0.8	64.86 ± 1.2	87.20 ± 1.4

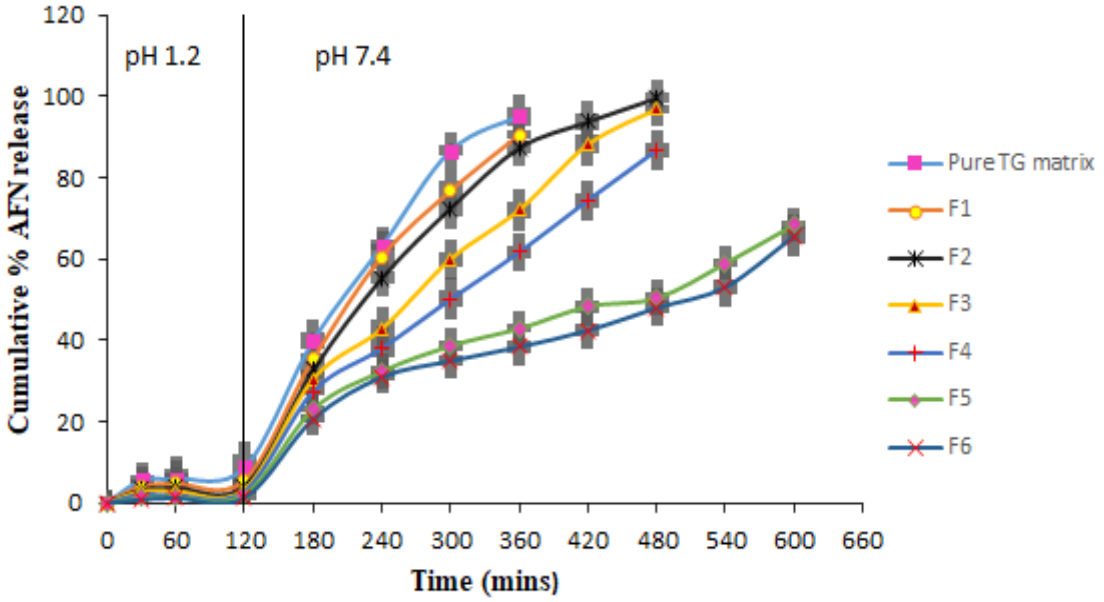

Fig. 8.9: Release Profiles of AFN From Pure TG Matrix and Hydrogel Matrix Tablet (F1-F6) in Dissolution Media

