UNVEILING THE SWELLING, DRUG RELEASE, AND STRUCTURAL PROPERTIES OF HYDROGELS: UNDERSTANDING KINETICS FOR ADVANCED APPLICATIONS

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CANDIDATE DECLARATION

I, Sakshi dang (2k22/MSCCHE/34) hereby certify that the work which is being presented in the dissertation enlightened **"Unveiling the Swelling, Drug release, and Structural Properties of Hydrogels: Understanding kinetics for Advanced Applications"** in partial fulfilment of the requirements for the award of the Degree of Master in Science, submitted in the Department of Applied Chemistry, Delhi Technological University is an authentic record of my own work carried out during the period from June 2023 to Mar 2024 under the supervision of Prof Roli Purwar.

The matter presented in the dissertation has not been submitted by me for the award of any other degree of this or any other institute.

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CERTIFICATE

Certified that Sakshi Dang (2k22/MSCCHE/34) has carried out her review work presented in this dissertation entitled **"Unveiling the Swelling, Drug release, and Structural Properties of Hydrogels: Understanding kinetics for Advanced Applications"** for the award of Master of Science from the Department of Applied Chemistry, Delhi Technological University, Delhi, under our supervision. The dissertation embodies results of original work, and studies are carried out by the student herself and the contents of the dissertation do not form the basis for the award of any otherdegree to the candidate or to anybody else from this or any other University/Institution.

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OBJECTIVE

- Investigate the fundamental mechanisms underlying the swelling behavior of hydrogels.
- Explore the kinetics of drug release from hydrogels and the factors influencing this process.
- Analyze the structural properties of hydrogels and their impact on swelling and drug release kinetics.
- Evaluate the applications of hydrogels in drug delivery systems and tissue engineering.
- Discuss the future perspectives and potential advancements in utilizing hydrogels for therapeutic delivery systems.
- Summarize recent research findings on the interactions between kinetic properties, swelling behavior, and structural features of hydrogels.
- Provide insights into how understanding these properties can lead to the development of more efficient and targeted drug delivery systems.

ABSTRACT

This review provides a thorough examination of hydrogels, versatile materials capable of absorbing and retaining large amounts of water. It covers their classification, synthesis, properties, and applications in various scientific fields such as biomedicine and environmental science. Hydrogels, defined as networks that swell when exposed to water but maintain their structure, possess biomimetic qualities like flexibility, softness, and compatibility with biological systems, making them ideal for uses like drug delivery and tissue engineering. The document discusses their classification based on natural or synthetic origins, detailing the distinct compositions and properties of each type. It also explains synthesis methods, including physical and chemical cross-linking techniques, and emphasizes the importance of understanding drug release kinetics for designing effective drug delivery systems. The increasing focus on hydrogel-based systems, particularly in drug delivery, is highlighted, indicating their growing recognition and potential across scientific fields. Compiled from various research articles and references, this review serves as a valuable resource for researchers, scientists, and enthusiasts interested in exploring hydrogel science further.

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LIST OF ABBREVIATIONS AND SYMBOLS:

1. PEG - Polyethylene Glycol
2. PVA - Polyvinyl Alcohol
3. PMMA - Polymethyl Methacrylate
4. PHEMA - Poly(2-hydroxyethyl methacrylate)
5. MAA - Methacrylic Acid
6. PAMPS - Poly(2-acrylamido-2-methylpropane sulfonic acid)
7. HEMA - 2-Hydroxyethyl Methacrylate
8. IPN - Interpenetrating Polymeric Network
9. NIPAAm - N-isopropylacrylamide
10. ε-polylysine - Epsilon-polylysine
11. PEGDA - Polyethylene Glycol Diacrylate
12. P(HEMA-co-MAA) - Poly(2-hydroxyethyl methacrylate-co-methacrylic acid)
13. PCL - Polycaprolactone
14. PAA - Poly(acrylic acid)
15. PVP - Polyvinylpyrrolidone
16. PAAm - Polyacrylamide
17. PNIPAAm - Poly(N-isopropylacrylamide)
18. PAAc - Poly(acrylic acid)
19. PVP - Polyvinylpyrrolidone
20. PAAm - Polyacrylamide

CHAPTER 1: INTRODUCTION TO HYDROGELS

1.1 Hydrogels: Definition and Structure

The unusual characteristics and diverse usefulness of hydrogels have made them an attractive class of materials that have attracted significant attention in both industrial and research applications. It's important to define hydrogels precisely and acknowledge their unique qualities in order to comprehend them. A cross-linked polymeric network that swells in the presence of water and is produced by the straightforward reaction of one or more monomers is one method to characterise a hydrogel (1). This definition focuses on the basic chemical makeup and hydrogel forming mechanism. Because it creates the scaffold that maintains structural integrity while enabling the material to inflate with water, the cross-linked network is essential.

As an alternative, hydrogels can be defined as polymeric materials that resist swelling and retain a significant amount of water inside their structure without dissolving in it (1). This explanation focuses on the physical characteristics of hydrogels, emphasising how important it is to their operation that they can absorb and hold onto water without disintegrating. The hydrophilic functional groups that are affixed to the polymer backbone and which draw and retain water molecules are the source of this special capacity. Even when completely hydrated, the hydrogel keeps its shape because to the cross-links that hold the network chains together.

1.2 Functional Properties

Hydrogels' ability to absorb water is facilitated by hydrophilic functional groups bound to their polymer backbone, and their resistance to dissolution is derived from cross-links between their network chains (1). Hydrogels' unique ability to absorb large volumes of water while retaining structural integrity is essential to their effectiveness in a variety of applications. For example, in biomedical applications, like in wound dressings, the capacity to absorb water can be essential for preserving a moist environment favourable to healing.

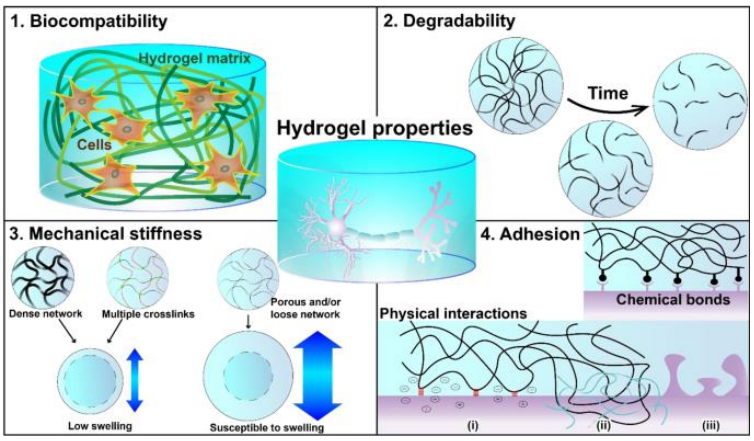

Figure 1.1 properties of hydrogels

The stability of hydrogels in the face of severe and varying temperatures is another noteworthy characteristic (2). Their usefulness in a variety of environmental settings and applications, including as environmental engineering and biomedical equipment, is increased by their temperature stability. The stability of hydrogels during changes in body temperature guarantees consistent performance and dependability in biomedical devices.

1.3 Mechanical and Biomimetic Characteristics

Notable biomimetic characteristics of hydrogels include their exceptional softness, biocompatibility, biodegradability, flexibility, and good swelling absorption capacity (3-5). They are also non-toxic. Because of these qualities, hydrogels are very useful in biomedical settings where materials that closely resemble biological tissues are highly desired, such as in tissue engineering, medication delivery, and wound care. Hydrogels' softness and flexibility enable them to adapt to biological tissues, lessening discomfort and enhancing body integration.

Any substance utilised in medical applications must be non-toxic and biocompatible. These conditions are satisfied by hydrogels, which guarantees that when implanted in the body, they won't cause an unfavourable immunological reaction. Another crucial feature is biodegradability, especially for transient medical applications such medication delivery systems where the substance should degrade Hydrogels' mechanical attributes can be altered to suit certain requirements thanks to their customisable mechanical qualities. This may entail modifying the cross-link density to change the hydrogel's firmness or swellability. This kind of flexibility is essential for creating specialised applications, such scaffolds for tissue engineering or contact lenses.

The special qualities of hydrogels have produced a multitude of uses. They are utilised in the biomedical industry for drug delivery systems that allow for the gradual, regulated release of

medication. They are perfect for wound dressings because of their capacity to absorb enormous volumes of water and keep an environment wet, which speeds up healing and lowers the danger of infection.

1.4 Hydrogel Applications

The special qualities of hydrogels have produced a multitude of uses. They are utilised in the biomedical industry for drug delivery systems that allow for the gradual, regulated release of medication. They are perfect for wound dressings because of their capacity to absorb enormous volumes of water and keep an environment wet, which speeds up healing and lowers the danger of infection.

Hydrogels are used in tissue engineering to facilitate the formation of new tissue by providing a transient framework on which cells can cling and multiply. Hydrogels are useful for building structures that closely resemble the mechanical characteristics of real tissues, like cartilage or skin, because of their flexibility and biocompatibility.Hydrogels are used in tissue engineering to facilitate the formation of new tissue by providing a transient framework on which cells can cling and multiply. Hydrogels are useful for building structures that closely resemble the mechanical characteristics of real tissues, like cartilage or skin, because of their flexibility and biocompatibility.

Hydrogels are utilised in agriculture, aside from medicine, to hold water in the soil and increase water usage efficiency in arid areas. Because of their great absorbency, they are also present in personal care goods like sanitary napkins and diapers.

Thus The capacity of hydrogels to generate cross-linked polymeric networks that swell with water without dissolving makes them useful and diverse materials. Their ability to absorb and retain large amounts of water while retaining their shape and form is largely due to their hydrophilic nature and structural integrity. Because of this, they work incredibly well in a variety of settings.

Hydrogels are versatile and can be used in a variety of environmental settings due to their resilience under temperature fluctuations. Their biomimetic characteristics, including as their softness, biocompatibility, non-toxicity, flexibility, and biodegradability, make them especially well suited for use in biomedical settings. Because of these characteristics, hydrogels can coexist peacefully with biological systems, imitating natural tissues and encouraging regeneration and healing.
Hydrogels' adaptability is further improved by their mechanical qualities that can be altered to suit particular requirements in a variety of industries. This flexibility is necessary for creating specialised solutions in fields like tissue engineering, drug delivery, and personal hygiene.

The ability of hydrogels to absorb and hold onto water has advantages in agricultural and environmental settings in addition to medical ones. Their usefulness for enhancing water efficiency in horticulture and agriculture stems from their capacity to retain moisture and release it gradually. Overall, hydrogels' special mix of chemical, biological, and physical characteristics makes them an essential material for developing technology and raising standards of living in a variety of fields. In order to prepare for a more in-depth examination of hydrogels' scientific and practical implications in the next chapters, this chapter offers a thorough overview of the material. We learn more about the potential and adaptability of hydrogels in a variety of sectors by carefully examining their definitions, characteristics, and uses.

CHAPTER 2: CLASSIFICATION OF HYDROGELS

Hydrogels can be categorised according to a number of factors because of their varied qualities and wide range of applications. This chapter examines the various classification schemes, offering a thorough grasp of the numerous kinds of hydrogels and their unique properties.

Hydrogels are categorised according to their source, polymeric composition, configuration, physical appearance, kind of cross-linking, and electrical charge. This classification offers a thorough framework for comprehending the wide range of characteristics and uses of hydrogels. Hydrogels can come from synthetic or natural sources, and each has unique benefits regarding biodegradability, biocompatibility, and qualities that can be customised. Whether they are homopolymeric, copolymeric, or interpenetrating polymer networks, their polymeric makeup enables customised properties to satisfy particular requirements.

Hydrogels can be amorphous, semicrystalline, or crystalline; this configuration affects their mechanical characteristics and possible uses. Their physical characteristics, which are dictated by the polymerization process, further expand their range of applications in different forms including microspheres, films, and matrices. The kind of cross-linking—chemical or physical—affects how stable and adaptable they are to changes in their surroundings.

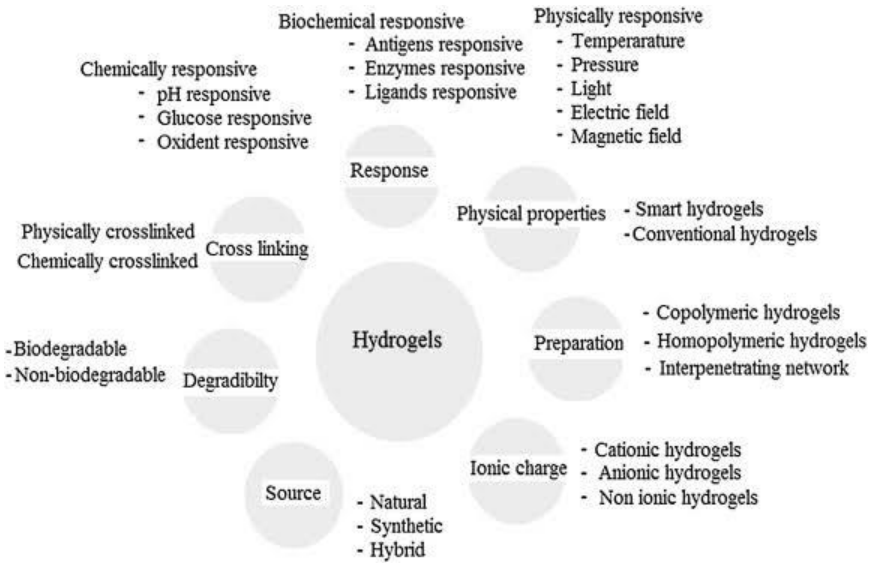

Figure 2.1- classification and processing of hydrogels

2.1 Classification by Source

Depending on where they come from, hydrogels can be divided into two categories: synthetic or natural (6).

Natural Hydrogels: Polymers derived from natural sources are used to create gel materials known as natural hydrogels (6). These include of proteins like collagen, gelatin, and fibrin, as well as polysaccharides including alginate, chitosan, cellulose, and starch. For biomedical applications, natural hydrogels are frequently preferred because of their innate biocompatibility, biodegradability, and low

toxicity. They can be utilised in scaffolds for tissue engineering, drug delivery systems, and wound dressings. These polymers' natural origins frequently lead to improved interactions with biological tissues, which support the adhesion, proliferation, and differentiation of cells.

Synthetic Hydrogels: Polyamides, polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polymethyl methacrylate (PMMA) are examples of synthetic polymers that can be used to create synthetic hydrogels, on the other hand (7). The features of synthetic hydrogels are engineered to be specific to specific uses. Controlled synthesis, repeatability, and the capacity to alter chemical structures to produce desired mechanical and physical qualities are some of its benefits. Because of their consistency and adjustable qualities, synthetic hydrogels are frequently utilised as scaffolds for tissue engineering, in contact lenses, and in drug delivery systems.

2.2 Polymeric Composition-Based Categorization

Hydrogels can also be categorised based on the type of polymer they are made of. Three primary types are included in this classification:

1-Homopolymeric Hydrogels: Derived from a single species of monomer (8), these hydrogels consist of networks formed from identical monomer units. They have consistent qualities, which is advantageous in some regulated applications. The manufacture of homopolymeric hydrogels is simple, and by adjusting the degree of cross-linking, these materials can be made with desired mechanical and swelling properties. Poly(2-hydroxyethyl methacrylate) (PHEMA), which is frequently utilised in biomedical implants and contact lenses, is one example.

2- Copolymeric hydrogels: Designed to blend the characteristics of several monomers, these hydrogels consist of two or more distinct monomer species with a minimum of one hydrophilic component (9). Because of its adaptability, the hydrogel's properties can be adjusted to better suit the needs of particular applications. For instance, hydrogels with enhanced mechanical strength and water absorption capacity can be created by copolymers of acrylamide and acrylic acid, which are beneficial in biomedical devices and agricultural applications.

3- Multipolymer Interpenetrating Polymeric Hydrogels (IPN): In a network structure, two separate cross-linked synthetic and/or natural polymer components make up multipolymer interpenetrating polymeric hydrogels (IPN) (10, 11). IPNs are appropriate for cutting-edge biomedical applications because of their complex structure, which can offer improved mechanical strength and stability as well as customised swelling and degradation rates. IPNs are able to combine the best qualities from each polymer network in a synergistic way, producing materials that perform better than hydrogels made of only one network. As an illustration, consider the biocompatibility and mechanical strength of

polyvinyl alcohol and chitosan together, which can be utilised to create scaffolds for tissue engineering and wound treatments.

2.3 Configuration-Based Classification

Three categories of hydrogels can be distinguished based on their configuration:

1- Amorphous hydrogels :Amorphous hydrogels are more elastic and flexible since they don't have a clear crystalline structure. They are frequently employed in applications that call for malleable, soft materials. Since they may take on a variety of shapes and forms and are generally simple to make, amorphous hydrogels are a good choice for drug delivery systems and wound dressings when application site conformity is crucial.

2- Semicrystalline Hydrogels: These hydrogels have intermediate qualities, combining strength and flexibility, and they contain both amorphous and crystalline regions. The hydrogel's thermal stability and mechanical strength can both be improved by the presence of crystalline areas. Applications requiring a compromise between elasticity and rigidity, like load-bearing scaffolds for tissue engineering, can benefit from the usage of semicrystalline hydrogels.

3- Crystalline hydrogels - Hydrogels with a highly organised structure are known as crystalline hydrogels. These hydrogels are generally more rigid and can be employed in situations where a stiffer material is beneficial. High mechanical strength crystalline hydrogels are employed in applications that need structural integrity and longevity, including in some biological implants and sensors.

2.4 Classification by Physical Appearance

Hydrogels can also be categorised according to how they physically look, which is determined by the method of polymerization used in the preparation phase (1). This group comprises:

1-Matrix Form: Continuous, bulk hydrogels, frequently utilised in drug delivery and tissue engineering applications. The diversity of matrix hydrogels' applications stems from their ability to be moulded into a wide range of forms and sizes. They are frequently utilised in tissue scaffolds, large-scale wound dressings, and in situ forming gels for targeted medication administration.

2- Film form -Hydrogel thin layers utilised in barrier membranes and wound dressings are known as the "film form." Large surface areas can be covered with film hydrogels, which also act as a barrier against infection and dehydration. They are extensively utilised in transdermal medicine delivery patches and wound care products.

3- Microsphere form - Hydrogel microspheres are small, spherical particles that are utilised as carriers for bioactive compounds and in targeted medicine delivery. Because of their controlled release capabilities, microsphere hydrogels can be utilised to deliver medications, proteins, or other

therapeutic substances to particular body locations. Additionally, they are utilised as fillers in minimally invasive surgical procedures and in diagnostic applications.

2.5 Grouping according to Cross-Linking Type

Hydrogel cross-linking techniques can also be utilised as a foundation for classification:

1- Physically Cross-Linked Hydrogels- Hydrogels that have been cross-linked physically are created via ionic, hydrophobic, or hydrogen bonding interactions. These hydrogels are frequently malleable and sensitive to changes in their surroundings. Ionic gelation, crystallisation, and phase separation are some of the techniques that can be used to create physical cross-linking. In situations where reversible gelation is advantageous, such as in drug delivery systems that react to pH or temperature changes, physically cross-linked hydrogels are employed.

2- Chemically Cross-Linked Hydrogels: Hydrogels that are chemically cross-linked are created when polymer chains form covalent bonds with one another. These hydrogels often operate consistently across a range of applications because they are less sensitive to changes in the environment and more stable. Usually, radiation or cross-linking agents are used to create chemical cross-linking. Applications needing long-term stability, like contact lenses, prostheses, and long-lasting medical implants, use chemically cross-linked hydrogels.

2.6 Electrical Charge-Based Classification

The cross-linked chains of hydrogels can be categorised according to whether or not they have an electrical charge (1). This group comprises:

1-Nonionic Hydrogels: These hydrogels are neutral and devoid of charge, making them a popular choice in applications that aim to minimise contact with charged molecules. Applications where neutrality is advantageous, such as drug delivery systems and contact lenses, are suited for nonionic hydrogels.

2- Ionic hydrogels: These can be further divided into cationic (positively charged) and anionic (negatively charged) groups based on the presence of charged groups. They are employed in processes like medication delivery and bioseparation, where interaction with opposing charges is advantageous. Whereas cationic hydrogels, like those based on chitosan, can connect to negatively charged biomolecules, anionic hydrogels, such those manufactured from alginate, can interact with positively charged medications or proteins.

3-Amphoteric Electrolyte (Ampholytic) Hydrogels: These hydrogels are helpful in controlled release systems because they can react to variations in pH and ionic strength because they contain both positive and negative charges. Amphoteric hydrogels can be engineered to precisely control

medication release or other therapeutic activities by shrinking or swelling in response to external stimuli.

4- Hydrogels with Zwitterionic (Polybetaines): These hydrogels are perfect for biomedical applications because they have both positive and negative charges on the same monomer unit and have special qualities like strong water retention and resistance to protein adsorption. Since they are very hydrophilic and fouling-resistant, zwitterionic hydrogels are appropriate for application in antifouling coatings, biosensors, and other medical equipment where surface cleanliness is crucial.

CHAPTER 3: MECHANISM OF FORMATION OF HYDROGELS

Different techniques can be used to create hydrogels, which then form their distinctive three-dimensional network topologies. Physical crosslinking and chemical crosslinking are the two primary categories into which these techniques can be generally divided. Every technique has unique mechanisms that affect the characteristics and uses of the hydrogels that are produced. These mechanisms will be thoroughly examined in this chapter, with an emphasis on both their benefits and drawbacks.

Physical and chemical crosslinking techniques are the two main categories into which the hydrogel generation mechanism falls. Non-covalent interactions such as hydrogen bonding, amphiphilic grafts and block polymers, ionic contacts, and protein interactions result in physically cross-linked hydrogels. These techniques have the benefit of not requiring chemical additives and preserving biocompatibility, but they could produce hydrogels that are sensitive to the environment and have reversible characteristics. Physically cross-linked hydrogels, for example, can be made to swell in response to particular stimuli, which makes them valuable for applications such as responsive biomaterials and smart drug delivery systems. Their susceptibility to changes in the environment, however, may prevent them from being used in some situations where stable and long-lasting qualities are necessary.

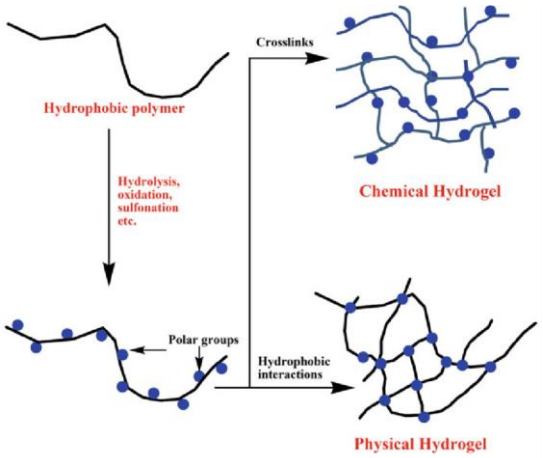

Figure 3.1 Schematic of formation of hydrogels by physical and chemical method

Covalent linkages allow hydrogels that are chemically cross-linked more stability and mechanical strength. The crosslinking process and the hydrogel properties that arise can be precisely controlled using techniques including click reactions, high energy radiation, enzyme reactions, interactions of complimentary chemical groups, and free-radical polymerization. Chemically cross-linked hydrogels are frequently utilised in applications like controlled drug delivery systems, long-lasting medical implants, and scaffolds for tissue engineering that call for mechanical robustness and stability over

time. Hydrogels with a wide range of biomedical and industrial applications can be designed with precise mechanical properties, degradation rates, and biocompatibility thanks to the capacity to modify the chemical composition and crosslinking density.