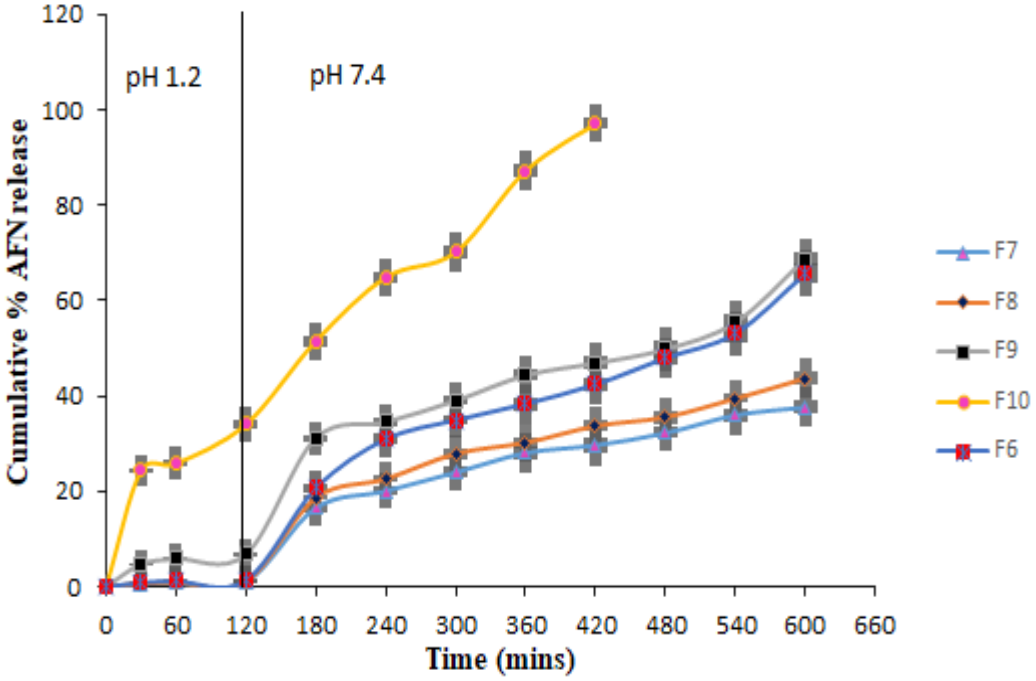

Fig. 8.10: Release Profiles of AFN From Hydrogel Matrix Tablet (F6-F10) in Dissolution Media

The AFN release from matrices is followed by the power law equation. Table 8.4 illustrates the AFN release mechanism from the matrices. The AFN release from hydrogel matrices followed Zero order kinetics which indicates that AFN release is constant per unit time but the rate is independent of the AFN concentration in the hydrogel tablet [12]. The AFN release from the hydrogel matrices (F1-F8) followed the super case II mechanism (r^2 values 0.74-0.87) as indicated by the release exponent (n) values was found to be $n > 1.0$. This indicates the erosion or mobility of the polymer chain determined the AFN release mechanism. A similar observation has been reported in the vitamin B12 release mechanism from chemically cross-linked microparticles [13]. The AFN release from the pure TG matrices and hydrogel matrices (F9) followed the non-fickian or anomalous transport mechanism (r^2 values of pure TG matrix is 0.66 and F9 is 0.89) as indicated by the release exponent (n) values were found to be $0.5 < n < 1.0$. This indicates that both diffusion and swelling are responsible for the controlled release of AFN from the hydrogel matrices. As the gum concentration increases the swelling increases. The swelling of the matrices enhanced the entrance of the dissolution fluid into the matrices and permitted the diffusion of AFN through the hydrogel matrices.

Table 8.4: Release Kinetics of AFN from Hydrogel Matrices

Formulation Code	Zero Order	First Order	Release Exponent (n)	Co-relation Coefficient (r^2)
Pure TG Matrix	0.955	0.858	0.953	0.66
F1	0.954	0.873	1.289	0.74
F2	0.958	0.894	1.360	0.722
F3	0.978	0.825	1.474	0.780
F4	0.980	0.897	1.579	0.797
F5	0.960	0.967	1.602	0.887
F6	0.959	0.955	1.697	0.874
F7	0.933	0.963	1.624	0.869
F8	0.934	0.966	1.635	0.871
F9	0.937	0.948	0.9789	0.898
F10	0.989	0.840	0.3981	0.841

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Chapter – 9
Summary and Conclusion

9.1. Summary

TG-B hydrogel is prepared by crosslinking Tara gum with borax which could be employed to develop a sustained-release matrix tablet. TG-B hydrogel was synthesized by dispersion of Tara gum in ice-cold deionized water and kept overnight in a magnetic stirrer at 840 rpm to prepare a homogenous solution of the gum. Then the borax solution was slowly added to the TG dispersion under constant stirring at 1000 rpm and kept there for 1h to effect a complete cross-link reaction. The formed hydrogel was washed with distilled water to remove excess unreacted borax. Then the hydrogel was dried at 40-45℃ in a dryer overnight, following which it was ground to # 250 mesh. The TG-B hydrogels can enhance the physical properties of the polymer. Borax reacts with water to produce boric acid and sodium hydroxide which then dissociates to release borate ions. The borate ion ($B(OH)_4^-$) can react with the mannose chain of TG by creating bonds between units of two diols and one borate ion to produce TG-B hydrogel.