It is crucial to comprehend the mechanics underlying hydrogel formation in order to choose the best technique for achieving the required characteristics in a given application. Whether the hydrogel is intended for industrial operations, environmental applications, or biomedical use, the decision between chemical and physical crosslinking will have a big impact on the hydrogel's compatibility and performance. A thorough review of these mechanisms is given in this chapter, setting the stage for future chapters that will delve deeper into the characteristics and uses of hydrogels. Subsequent investigations could concentrate on merging physical and chemical crosslinking techniques to generate hybrid hydrogels that capitalise on the benefits of both strategies, generating materials with improved performance and wider potential applications.

3.1 Physical Crosslinking

Non-covalent interactions generate a network in physical cross-linked hydrogels without the requirement for chemical additions. Amphiphilic grafts and block polymers, hydrogen bonding, ionic contacts, and protein interactions are some examples of these interactions.

Hydrogen Bonding: This technique forms a nanostructured network that serves as a cross-linking mechanism by forming hydrogen bonds between polymeric chains (12). When hydrogen atoms interact with lone pairs of electrons on other electronegative atoms, such as oxygen or nitrogen, which they are covalently bound to, hydrogen bonding takes place. This kind of crosslinking is beneficial since it preserves the hydrogel's biocompatibility by avoiding the use of chemical crosslinkers that may be hazardous. However, external factors like pH and temperature can affect the hydrogel's stability by breaking down hydrogen bonds and changing the hydrogel's characteristics.

Amphiphilic Grafts and Block Polymers:Hydrophilic and hydrophobic segments can be found in amphiphilic grafts and block polymers. While the hydrophilic segments create the hydrogel network, the hydrophobic segments have the ability to self-assemble into micellar structures (13). This process can produce hydrogels with special qualities, such their ability to react to external stimuli, but it can also produce intricate structures that might be challenging to properly regulate.

Ionic Interactions: To create an ionic network, charged polymers are used in ionic crosslinking to interact with ions that have opposite charges (14). For instance, calcium ions can be used to cross-link alginate hydrogels. Because of their reversibility and susceptibility to pH and ionic strength variations, ionic interactions make these hydrogels ideal for applications requiring controlled release, such as medication administration.

Protein Interactions: Hydrogels can be formed by proteins interacting with one another through hydrophobic, ionic, and hydrogen bonding interactions (15). Because protein-based hydrogels are biocompatible and biodegradable, they are very helpful in biomedical applications. However, controlling the development and stability of these hydrogels can be difficult due to the intricacy of protein structures.

Physically cross-linked hydrogels have several benefits, including exceptional flexibility and the lack of chemical additions needed to achieve the desired cross-linked structure, which frequently compromises vital characteristics like biocompatibility or raises toxicity issues after implantation (18). Their reversible nature and reliance on outside variables like pH and temperature, which results in unstable qualities, are their primary disadvantages, though.

3.2 Chemical Crosslinking

Covalent connections between polymer chains generate chemically cross-linked hydrogels, which offer improved mechanical and stability characteristics. Enzymatic reactions, interactions between complementary chemical groups, high-energy radiation, free-radical polymerization, and click reactions are a few examples of these techniques.

Enzymatic Reactions: A cross-linked network can be created by using enzymes to catalyse the creation of covalent connections between polymer chains (16). Because of its gentle reaction conditions and selectivity, this approach can protect the integrity of biological molecules that are sensitive. The creation of hydrogels for tissue engineering and medication delivery frequently involves enzymatic crosslinking.

Reaction of Complementary Chemical Groups: Covalent bonds can be formed and the hydrogel network cross-linked by chemical groups that particularly react with one another. One example is the formation of amide bonds when an amine reacts with carboxyl groups. With this technique, the hydrogel's mechanical characteristics and crosslinking density may be precisely controlled.

High Energy Radiation: When high energy radiation, like gamma rays or electron beams, are exposed to polymer chains, they can create free radicals that can cause crosslinking (17). Chemical crosslinkers are not needed for this procedure, which can be helpful in preserving biocompatibility. Radiation therapy can be complicated to use, though, and special tools are needed.

Free-Radical Polymerization: This type of polymerization, which is triggered by radiation or chemical initiators, creates free radicals that cause crosslinking. Because of its adaptability and capacity to produce hydrogels with a broad variety of properties, this technique is widely employed. On the other hand, toxicity issues may arise from the existence of leftover initiators or monomers.

Click Reactions: Under mild conditions, click chemistry involves extremely selective and efficient

chemical reactions that result in the formation of covalent bonds. Azide-alkyne cycloaddition and thiol-ene reactions are two examples. Click reactions are useful for biomedical applications because of their high yield, ease of use, and capacity to function under physiological settings.

The hydrogels created by chemical cross-linking techniques stand out for having better mechanical qualities and stability. Chemically cross-linked hydrogels are less susceptible to changes in the environment than physically cross-linked hydrogels because of the covalent connections that are created. Applications that need steady performance over an extended period of time, such long-term medication delivery systems and robust medical implants, depend on this stability.

CHAPTER 4: INJECTABLE HYDROGELS

Because injectable hydrogels do not require invasive surgical implantation, they overcome the drawbacks of pre-formed hydrogels and represent a significant development in biomedical engineering. This chapter examines the properties, uses, and workings of injectable hydrogels, highlighting the advances and benefits that make them a competitive option for a range of medical uses.

4.1 Introduction to Injectable Hydrogels

Because pre-formed hydrogels need to be inserted into the body at a precise place, an invasive surgical procedure is required, which can be costly, time-consuming, and uncomfortable for the patient (10, 11). This necessity presents a number of difficulties, mainly with regard to overall healthcare expenses, recuperation times, and patient comfort. Thus, there has been a lot of interest in the development of injectable hydrogels, which provide a less intrusive option that makes administration easier and improves patient outcomes.Because injectable hydrogels have the necessary physicochemical properties to be injected intraperitoneally, they can be used for a variety of purposes, such as tissue engineering, dermal fillers, and medicine administration (19, 20, 21, 22). Since these hydrogels are meant to be injected into the body in a liquid condition, they may be easily administered and will later solidify in the body. This capacity greatly lessens the invasiveness of therapies and can be used in a variety of clinical settings, such as regenerative medicine and cosmetic procedures.

4.2 Characteristics of Injectable Hydrogels

Non-toxicity and biocompatibility are essential requirements for a successful injectable hydrogel technology. Another important factor is the hydrogel porosity; highly connected networks are preferred because they enhance tissue flexibility and nutrition transfer. To guarantee that when injectable hydrogels are injected into the body, they do not cause toxicity or unfavourable immunological reactions, they must adhere to strict biocompatibility guidelines. For its usage in medical applications, where patient safety and treatment efficacy are crucial, this need is essential.

The idea behind injectable hydrogels is generally that a solid hydrogel can form in situ by injecting liquid biomaterials into the human body (23). Within the body, this transition from a liquid to a gel state enables the hydrogel to be precisely delivered and localised, enabling targeted therapy. Several characteristics, including shear-thinning and self-healing, can be engineered into injectable hydrogels to increase their adaptability and usefulness in medical settings.

Shear-Thinning Properties: When injection occurs, shear-thinning hydrogels can flow under shear stress, but as soon as the stress is released, they rapidly return to their gel form. This characteristic is especially helpful for minimally invasive operations where catheters or needles with tiny gauges are required to inject the hydrogel.

Self-Healing Properties: Hydrogels with self-healing properties are able to regain their structure after being damaged, which is advantageous for applications needing resilience and long-term durability. Because of this property, the hydrogel can continue to operate and remain intact even after being damaged or mechanically deformed.

4.3 Mechanisms of Injectable Hydrogels

Because of their shear-thinning and self-healing properties, injectable hydrogels can be given immediately in a gel form, which qualifies them as injectable biomaterials (24, 25, 26). These hydrogels can also be engineered for in situ gelation, in which the liquid precursor is injected and, as a result of variations in pH, ionic strength, or temperature, gels into a gel.

These hydrogels may be made to crosslink using a variety of synthetic techniques, and their chemical structure shows that they have both chemical and physical bonds (27, 28). In addition to chemical bonding through covalent bonds, crosslinking methods can also involve physical interactions like hydrogen bonding and ionic interactions. The hydrogel's mechanical characteristics, rate of breakdown, and biocompatibility can all be tailored to a certain application by selecting a different crosslinking technique.

Physical Crosslinking: Hydrogen bonding, ionic interactions, and hydrophobic interactions are examples of non-covalent interactions that take place during physical crosslinking. These interactions may give the hydrogel stimuli-responsive and reversible qualities that enable it to adjust to shifting physiological situations.

Chemical crosslinking: This process creates covalent connections between polymer chains to make the network more robust and stable. By using this technique, the hydrogel's mechanical strength and durability can be increased, making it appropriate for uses that need for extended stability.

4.4 Enhancing Stability and Functionality

One of the difficulties in using injectable hydrogels based on hyaluronic acid (HA) is that these gels usually only last a few hours in the body because of hyaluronidase's quick enzymatic degradation. In order to get over this restriction, injectable hydrogels based on HA are usually created using chemical crosslinking agents such divinyl sulfone (DVS) and 1,4-butanediol diglycidyl ether (BDDE) (29). By stabilising the hydrogel structure, these crosslinking agents increase the hydrogel's therapeutic potential and prolong its useful life inside the body.

In addition to making HA-based hydrogels more resilient, chemical crosslinkers also enable the modification of the hydrogels' mechanical and degrading characteristics. Their adaptability renders them appropriate for an array of uses, ranging from delivering continuous medication release to functioning as scaffolds for tissue restoration. Controlling the crosslinking density and network

topology is essential for creating hydrogels that can adapt to the unique requirements of various medical procedures.

4.5 Applications of Injectable Hydrogels

Because of their adaptability and simplicity of use, injectable hydrogels have several uses in the medical industry. Among the important applications are:

Dermal Fillers: To improve facial lines, smooth wrinkles, and restore volume, injectable hydrogels are frequently used in cosmetic dermatology. They are perfect for minimally invasive aesthetic operations since they can be precisely injected and produce stable gels in situ.

Drug Delivery: Localised and regulated release of therapeutic drugs is made possible by injectable hydrogels, which are efficient drug delivery methods. Their capacity to encapsulate medications and release them in response to particular stimuli—such as variations in pH or temperature—improves the effectiveness of treatment and lessens systemic side effects.

Tissue Engineering: Injectable hydrogels are utilised as scaffolds in tissue engineering to promote tissue regeneration and cell proliferation. They are appropriate for replacing or mending injured tissues due to their biocompatibility, mechanical qualities that may be adjusted, and their capacity to create gels in place. It is possible to add cells and growth factors to injectable hydrogels to encourage in-situ tissue regeneration and healing.

Wound Healing: Applications for injectable hydrogels are also used in wound healing. They lessen the chance of infection and hasten the healing process by preserving a moist environment, provide structural support, and delivering bioactive molecules straight to the wound site.

Orthopaedic Applications: Hydrogels that can be injected can be used to regenerate and repair cartilage in orthopaedic applications. They can be used to treat degenerative diseases and joint injuries because of their capacity to create a gel in situ and promote chondrocyte development.

Ophthalmic Applications : Injectable hydrogels can give structural support and administer therapeutic substances straight to the eye in ocular surgery and treatments, such as the repair of retinal detachments.

Cancer Therapy: Injectable hydrogels can be used to administer chemotherapy medications locally, lowering systemic toxicity and increasing therapeutic index.

4.6 Future Directions

Research on injectable hydrogels is still being conducted in order to enhance their characteristics and broaden the range of uses for them. Potential future developments could centre around:

Smart Hydrogels : The creation of hydrogels that react to a variety of stimuli, including temperature, pH, and certain biological signals, in order to improve their effectiveness and adaptability in a range of medical applications, is known as "smart hydrogels." Precise control over therapeutic results can be achieved using smart hydrogels because they can enable on-demand medication release or structural modifications in response to the physiological environment.

Biodegradable Hydrogels : Hydrogels that are biodegradable are created by carefully regulating their rate of degradation to correspond with the process of tissue regeneration. This guarantees that the scaffold breaks down at the proper pace when new tissue grows. Biodegradable hydrogels have the potential to minimise long-term foreign body reactions and lessen the necessity for surgical removal.

Personalised Medicine: It involves developing injectable hydrogels that are customised for each patient's needs and include bioactive chemicals and patient-specific cells to improve therapy results. Hydrogels that are tailored to an individual patient's biological milieu can enhance their compatibility and effectiveness.

Combination therapies: Investigating how injectable hydrogels might be used in conjunction with other therapeutic methods, such immunotherapy and gene therapy, to create all-encompassing treatment plans for illnesses that are difficult to cure. Combination therapy have the potential to provide synergistic benefits by utilising the advantages of several techniques.

Advanced Imaging and Monitoring: By adding sensors and imaging agents to injectable hydrogels, real-time monitoring of the hydrogel's effectiveness and the course of the treatment is made possible. Cutting-edge imaging methods can offer insightful information about the hydrogel's behaviour in vivo, allowing for prompt modifications to the treatment plan.
Regenerative Medicine: Increasing the use of injectable hydrogels to more intricate organs and tissues, like the heart, liver, and nerves. The goal of this research is to create hydrogels that can aid in the repair of damaged organs and promote the growth of new functioning tissues.

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CHAPTER 5: CHARACTERIZATION OF INJECTABLE HYDROGELS

In order to produce injectable hydrogels with the right tunable properties and to satisfy the requirements and standards for upcoming applications, hydrogel characterization is very crucial. There are five types of characterization procedures: morphological, mechanical, thermal, physicochemical, and biological (1). Thorough characterisation guarantees that the hydrogels have the appropriate qualities for certain uses, such medication administration, tissue engineering, or cosmetic procedures. Each category will be thoroughly examined in this chapter, with an emphasis on the methods used and their significance for the creation of potent injectable hydrogels. Injectable hydrogels must be thoroughly characterised in all dimensions (physicochemical, structural, mechanical, thermal, and biological) to guarantee that they satisfy the high standards needed for biomedical applications. Every characterisation method offers vital information that directs hydrogel design, optimisation, and application, ensuring their safe and efficient usage in a variety of medical procedures. The Quality by Design (QbD) approach is integrated to further improve the development process and guarantee the greatest quality and consistency in injectable hydrogel production.

5.1 Physicochemical Characterization

Understanding the physical and chemical characteristics of hydrogels, such as the identification of various functional groups and their molecular interactions, is possible through physicochemical characterisation. This kind of characterization encompasses a number of important elements:

Gelation Time: After the hydrogel is injected into the body, it is essential to ascertain the gelation time to guarantee that it forms at the appropriate rate. The hydrogel's ultimate structural integrity and ease of application are influenced by the gelation time. For in situ applications where the material needs to fast stabilise in the body, rapid gelation times are frequently necessary.

Rheology: Rheological investigations evaluate the hydrogels' flow and deformation characteristics. Measuring viscosity, elasticity, and viscoelastic qualities is part of this process because these characteristics are essential to comprehending the hydrogel's injectability and mechanical stability. The hydrogel's performance in physiological conditions and its ease of injection are influenced by its rheological qualities. For instance, a hydrogel with the right viscoelastic characteristics can pass through a needle with ease while simultaneously holding its shape after injection.

Syringeability and Injectability Evaluation: This assessment looks at how simple it is to give the hydrogel using a syringe or catheter, making sure it can be done so without clogging or using too much force. Injectability is the force needed to force the hydrogel through a needle, whereas syringeability is the ease with which the hydrogel may be loaded into and ejected from a syringe. For real-world clinical applications, both factors are essential.

Techniques for spectroscopic and Spectrometry: A variety of spectroscopic methods are used to ascertain the composition and structure of injectable hydrogels. Among them are:

- Solution- and Solid-State Nuclear Magnetic Resonance Spectroscopy (NMR) (30, 31): NMR offers comprehensive details regarding the molecular dynamics and structure of hydrogels. It is applicable to both solution- and solid-state NMR. It can track alterations in the hydrogel's chemical composition and detect the existence of particular functional groups.

- Fourier-Transform Infrared Spectroscopy (FTIR) (32, 33): Using Fourier-Transform Infrared Spectroscopy (FTIR), one can determine the hydrogel's functional groups and chemical bonds. Verifying the existence of crosslinking agents and other chemical changes is especially helpful.

- Ultraviolet-Visible Absorption Spectroscopy (UV-Vis) (34):This technique analyses light absorption to reveal information about the concentration and electronic structure of the hydrogel's constituents. This method can be used to track the addition of medications or compounds that respond to light.

- Raman Spectroscopy (35): By examining the hydrogel molecules' vibrational modes, Raman spectroscopy provides supplementary structural information. It is helpful for researching changes in the hydrogel matrix's structure and molecular interactions.

Swelling Ability: Hydrogels' ability to expand and absorb water is determined by analysing their swelling behaviour. This is crucial information for applications that call for controlled release of encapsulated chemicals and volumetric changes. The crosslinking density, the polymer's composition, and external factors like pH and ionic strength all affect swelling behaviour.

Stability and degradation: Assessing hydrogels' stability and deterioration over time sheds light on how long-lasting and appropriate they are for use throughout extended periods of time. Studies on stability make sure the hydrogel keeps its characteristics in physiological settings. For biodegradable hydrogels used in tissue engineering and drug administration, where controlled degradation is necessary for the progressive release of therapeutic compounds or to permit tissue regeneration, degradation behaviour is especially significant.

Dynamic Light Scattering (DLS): This technique provides information on the homogeneity and colloidal stability of hydrogel particles by measuring their size distribution and molecular weight. It is

helpful for describing microspheres and nanoparticles that are enmeshed in the hydrogel matrix.
Zeta Potential: Hydrogel particle stability and interactions with biological tissues are influenced by the surface charge of the particles, which is measured using zeta potential. Good colloidal stability and less aggregation are indicated by a high zeta potential, which is crucial for injectable formulations.
Diffraction Methods: Methods such as X-ray diffraction (XRD) can reveal details on the phase composition and crystalline structure of hydrogels. These methods aid in the comprehension of the degree of crystallinity and the configuration of polymer chains, both of which have an impact on the hydrogel's mechanical and thermal characteristics.

5.2 Structural/Morphological Characterization

The porous structure and internal and external architecture of hydrogels are revealed by structural and morphological characterisation. Important methods consist of:
Using high-resolution images of the hydrogel surface, scanning electron microscopy (SEM) can give information about the size, distribution, and surface shape of the pores. Understanding the hydrogel's interactions with cells and tissues as well as its capacity for waste and nutrition exchange requires knowledge of this information.

Transmission Electron Microscopy (TEM): TEM provides fine-grained images of the hydrogels' internal structure at the nanoscale, which aids in the comprehension of the crosslinking density and polymer chain arrangement. When examining nanocomposites and hybrid hydrogels incorporating nanoparticles or other nanomaterials, TEM is especially helpful.
Atomic force microscopy (AFM): AFM gives mechanical properties of hydrogels at the micro and nanoscale, as well as topographical pictures, providing information about stiffness and surface roughness. AFM provides comprehensive information on the mechanical characteristics and interactions of the hydrogel surface by measuring forces at the molecular level.

Scanning Tunneling Microscopy (STM): It stands for scanning tunnelling microscopy, and it is used to examine the surface structure and electrical characteristics of conductive hydrogels. For the purpose of characterising conductive and semi-conductive hydrogels utilised in electrical or sensing applications, it offers atomic-level resolution.
Confocal Microscopy: This technique shows the internal structure and dispersion of encapsulated substances in hydrogels by producing three-dimensional images of the material. It is especially helpful for examining how fluorescently labelled molecules or cells are distributed spatially inside the hydrogel matrix.

5.3 Thermal and Mechanical Characterization

The response of hydrogels to mechanical stresses and temperature variations is assessed using thermal

and mechanical characterisation.

Thermal studies: These studies rely on changes in hydrogel structure brought about by changes in temperature. Methods consist of:

- Thermogravimetric Analysis (TGA) (36): Weight loss as a function of temperature is measured by TGA, which sheds light on the composition and thermal stability of hydrogels. It facilitates the determination of volatile component presence, decomposition temperature, and moisture content.

- Differential Scanning Calorimetry (DSC) (37): DSC provides information about the thermal characteristics and phase behaviour of hydrogels by measuring heat flow related to thermal transitions like melting or crystallisation. Glass transition and crystallisation temperatures, as well as the melting characteristics of individual polymer segments, can all be determined using DSC.

- Dynamic-Mechanical Thermal Analysis (DMTA) (38): DMTA evaluates hydrogels' viscoelastic characteristics at various temperatures, offering information into the mechanical stability and performance of the material. The material's stiffness, energy dissipation, and damping qualities are shown by the storage modulus, loss modulus, and tan delta, which are measured by DMTA.

Mechanical Tests: Under load, these tests reveal the stiffness and strength of crosslinked polymeric chains. Compressive stress/strain tests are one method used to assess how well hydrogels can endure mechanical forces without breaking down or deforming. Additional mechanical tests include shear testing, which assesses the hydrogel's reaction to shear stress, and tensile testing, which gauges the material's reaction to stretching pressures.

5.4 Biological Characterization

The use of injectable hydrogels in biomedical domains is supported and knowledge gained from biological characterisation, which also protects human life from potentially hazardous biological reactions resulting from the use of these injectable materials. Methods consist of:

Cell Proliferation and Differentiation Experiments (39): These studies evaluate hydrogels' capacity to promote cell proliferation and differentiation, highlighting its applicability for tissue engineering uses. Assays for assessing cell viability, such MTT or Live/Dead staining, gauge the metabolic activity and longevity of cells enclosed in hydrogel.

Wound-Healing Assays (40): Assays for wound healing assess how well hydrogels support tissue regeneration and repair, offering information on their potential applications in medicine. In vitro scratch tests are one type of experiment that can be used to evaluate a hydrogel's capacity to encourage cell migration and wound closure by scratching a cell monolayer.

Antibacterial or Anti-Inflammatory Tests (41): These tests assess how well hydrogels inhibit bacteria or lessen inflammation, frequently by releasing medications that are encapsulated over an extended period of time. Agar diffusion assays are one type of antibacterial test in which the hydrogel's capacity to stop bacterial growth is assessed by placing it on a bacterial culture.