The TG-B hydrogel was characterized by its flow properties. The Hausner's ratio, Carr's index, and angle of repose of the TG-B hydrogel were determined. All hydrogel powders except H6, H7, and H10 show the angle of repose (11.17-20.55) indicating excellent flow properties. H6 has good flow properties as they show the value of the angle of repose is 26.56. The angle of repose of H7 and H10 shows (31.52- 34.59) indicates passable flow properties. Carr's index of all hydrogel powder (H1-H10) shows excellent to good flow properties as the value indicates (5.26-13.63). All hydrogel powder (H1-H10) show Hausner's ratio (1.05- 1.15) indicating lower friction (interparticle) and excellent to good flowability.

The crosslinking reaction between TG and borax was confirmed by the FTIR study. The IR spectrum of TG-B hydrogels also had almost similar spectrums to that of the TG spectrum. However, the FTIR spectra of TG at 3300 cm^{-1} were slightly shifted towards a large wavelength in the spectrum of hydrogel (TG-B), being displayed at 3363 cm^{-1} due to the -OH stretching vibration of the hydrogel's molecule.

The swelling index of TG-B hydrogel powder declined significantly with the increase in the concentration of borax in the TG-B hydrogel powder composition. TG is a hydrophilic polymer network that contains a lot of number of hydroxyl groups in its polymer chains. When borax is cross-linked with polymer reduces the OH group of the polymer which is responsible for water absorption. Borax produces covalent bonds between TG molecules which create a more rigid

and dense network which decreases water absorption ability. Polymer chains become more compact and entangled which reduces the space available for penetrating water molecules and swelling of the gum. H6 shows the lowest swelling ratio as it contains 18% of the borax in the TG-B hydrogel composition and the pure TG shows the highest swelling ratioas it does not contain borax as a crosslinking agent. The swelling ratio of TG-B hydrogel powder increased significantly with the increase in the concentration of TG in the TG-B hydrogel powder composition. With an increase in the concentration of TG in the TG-B hydrogel composition, the swelling index of this hydrogel powder becomes greater. The OH group of the TG increases with increasing the concentration of TG resulting in increasing hydrophilicity of the hydrogel, allowing it to absorb more water and leading to increased swelling. H7 shows the lowest swelling ratio as it contains 0.5% of the TG in the TG-B hydrogel composition and H10 shows the highest swelling ratio as it contains 1.5% of the TGin the composition of TG-B hydrogel.

After the characterization of borax cross-linked hydrogel powder, matrix tablets were prepared using this hydrogel powder with aceclofenac and blended this mixture manually. Distilled water was added to the mixture and triturate very well until a cohesive, moist mass was formed. The moist mass was then passed through #18 mesh and dried in a hot air oven at 45-50ºC for 15 minutes. The dried granules then were passed through #22 mesh and were dried in a hot air oven at 45-50ºC for 20 minutes. The completely dried granules were mixed with talc as a lubricant, blended, and then compressed using a 6 mm flat-faced punch in a 10-station rotary tablet machine. Drug content was determined by spectrophotometric analysis. The size, hardness, morphological evaluation of tablets, and *in-vitro* release of AFN from matrix tablets and release kinetics of matrices were determined.

FTIR, XRD, and DSC studies assessed the compatibility of drug excipients. The IR spectrum of the AFN-loaded hydrogel tablet showed peaks at almost similar wave numbers that the pure AFN showed. This result confirmed the compatibility of AFN in hydrogel tablets. XRD studies were done to precisely know the state of AFN in the hydrogel matrix. The intensities of peaks of AFN are completely absent at 2θ values in AFN-loaded hydrogel tablets which can indicate drug was present in an amorphous state. DSC study was done to know the physical state of the AFN in the matrix of hydrogel tablet. The DSC thermogram of the AFN-loaded hydrogel tablet did not show any peak. The absence of a peak represents the drug (AFN) transformation to an amorphous state during the preparation of the matrix tablet.