5.5 Quality by Design (QbD) Approach

The injection hydrogel production process needs to be carefully planned, starting with the quality by design (QbD) approach. QbD predetermines the properties of the specific injectable hydrogel. It is based on statistical, analytical, and risk-management methods for understanding the product and the manufacturing process (42). By guaranteeing that the hydrogels constantly fulfil the required parameters, QbD improves the hydrogels' dependability and effectiveness for medical use.
Risk Management: identifying and reducing any hazards throughout the development and production of hydrogels in order to guarantee the quality and safety of the final product. This entails identifying possible failure modes and putting preventative measures in place.

Statistical Analysis: Data analysis and formulation and process parameter optimisation for hydrogels using statistical methods. Critical process factors and their interplay are identified with the aid of multivariate analysis and design of experiments (DoE).
Analytical Techniques: Using cutting-edge analytical techniques to thoroughly characterise hydrogels and make sure they adhere to the requirements needed for use in medicine. These methods enable the production of sturdy and dependable goods by offering comprehensive information regarding the physical, chemical, and biological aspects of the hydrogel.

CHAPTER 6: APPLICATIONS OF INJECTABLE HYDROGELS IN BIOMEDICAL FIELDS

Recently, injectable hydrogel technologies have advanced significantly in the area of biological applications. The use of these biomaterials has several advantages. Numerous therapeutic domains, such as the therapy of ocular problems (43), joint ailments (44), postoperative analgesia (45), and heart regeneration (46), have demonstrated their promise. This chapter highlights the multifunctional roles and therapeutic benefits of injectable hydrogels as well as their broad and prospective applications in a range of biomedical sectors.

6.1 Ophthalmic Disorders

Ophthalmic illnesses provide distinct problems because of the delicate and intricate structure of the eye. As a potential option for ocular drug administration, injectable hydrogels allow for the regulated release of medications to target particular ocular tissues. These hydrogels improve patient compliance and treatment results by providing benefits such extended drug retention, increased bioavailability, and decreased dosage frequency (43). For the treatment of eye illnesses, injectable nano-enabled thermogels have demonstrated potential in generating a controlled release of anti-angiogenic peptides. For diseases like diabetic retinopathy and age-related macular degeneration that need for continuous medication delivery, this extended-release capability is especially helpful (43).

Precise and targeted medication distribution is crucial in ophthalmology to treat a variety of eye disorders with the least amount of systemic side effects. This is where injectable hydrogels come into play, giving a substrate for the sustained release of therapeutic chemicals right into the eye. By lowering the frequency of administration and increasing the therapeutic efficacy of medications, this focused strategy improves patient compliance and comfort. Hydrogels can also be designed to break down in reaction to particular physiological cues, which enables the regulated release of medications over a predefined time frame.

6.2 Joint Diesease

Treatment of degenerative joint diseases, such osteoarthritis, presents major obstacles to tissue regeneration and pain control. A novel method of intra-articular medication administration is offered by injectable hydrogels, which provide growth factors, analgesics, and anti-inflammatory drugs to the injured joint area over an extended period of time (44). These hydrogels not only reduce pain and inflammation but also encourage the regeneration and repair of cartilage, which slows the advancement of illness and enhances joint function. Injectable hydrogels provide a biomimetic environment favourable to tissue healing and repair by emulating the biomechanical characteristics of native cartilage and synovial fluid. This characteristic makes them a promising option for intra-articular therapy (44).

Degradation of articular cartilage and inflammation of the synovial membrane are two of the crippling symptoms of osteoarthritis. By delivering targeted therapy directly to the injured joint, injectable hydrogels containing growth factors or anti-inflammatory medications can lessen discomfort and encourage tissue healing. Hydrogels' viscoelastic qualities can also enhance joint cushioning and lubrication, which can reduce discomfort and enhance joint function. Furthermore, these hydrogels can be engineered to release medicines in response to enzymatic activity or mechanical stress, offering a patient-specific treatment that is responsive to their demands.

6.3 Postoperative Analgesia

In order to maximise patient happiness and recovery, postoperative pain management must be done effectively. With injectable hydrogels, analgesic drugs can be delivered locally and continuously, reducing the risk of systemic adverse effects and enhancing pain management after surgery (45). With the ability to release analgesics at a controlled rate, these hydrogels can guarantee long-lasting pain relief while lowering the requirement for opioid-based drugs. Injectable hydrogels provide a safe and efficient method of managing pain following surgery by encapsulating analgesic medications in a biocompatible and biodegradable matrix. This enhances patient comfort and expedites early mobilisation and rehabilitation (45).

A crucial component of surgical care is postoperative pain management, since poor pain management increases the risk of complications, prolongs recovery, and causes discomfort for the patient. Because injectable hydrogels can administer analgesic drugs directly to the surgical site, they provide a tailored approach to pain treatment. By limiting the systemic exposure to painkillers, this localised distribution lowers the possibility of side effects like nausea, vertigo, and respiratory depression. Moreover, hydrogels can be designed to release analgesics in two ways: first, burst shortly after surgery, and then, gradually, to control pain as the patient recovers.

6.4 Cardiac Therapy

Globally, cardiac diseases—myocardial infarction and heart failure, for example—are the primary causes of morbidity and mortality. With the ability to deliver therapeutic molecules to the damaged heart in a targeted and sustained manner, injectable hydrogels have enormous potential for cardiac regeneration and repair (46). By imitating the natural extracellular matrix of heart tissue, these hydrogels can be designed to offer mechanical support as well as an environment that is favourable for tissue regeneration and cell proliferation. Injectable hydrogels provide new hope for patients with cardiovascular problems by promoting angiogenesis, reducing fibrosis, and enhancing cardiac function directly to the heart by the delivery of growth factors, stem cells, or genetic material (46).

Globally, heart failure and myocardial infarction are the main causes of illness and death. Promising as regenerative therapeutics for the restoration of injured cardiac tissue and heart function are injectable hydrogels filled with growth hormones, stem cells, or genetic material. These hydrogels can be injected straight into the heart, where they create a scaffolding that supports tissue regeneration and serves as a reservoir for healing substances. In addition, hydrogels can be designed to release medication or bioactive compounds in response to variations in temperature, pH, or enzyme activity. This allows for a treatment that is dynamic and can adjust to the changing requirements of the damaged tissue.

6.5 Bone and Cartilage Tissue Engineering

Defects in bone and cartilage brought on by illness, injury, or ageing pose serious clinical problems. With a three-dimensional matrix that promotes cell adhesion, proliferation, and differentiation, injectable hydrogels have become increasingly attractive as scaffolds for bone and cartilage tissue engineering (47). To promote tissue regeneration and repair, these hydrogels can be filled with bioactive substances including growth factors and osteoinductive agents. Additionally, biomimetic microenvironments are provided by injectable hydrogels loaded with nanoparticles, such as nano-hydroxyapatite, which encourage osteogenesis and mineralization and aid in bone healing and regeneration (48). Hydrogels that contain chondroitin sulphate, hyaluronic acid, and proteins specific to cartilage offer a favourable environment for the development of chondrogenic differentiation and the deposition of cartilage matrix. As such, they represent a viable option for the restoration and regeneration of cartilage (47).

When it comes to craniofacial bone regeneration, a hydrogel that combines FGF-18, bioglass or whitlockite nanoparticles, and chitin-PLGA showed a prolonged release of FGF-18, which in cases with cranial bone defects led to nearly full bone repair (55). These illustrations demonstrate the adaptability and potency of injectable hydrogels in encouraging tissue repair and regeneration. In order to facilitate long-term tissue repair, hydrogels can also be engineered to break down in a regulated way, releasing their therapeutic payload over several weeks or months.

6.6 Cancer Therapy

Cancer is still a difficult disease to treat in modern medicine, requiring novel therapeutic strategies. When it comes to cancer treatment, injectable hydrogels have special possibilities for combination therapy and tailored medication delivery (49). These hydrogels can be designed to contain gene therapy vectors, immunomodulatory substances, or chemotherapeutic medications, allowing for the targeted and prolonged delivery of treatments to tumour locations with the least amount of systemic

harm. Injectable hydrogel systems containing glutathione-responsive drug release and tumor-targeting nano-micelles have demonstrated enhanced anticancer efficacy and a potent inhibitory effect on tumour growth (49). Hydrogels that incorporate stimuli-responsive materials, including thermoresponsive nanoparticles and pH-sensitive polymers, also improve therapeutic selectivity and allow for on-demand drug release, opening up new possibilities for customised cancer treatment (49). Cancer is still a major worldwide health concern, and conventional treatments are frequently linked to serious side effects and low effectiveness. A promising platform for precisely delivering drugs to tumour locations while reducing systemic toxicity and optimising therapeutic efficacy is provided by injectable hydrogels. Additionally, combination therapies can overcome drug resistance and improve treatment outcomes by including numerous therapeutic agents due to the adjustable features of hydrogels. To enhance therapeutic outcomes, for instance, innovative hydrogel formulations have been developed in the field of chemo-photothermal therapy. A study showing the possibility for combination chemotherapeutic and photothermal treatment examined the potential of resveratrol and dopamine-reduced graphene oxide (DOPA-rGO) in an in-situ-forming hydrogel for breast cancer therapy (58).

6.7 Drug Delivery System

Drug delivery can be facilitated by injectable hydrogels, which provide accurate control over the kinetics of drug release and its biodistribution (52). These hydrogels are adaptable enough to hold a broad variety of therapeutic agents, such as proteins, nucleic acids, small molecules, and nanoparticles, which makes it easier to create innovative drug delivery systems for a range of medicinal uses. Injectable hydrogels provide tailored drug delivery to particular tissues or cell types by combining stimuli-responsive polymers and bioactive ligands. This maximises therapeutic efficacy and reduces off-target effects. Hydrogels can also be designed to react to physiological stimuli, such pH, temperature, or enzyme activity variations, allowing for on-demand therapy and triggered drug release (52). Injectable hydrogels' adjustable qualities provide designers flexibility in creating unique medication delivery systems that meet the various needs of different therapeutic applications and patient populations. A novel strategy is based on a cell-penetrable nano-polyplex hydrogel technology that allows for localised delivery of siRNA, allowing for site-specific and sustained gene silencing with a single injection (52). By providing exact control over the location and timing of genetic material release, these technologies pave the way for novel applications in personalised medicine and gene therapy.

6.8 Wound Healing and Anti-Inflammatory Applications

Inflammatory diseases and chronic wounds place a heavy cost on global healthcare systems. Because injectable hydrogels provide a supporting matrix that encourages tissue regeneration and lowers inflammation, they present promising treatments for anti-inflammatory therapy and wound healing (57). To promote wound healing and reduce inflammation, these hydrogels can be loaded with bioactive substances like growth factors, antimicrobial peptides, and anti-inflammatory medications. For example, the berberine-treated ZnO nano-colloid hydrogel had excellent moisturising qualities, anti-inflammatory effects, and notable wound healing capabilities, suggesting that it could be a viable therapy option for diabetic wounds (57).

Injectable hydrogels offer a moist, encouraging environment that aids in tissue repair and lowers inflammation in wound healing applications. These hydrogels have antibacterial qualities that lower the chance of infection in addition to hastening the healing of wounds. Furthermore, hydrogels can be engineered to disintegrate in reaction to particular environmental stimuli, including pH shifts or alterations in enzyme activity, offering a flexible and adaptive therapy that adjusts to the requirements of the mending tissue.

6.9 Immunotherapy and Additional Therapeutic Uses

Using the body's immune system to target and destroy harmful cells, immunotherapy has become a viable treatment option for autoimmune illnesses and cancer. When it comes to immunotherapy, injectable hydrogels are particularly advantageous because they offer a way to administer immunomodulatory drugs such immune checkpoint inhibitors, cytokines, and antibodies locally (7). By designing these hydrogels to produce an immunosuppressive or immunostimulatory milieu, systemic toxicity can be reduced and immunotherapy effectiveness increased (7).

Furthermore, a customised approach to cancer immunotherapy is provided by injectable hydrogels laden with antigen-presenting cells or tumor-specific antigens, which stimulate a focused immune response against tumour cells while protecting healthy tissues. Moreover, hydrogels can be designed to release immunomodulatory substances in response to particular immunological cues, offering a flexible and dynamic therapeutic option that strengthens the body's defences against disease. Additionally, injectable hydrogels are being investigated for cancer treatments, cardiovascular disorders, ischemic brain damage treatment, and cartilage restoration. They are appropriate for these wide range of applications due to their capacity to deliver localised, prolonged release of immunomodulatory drugs or therapeutic compounds. For example, hydrogels can transport neuroprotective medicines directly to the site of injury in ischemic brain injury, thereby facilitating tissue regeneration and neuronal survival. Hydrogels have the ability to release angiogenic factors

continuously, which can aid in the development of new blood vessels and enhance tissue perfusion in cardiovascular disorders.

CHAPTER 7: SWELLING PROPERTIES OF HYDROGELS

Hydrogels are essential in many biological and tissue engineering applications because of their exceptional capacity to absorb and hold large volumes of water. This chapter explores the mechanics, chemical effects, and other factors that affect the swelling behaviour of hydrogels as they relate to swelling.

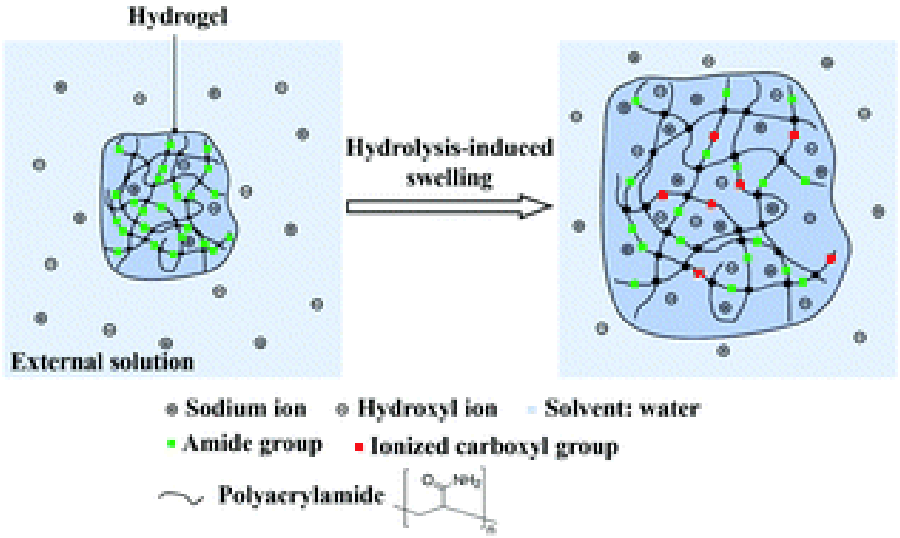

Figure 7.1 Hydrogel swelling

7.1 Fundamental mechanism of hydrogel swelling

The hydrophilic polymeric networks of hydrogels are the main source of their swelling behaviour. These networks have a high affinity for water because they contain functional groups like hydroxyl (-OH), carboxyl (-COOH), amide (-CONH-), primary amide (-CONH2), and sulfonic (-SO3H) groups (59,60,61,62). The ability of hydrogels to absorb and hold large amounts of water is made possible by these hydrophilic groups interacting with water molecules. This property is crucial for applications like drug delivery, where the hydrogel matrix acts as a conduit for drug diffusion (63).

Compatible solvent molecules attack the hydrogel surface and penetrate the polymeric network when they come into contact with hydrogels. Between the rubbery hydrogel area and the unsolvated glassy phase, this contact forms a moving border. The hydrogel swells as additional solvent molecules enter it as the network meshes in the rubbery phase expand (63). An elastic force acting against the osmotic force causing the swelling balances the edoema. When these forces equalise, additional swelling is prevented and equilibrium is established.

The ideas of mixing free energy (ΔG_mix), which comes from interactions between the polymer and solvent, and elastic free energy (ΔG_elastic), which comes from the crosslinked network, can both be used to thermodynamically describe the swelling behaviour of hydrogels (64). The system's total free energy change (ΔG_system) can be written as follows:

$\Delta Gelastic + \Delta Gmix = \Delta G_{system}$

When swelling first begins, ΔG_{mix} is quite negative, which encourages solvent diffusion into the network, and $\Delta G_{elastic}$ is positive, which opposes this growth. Swelling occurs until there is no net free energy change and the magnitudes of ΔG_{mix} and $\Delta G_{elastic}$ equalise:

$|\Delta Gmix| = |\Delta Gelastic|$

$\Delta Gsystem = \Delta Gmix + \Delta Gelastic = 0$

This equilibrium state signifies the cessation of swelling.

7.2 Swelling in Response to Stimuli

Smart hydrogels, often referred to as stimuli-sensitive hydrogels, show notable alterations in their swelling ratios in reaction to slight adjustments in their surrounding environment. pH (65,66), temperature (67), light (68), electric fields (69,70), pressure (71), carbohydrates (72), and antigens (73,74) are some examples of these stimuli. The potential of pH-sensitive hydrogels in the development of sophisticated drug delivery systems has been thoroughly examined (75). The kinetics of swelling in response to these stimuli can be delayed, taking hours or days to reach equilibrium, despite their sensitivity.

Researchers have created comb-type polymers to improve response times; these polymers show faster swelling dynamics because their hydrophobic pendant chains break down faster than those of conventional hydrogels (76). A crucial characteristic that is affected by a number of physicochemical elements, chiefly the kind and extent of porosity in the hydrogel network, is the rate of swelling.

7.3 Hydrogel Classification and Swelling Rates

Based on the structure of their pores, hydrogels can be divided into four types: non-porous, micro-porous, macro-porous, and super-porous. Different swelling behaviours and applications are displayed by each category:

1- Non-Porous Hydrogels: These hydrogels are homogeneous in structure and do not exhibit any observable porosity. Within the polymer network, diffusion through free volumes is the main process responsible for swelling. The pace at which non-porous hydrogels swell is greatly dependent on the size of the sample. Because of their ability to manage swelling and release, these hydrogels are frequently utilised in applications such as wound dressings, contact lenses, artificial muscles, and drug delivery patches.

2- Micro-porous hydrogels -Micro-porous hydrogels, which are characterised by small, closed-cell porosity structures that typically range between 100 and 1000 Å, primarily swell through molecular

diffusion and convection within water-filled pores. Sample size affects the sluggish pace of swelling. In controlled release formulations and biomedical devices, where a slow and steady release of medicinal substances is preferred, these hydrogels are often utilised.

3-Macro-porous hydrogels - These hydrogels have greater closed-cell porosity structures, usually ranging from 0.1 to 1 μm. Diffusion in water-filled pores is the main mechanism of swelling, which leads to a higher rate of swelling than in micro-porous hydrogels. Because of their rapid and significant water absorption capacity, macro-porous hydrogels are widely employed as superabsorbents in personal care items like infant diapers and in a variety of agricultural applications.

4-Super-Porous Hydrogels- Super-porous hydrogels rely on capillary forces to cause swelling because they have linked open-cell architectures and high porosity. They swell quite quickly, regardless of the size of the sample. These hydrogels are perfect for scaffolds used in tissue engineering and improved drug delivery systems, where high water absorption and fast reaction times are essential.This can be shown as-

	Non-porous	Micro-porous	Macro-porous	Super-porous
Morphology	Without network porosity	Various porosity with closed-cell structure (100-1000 A)	Various porosity with closed-cell structure (0.1 -1 μm)	High porosity with interconnected opencell structur
Type of absorbed water	Mostly bound	Mostly bound	Mostly bound	Mostly free
Major swelling mechanismMajor swelling mechanism	Diffusion through free volumes	Combination of molecular diffusion and convection in the water filled pores.	Diffusion in the water filled pores	Capillary forces
Swelling rate	Very slow, sample size-dependent	Slow, sample sizedependent	Fast, sample sizedependent	Very fast, sample size-independent
Application	Various uses from contact lenses to artificial muscles, etc.	Mainly in biomedical applications and controlled release technology	Mainly in form of superabsorbents in baby diapers, etc.	DDS (particularly in the gastrointestinal tract), tissue engineering, etc.

Table 1 – Hydrogel Classification and Properties

7.4 Approaches Theoretical and Modelling

Over the past few decades, significant progress has been achieved in modelling the swelling behaviour of polymeric networks at different sizes, from macroscopic to microscopic (78). For example,

statistical theories offer strong rationales for the polyelectrolyte gels' global swelling ratio. The foundation of these macroscopic theories is the idea that Gibbs free energy (ΔF), which is used to stimulate both chemically and thermally, must be at least minimal to reach an equilibrium state (79,80,81).

The theory of mixtures is extended by the idea of porous media, which is a kind of macroscopic or mesoscopic continuous theory. Despite the lack of comprehensive knowledge about the true geometrical distribution of each element and the local porous microstructure, this theory uses homogenised models to average geometrical and physical parameters (82,83,84). The multi-field formulation, a chemo-electro-mechanical model, combines a number of balancing equations to span the fields of mechanical, electrical, and chemistry research in order to describe momentum, diffusion, and Poisson's equations, respectively (85,86).

Furthermore, the micromechanical behaviour of hydrogels is explained by the discrete element theory, which focuses on the mechanical interactions between particles scattered across the hydrogel network (87). The microscale dynamics influencing the macroscopic swelling behaviour of hydrogels are explained in depth by this theory.

7.5 Applications and Future Perspectives

Hydrogels' ability to swell makes them useful for a wide range of applications, especially in the disciplines of biomedical and tissue engineering. Hydrogels, for example, are perfect for drug delivery systems because of their capacity to swell and hold huge volumes of water, which allows for the regulated release of medicinal chemicals. Smart hydrogels' ability to react to external stimuli presents a viable avenue for the development of sophisticated drug delivery platforms that may modify drug release rates based on certain physiological parameters.

Hydrogels are scaffolds used in tissue engineering that replicate the extracellular matrix and promote cell adhesion, proliferation, and differentiation. Because of their capacity to swell, they can keep the environment moist, which promotes tissue regeneration and cell proliferation. Fast-swelling hydrogels have also been developed, which makes them more useful in clinical settings where quick reaction times are frequently essential.

Future studies on the swelling characteristics of hydrogels will probably concentrate on strengthening their mechanical qualities, increasing their sensitivity to stimuli, and investigating new uses in cutting-edge therapeutic delivery systems, regenerative medicine, and personalised health. By incorporating bioactive compounds and nanotechnology into hydrogel networks, next-generation hydrogels with previously unheard-of activity and versatility may be created.

CHAPTER 8: KINETICS OF SWELLING PROPERTIES OF HYDROGELS

To maximise the performance of hydrogels in a variety of applications, including drug delivery, tissue engineering, and environmental engineering, it is essential to comprehend the kinetics of hydrogel swelling. The kinetic processes that underlie hydrogel swelling are examined in this chapter, along with the different kinds of transport mechanisms, the rate at which swelling occurs, and the impact of environmental variables.