The hardness of all tablets was 4 Kg/cm^2. From the figure of morphological evaluation of the tablet, we can see that an increase in the concentration of borax in the TG-B hydrogel composition produces a rigid and stable matrix that swells less and retains its morphological structure for a prolonged time. Matrix F6 is more stable than matrix F1. An increase in the concentration of TG in the TG-B hydrogel composition increases the swelling of the matrix. The swelling results in increased erosion of the matrix. This decreases the rigidity, stability, and intactness of the matrix. The matrix F10 is less rigid and intact than the matrix F7.

The *in-vitro* release of AFN from the matrix tablet was performed at pH 1.2 for 2h and then at pH 7.4 for 6h. AFN release from TG-B hydrogel declined significantly with the increase in the concentration of borax in the TG-B hydrogel composition. When borax is cross-linked with the OH group of polymers, the polymer's chain movement is hindered as a result the development of rigid viscous layer around the surface of the matrix tablet and reduced the drug release rate. F7 shows the slowest release of AFN from the matrix as it contains 18% of the borax in the TG-B hydrogel and F1 shows the fastest release of AFN from the matrix as it does not contain borax as a crosslinker. With an increase in the concentration of TG in the TG-B hydrogel composition, the drug release from the matrices becomes greater. The OH group of the TG makes it more hydrophilic, absorbing more water and promoting swelling and drug release. F8 shows the slowest release of AFN from the matrix as it contains 0.5% of TG in the TG-B hydrogel and F11 shows the fastest release of AFN from the matrix as it contains 1.5% of TG in the TG-B hydrogel composition.

The AFN release from matrices is followed by the power law equation. The AFN release from hydrogel matrices followed zero order kinetics which indicates that AFN release is constant per unit time but the rate is independent of the AFN concentration in the hydrogel tablet. The AFN release from the hydrogel matrices (F1-F8) followed the super case II mechanism (r^2 values 0.74-0.87) which indicates the erosion or mobility of the polymer chain determined the AFN release mechanism. The AFN release from the pure TG matrices and hydrogel matrices (F9) followed the non-fickian or anomalous transport mechanism (r^2 values of pure TG matrix is 0.66 and F9 is 0.89) which indicates that both diffusion and swelling are responsible for the controlled release of AFN from the hydrogel matrices.

9.2. Conclusion

TG was cross-linked with borax to synthesize TG-B hydrogel. AFN-loaded TG-B hydrogel matrices were developed for sustained release of AFN from the matrices. FTIR, XRD, and DSC studies were performed for the determination of the compatibility of AFN in hydrogel matrices. The impact of borax on swelling and AFN release from the matrices was investigated. An increase in the concentration of borax decreases the swelling, which subsequently decreases the AFN release rate from the matrices. Borax is cross-linked with the OH group of polymer, the polymer's chain movement is hindered as a result of the development of a rigid viscous layer around the surface of the matrix tablet, and that reduced the drug release rate. TG-B hydrogel matrices show higher crosslinking density and produce a highly rigid hydrogel layer at the surface of the matrix tablet than pure TG matrices. The AFN release rate from TG-B hydrogel matrices is slower than pure TG matrices. By keeping the concentration of borax constant, the TG concentration was increased from 0.5% to 1.5% as a result the swelling ratio of TG-B powder was increased leading to an increase in the AFN release rate due to the OH group of the TG making it more hydrophilic, absorbing more water and promoting swelling and drug release. The drug release rate is slower at pH 1.2 for 2h and gradually increases the release rate for 6h. The AFN release from the matrices is followed by the super case II transport mechanism and non-fickian or anomalous transport mechanism. From the investigation, it can be concluded that borax cross-linked hydrogel matrices could be used as a gastro-protective sustained delivery of water-insoluble drug.