8.1 Fundamental Mechanisms of Hydrogel Swelling

The constant change from an unsolvated glassy or partially rubbery condition to a fully relaxed rubbery state is known as swelling. In polymer-solvent systems, the sorption processes are frequently not well described by classical diffusion theory, particularly when the polymer is near or below its glass transition temperature (T_g) (88). Many anomalous effects can arise from the reorientation of polymer molecules during sorption and penetration testing. Fickian (or Case I) transport and non-Fickian diffusion are the two categories into which Bajpai divides the basic forms of diffusion (89).

1-Fickian (First Case) Transport: This is the result of the polymer chains' strong mobility when its T_g is much lower than the medium temperature. Since $R_{diff} << R_{relax}$, the polymer chain relaxation rate (R_{relax}) is greater than the solvent diffusion rate (R_{diff}) as a result of the water diffusing quickly into the rubbery network (90).

2-Non-Fickian Diffusion: This happens when the Tg of the polymer is much greater than the temperature used in the experiment. As a result, the water seeps into the polymer core more slowly and the polymer chains become less dynamic. Two further categories of non-Fickian diffusion are "anomalous transport" and "Case II transport":

- Case II Transport: Dominant when diffusion happens more quickly than relaxation ($R_{diff} >> R_{relax}$) and relaxation happens at an observable pace. In this case, the swelling and the mass absorption rate have a linear connection.

When the rates of relaxation and diffusion are comparable ($R_{diff} = R_{relax}$), anomalous transport is identified.

8.2 Swelling Rate

The following formula can be used to calculate a hydrogel's swelling rate, which is defined as the change in swelling content per unit of time:

$$[S_{[t+\Delta t]} - S_t]/\Delta t = S_R$$

where S_t is the swelling content at any time (g/g d.b.) and $S_{t+\Delta t}$ represents the swelling content based on the dry content at "$t + \Delta t$."[2]

8.3 Diffusion of Water

The kinetics of swelling and diffusion in polymeric materials are often described by Fick's laws. Peppas et al. (91,92) state that:

$F = S_t/S_e = kt^n$ {4.4}

where the swelling fraction is represented by F .

The hydrogel's equilibrium swelling content is represented by S_e, the diffusion exponent is represented by n, and the constant K depends on the network structure of the gel. Finding the parameter nn aids in determining the kind of diffusion. Diffusion exponent n can be estimated by graphing lnF against lnt during the first swelling phase and determining the slope:

It is indicated by

-n = 0.5 for Fickian diffusion.

-Anomaly transport is indicated by n > 0.5.

-Case II (relaxation-controlled) transport is shown by n = 1.

8.4 Temperature's Effect on Swelling Kinetics

The swelling dynamics of hydrogels are strongly influenced by temperature. For example, the swelling equilibrium values at 25°C, 40°C, and 60°C were determined to be 30.19, 47.18, and 74.07 g water/g dry hydrogel, respectively, in a study on acrylamide-sodium acrylate hydrogel. The findings showed that when temperatures rose, there was an increase in both the amount and rate of edoema (93). This is explained by the fact that at higher temperatures, solvent diffusion rates increase and polymer chains become more mobile.

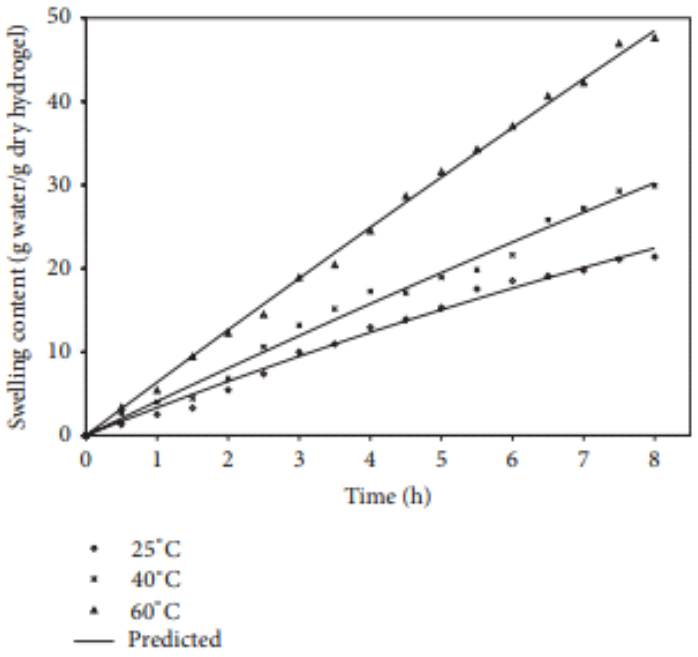

Figure 8.1 Hydrogel swelling Content values for both experimental and predicted values based upon to the exponential association model

8.5- Modelling swelling kinetics

A number of models have been created to explain and forecast how hydrogels would swell. These models include microscopic and mesoscopic continuous theories that take into account intricate molecular interactions, as well as macroscopic theories that give a broad picture of the swelling ratio.

-Macroscopic Theories: These explain the global swelling ratio of polyelectrolyte gels and are based on the idea that equilibrium must be reached by a minimum Gibbs free energy (ΔF) (78).

-Porous Media Theory: Using volume fractions as an extension of the mixture notion, this mesoscopic theory creates a homogenised model in which all geometrical and physical parameters are averages of real data (82).

-Multi-Field Formulation: This chemo-electro-mechanical model describes the momentum, diffusion, and Poisson's equations, respectively, using balance equations from the mechanical, electrical, and chemical sciences (85).

-Discrete Element Theory: By taking into account the mechanical interactions between particles inside the hydrogel network, this microscopic theory explains the micromechanical behaviour of hydrogels (87).

8.6 Uses and Prospective Routes

To maximise the usage of hydrogels in a variety of applications, one must comprehend the dynamics

of hydrogel swelling. Precise regulation of swelling rates can facilitate the customised release of therapeutic substances in drug delivery. Rapid swelling can help create hydrogels in tissue engineering that imitate the extracellular matrix naturally and encourage cell attachment and development. Hydrogel swelling kinetics research in the future is probably going to concentrate on improving the responsiveness of hydrogels to stimuli, creating models that more accurately predict behaviour in varying environmental circumstances, and investigating novel materials and composites to enhance performance. Hydrogels have many practical uses; nevertheless, further development of the area and experimental confirmation of these applications will require the integration of sophisticated simulation techniques.

Thus The dynamic mechanisms involved in solvent molecules being absorbed by hydrogel networks are included in the kinetics of hydrogel swelling. Variations in temperature, polymer composition, and crosslinking density can all have an impact on these processes. Fickian and non-Fickian diffusion are two types of hydrogel swelling, with abnormal behaviours occurring at or below the glass transition temperature. The kinetics of solvent absorption are shown by the swelling rate, which is measured as the change in swelling content per unit of time. Equations based on mathematics, like the ones put forth by Peppas et al., incorporate variables such as solvent diffusion exponential, swelling percentage, and equilibrium swelling content to characterise the kinetics of polymer swelling. The temperature dependence of swelling kinetics is demonstrated by experimental experiments, such as the one using an acrylamide-sodium acrylate hydrogel, underscoring the significance of environmental conditions in hydrogel applications. In general, the kinetics of hydrogel swelling must be understood in order to customise the properties of hydrogels for particular uses in industries like tissue engineering and drug delivery.

CHAPTER 9: DRUG RELEASE PROPERTIES OF HYDROGELS

9.1- Introduction to drug release properties of hydrogels

To optimise the therapeutic efficiency of pharmaceuticals, drug delivery systems play a crucial role in controlling drug release (94, 95), concentrating on particular tissues or organs (96, 97, 98, 99), and minimising any adverse effects (100, 101, 102). These systems are painstakingly engineered to guarantee that medications are given at the ideal location, moment, and concentration, increasing their efficacy and reducing side effects. Because of their special and remarkable qualities, hydrogels have become one of the most promising options for drug delivery systems【103】. Because of their high permeability and inherent swelling and cross-linking properties, hydrogels have a high porosity, which makes them perfect for effectively loading and releasing a wide range of drugs【104】. Hydrogels possess a significant benefit in that they can administer high drug concentrations for extended durations to particular body parts【105】. This is especially important for chronic illnesses that need consistent dosages of treatment. Furthermore, hydrogels' potential for long-term medication delivery through gastro-retentive processes has been thoroughly investigated【106】. Hydrogels are a suitable platform for controlled drug release because of their high biocompatibility, inertness, and capacity to release pharmaceuticals in aqueous settings. They can also be easily regulated by altering the density of crosslinking and water swelling.

9.2 - Classification of Drug Delivery Systems

Conventional or traditional drug delivery systems and novel or controlled-release drug delivery systems (108,109,95,110,111) can be the two basic categories into which drug delivery systems can be roughly classified. Oral, buccal or sublingual, rectal, intravenous, subcutaneous, and intramuscular delivery are examples of traditional delivery techniques. The lack of synchronisation between the time required to obtain therapeutically effective plasma drug concentrations and the actual drug release profile of the dosage form can pose a substantial constraint to these approaches, despite their widespread usage and simplicity【113】. However, by offering more exact control over drug release kinetics and focusing on certain tissues or organs, innovative or controlled-release drug delivery systems aim to get around these drawbacks. Activation-modulated, feedback-regulated, rate-preprogrammed, and site-targeting drug delivery systems are some of these cutting-edge systems【112】. By delivering medications in a way that better matches the body's requirements and the

pharmacokinetics of the drug, these advanced systems seek to improve therapeutic outcomes and minimise side effects.

9.3- Evolution and Mechanisms of Hydrogels

Hydrogels were previously described as three-dimensional (3D) gum and hydrophilic natural polymer networks that were produced by chemical or physical crosslinking. These conventional hydrogels were mostly used in the swelling-deswelling process, which was contingent upon the surrounding water availability (Lee et al., 2013). Drug administration and wound dressings are two biomedical applications where this swelling-deswelling behaviour proved essential. A major turning point in the history of hydrogel research was reached in 1960 when Wichterle and Lim created the first modern hydrogel. Since then, there has been a significant evolution in the subject, with modern smart hydrogel applications falling into four main categories: drug delivery, tissue engineering, biosensors, and bioseparation. These uses demonstrate the adaptability and promise of hydrogels in a range of biomedical domains. Hydrogel-based drug carriers are intended to distribute drugs to specific body sites, regulate drug release【114,115】, improve drug stability】118,119】, and improve therapeutic outcomes】116,117】. Additionally, these carriers can prevent medications from degradation (123,124), increase their solubility (120,121,122), enable targeted administration (108,109,110), offer continuous release (125,126), and improve the stability and bioavailability (118,119,109,102). The development of hydrogel technology has improved its efficacy as a drug delivery platform and greatly broadened its range of uses.

9.4 Properties and Advantages of Hydrogel-based Drug Delivery Systems

The special qualities of hydrogel-based drug delivery systems, such as zero-order kinetics【113】, temperature sensitivity, swelling behaviour in aquatic settings, and pH sensitivity, make them valuable. Because of these characteristics, hydrogels can precisely regulate the release of drugs, which makes them appropriate for a wide range of biological uses. Improved drug binding to the hydrogel matrix can be achieved by the use of both chemical and physical approaches, which will extend the drug release time【127】. Because most hydrogels have a high water content, hydrophilic medicines usually escape from the gel matrix over the course of hours or days. When compared to release profiles obtained with more hydrophobic polymers, such as PLGA, this one is noticeably shorter. As a result, several tactics have been investigated to reduce the speed at which drugs release from hydrogels.These strategies can be categorized based on whether they enhance the interaction

between the drug and hydrogel matrix or increase the diffusive barrier that hinders drug release【128】.

- Drug-Hydrogel Interactions: The duration of release may be extended by strengthening the bond between the hydrogel matrix and the drug that is loaded. Physical interactions including hydrophobic interactions, hydrogen bonding, and electrostatic attractions can do this. Alternatively, stronger and more stable bonds between the medication and the hydrogel can be created by covalent bonding.

- Gel Network Engineering: Modifying the gel network to regulate drug release involves the use of strategies including surface diffusion control, interpenetrating polymer networks (IPNs), and composite hydrogels. In order to produce a more complicated structure that can better control drug release, IPNs involve merging two or more polymer networks. Drug diffusion can be slowed down by altering the hydrogel's surface characteristics through surface diffusion control. To improve hydrogels' mechanical characteristics and drug release patterns, composite hydrogels mix hydrogels with other materials.These cutting-edge techniques guarantee that hydrogel-based systems may be precisely adjusted to satisfy particular therapeutic requirements, offering a flexible and efficient drug delivery platform.

9.4 Mechanical Properties of Hydrogels for drug delivery

For drug delivery systems, the mechanical characteristics of polymer-based hydrogels are essential because they dictate the hydrogel's functionality, stability, and capacity to interact with biological tissues and release pharmaceuticals under regulated conditions【129,130,131,132,133】. Drug delivery systems are particularly interested in a few important mechanical properties:

- Elasticity and Flexibility: Hydrogels need to have adequate flexibility to mould themselves into the contours of the tissue in which they are inserted without cracking. During drug distribution, elasticity aids in preserving the hydrogel's structural integrity. The hydrogel's ability to adapt to changing biological settings without sacrificing its structural or functional integrity is ensured by its flexibility.

- Chemical Composition: The chemical composition of hydrogels significantly affects their mechanical properties and their interaction with drugs and biological tissues. Researchers can customise hydrogels for particular uses, such improving their mechanical strength, biocompatibility, or drug release patterns, by changing their chemical composition.

- Swelling Behaviour: Drug loading and release depend heavily on hydrogels' capacity to absorb water and swell. The administration of medications at the intended rate and duration is guaranteed by controlled swelling behaviour. Precise control over medication distribution is made possible by adjusting the crosslinking density and hydrogel composition to modify the degree of swelling.

- Viscoelasticity: Hydrogels can react to mechanical stresses and deformations because they have both viscous and elastic properties. This characteristic is crucial for guaranteeing that the hydrogel can endure physiological circumstances and continue to function over time. Viscoelastic characteristics can be adjusted to match the target tissue's mechanical characteristics, improving the hydrogel's efficacy in drug delivery applications.

- Adhesion and Cohesion: Hydrogels' potent adhesive qualities allow them to stick to biological tissues, keeping them in situ at the drug delivery site. The hydrogel's cohesive qualities guarantee that it keeps its structure throughout the drug delivery process, avoiding early deterioration or disintegration.

Hydrogels' mechanical strength plays a crucial role in preserving their structural integrity when subjected to mechanical pressures, guaranteeing their robustness throughout the drug delivery, implantation, and manufacturing processes【134,135】. By utilising diverse engineering strategies to improve these mechanical qualities, hydrogels can be utilised in a multitude of biological applications with successful outcomes.

9.5- Applications of Hydrogel-based Drug Delivery Systems

Hydrogels find applications in various drug delivery systems, including:

- Controlled Drug Release: By creating hydrogels with controlled drug release, adverse effects can be minimised and therapeutic efficacy can be increased. There are a number of ways to accomplish this controlled release, including diffusion, swelling, or hydrogel matrix disintegration.
- Targeted Drug Delivery: Hydrogels have the ability to distribute medications to certain organs or tissues, increasing the concentration of the medication at the intended location and reducing systemic exposure. When treating localised illnesses like tumours or infections, when large drug concentrations are required at certain areas, targeted delivery is especially helpful.
- Oral Drug Delivery: When administered orally, hydrogels can shield medications from the harsh conditions of the gastrointestinal tract and offer a continuous release of medication. This

is particularly crucial for medications that are susceptible to alterations in pH or enzymatic breakdown in the intestines and stomach.

- Transdermal Drug Delivery: Hydrogels can be utilised in patches that penetrate the skin to distribute medications, providing a controlled and non-invasive way to do so. Transdermal delivery devices can improve patient compliance and convenience by delivering continuous drug release over prolonged periods of time.
- Implantable Drug Delivery Systems: Hydrogels are a viable treatment option for chronic illnesses requiring continuous medication since they can be permanently released into the body through implantation. Drugs can be released from implantable systems over a period of weeks, months, or even years, which can improve patient outcomes and minimise the need for regular dosage.

- Gene Delivery: For gene therapy applications, hydrogels can be used to transfer genetic material, such as DNA or RNA. Hydrogels are a suitable substrate for gene delivery because of their capacity to protect genetic material and allow regulated release, which may lead to the development of remedies for diseases and disorders caused by genetics.

The expanding number of research articles on polymer-based hydrogels, especially in drug delivery【102,136,137,138,139】, reflects the growing interest in and recognition of the potential of hydrogel-based systems in biomedical applications. Over time, there has been a noticeable increase in publications focusing on drug delivery applications, along with a large increase in research activities. For example, in 2005 there were fewer than 400 drug delivery-focused publications out of over 1,000; by 2015, however, nearly 4,000 publications included approximately 1,650 drug delivery-related articles. More than 12,000 papers were published by 2022, with more than 5,000 of them concentrating on drug delivery【112】. This study's exponential expansion demonstrates how hydrogels are becoming more widely acknowledged as a flexible and efficient drug delivery platform.

9.6 Future Directions and Conclusion

One area of hydrogel drug delivery research that is still expanding is the creation of complex drug delivery systems, such as self-regulating insulin administration systems【113】. Hydrogel-based drug delivery systems are expected to undergo further developments in the future that will likely concentrate on improving their mechanical characteristics, maximising drug release patterns, and broadening their use in customised medicine. For instance, studies on stimuli-responsive hydrogels, which respond to variations in temperature, pH, or other environmental conditions, may result in even

more specialised and focused drug delivery systems. These intelligent hydrogels can be engineered to release medication in response to particular physiological cues, enabling on-demand medication delivery customised to meet the needs of each patient.

Additionally, new avenues for improving medication delivery and therapeutic results may arise from the incorporation of nanotechnology with hydrogel systems. With the addition of nanoparticles to the hydrogel matrix, nanocomposite hydrogels can provide targeted delivery, controlled drug release, and enhanced mechanical qualities. These cutting-edge materials can be designed to carry proteins, nucleic acids, and small molecule medications, among other therapeutic agents.

Moreover, a potential field of study is the investigation of biodegradable hydrogels, which break down into non-toxic byproducts after serving as drug delivery vehicles. Biodegradable hydrogels have the potential to improve the safety and convenience of drug delivery systems by lowering the requirement for surgical implant removal and lowering the danger of long-term problems.

Through persistent efforts to overcome existing constraints and the utilisation of hydrogels' distinct characteristics, scientists can create more efficient and focused medication administration approaches that enhance patient results. Significant improvements in medication delivery are anticipated as a result of the continuous research and innovation in this area, which will ultimately help treat a variety of illnesses and enhance patient quality of life.

To sum up, hydrogels are a flexible and exciting platform for regulated drug delivery systems. They are perfect for a variety of biomedical applications due to their special qualities, which include high porosity, biocompatibility, and the capacity to be finely tailored for certain applications. The fact that research and development in this field are still expanding shows how hydrogels have the potential to transform drug delivery and improve therapeutic results. We may anticipate seeing even more cutting-edge and practical hydrogel-based medication delivery solutions as the industry develops, ones that adapt to the changing requirements of both patients and healthcare professionals.

CHAPTER 10: KINETICS OF DRUG RELEASE PROPERTIES OF HYDROGELS

Due to their unique capacity to regulate the release of medications that are soluble in water through a swelling-controlled diffusion process, hydrogels have attracted a lot of attention. When water and medication are absorbed simultaneously in dehydrated hydrogel matrices, this process works especially well. Water penetrates the hydrogel and causes it to expand, which lowers the polymer's glass transition temperature and facilitates the dispersion of the dissolved drug into the surrounding medium. However, because of another molecular relaxation process【107】, this process does not follow a Fickian diffusion mechanism. Developing efficient drug delivery systems requires an understanding of the mechanics underlying drug release from hydrogels. The release kinetics are mostly determined by the swelling-controlled diffusion process, which is governed by variables including crosslinking density and drug-polymer interactions. Furthermore, the release dynamics are further complicated by the existence of non-Fickian behaviour resulting from molecular relaxation processes. Through the clarification of these mechanisms, scientists can create hydrogel-based systems that offer consistent and regulated drug release, improving patient outcomes and therapeutic efficacy.

10.1 Swelling-Controlled Diffusion

The therapeutic efficacy and duration of the drug's effect are largely dependent on the kinetics of the drug's release from hydrogels. The drug's rate of diffusion, the degree of crosslinking within the hydrogel matrix【140】, and the hydrogel's swelling behaviour are the main variables influencing the release process. Hydrogels absorb water and swell when they are in an aqueous environment. The swelling causes the mesh size of the polymer network to expand, allowing drug molecules to diffuse out of the hydrogel matrix. The swelling-controlled diffusion process explains the direct correlation between the size of the dispersing drug molecules and the rate of hydrogel swelling and the drug release rate.

The relationship for swelling-controlled diffusion can be expressed with the following equation:

$F = S_t/S_e = kt^n$

Here, F represents the fraction of drug released, S_t and S_e are the swelling at time t and at equilibrium, respectively, k is a constant, and t and n are time and the release exponent, respectively.

10.1.1 Factors Affecting Controlled Diffusion by Swelling

-Polymer Structure and Composition: The swelling behaviour and, in turn, the drug release profile are greatly influenced by the molecular structure and makeup of the polymer. Drug molecules diffuse more readily in aquatic settings when hydrogels made of hydrophilic polymers swell more. It is possible to build crosslinked polymer networks with different densities to regulate the pace of release and the degree of swelling.

-Environmental Factors: Hydrogel swelling behaviour can be influenced by the pH, temperature, and ionic strength of the surrounding environment. For instance, pH-sensitive hydrogels have the ability to swell or deswell in response to variations in pH, which offers a means of releasing drugs when the pH changes. Similar to this, temperature-sensitive hydrogels can change phases at particular temperatures, enabling controlled administration of drugs.

-Drug Properties: Important roles are also played by the drug's diffusivity, solubility, and molecular size in the swelling-controlled diffusion mechanism. More solubility and smaller drug molecules diffuse more easily through the enlarged hydrogel matrix.

10.2 Crosslinking Density

The kinetics of drug release are strongly influenced by the hydrogel's degree of crosslinking. Smaller mesh sizes in highly crosslinked hydrogels limit drug molecule mobility and decrease release rate. On the other hand, hydrogels with lower crosslinking have bigger mesh sizes, which promotes quicker drug dispersion. The following equation can be used to represent this relationship between medication release and crosslinking density:

$D=D_0\exp(-Ec/RT)$

Where:

- D is the diffusion coefficient of the drug,
- $D_0$is the pre-exponential factor,
- Ec is the activation energy for diffusion,
- R is the gas constant,
- T is the temperature【141】.

10.2.1 Crosslinking Density Effects

Mechanical Properties: The crosslinking density affects the mechanical stability and strength of hydrogels. Increased stiffness and resistance to deformation are characteristics of highly crosslinked hydrogels, which may be advantageous for preserving structural integrity during drug delivery. On the other hand, over-crosslinking may reduce the hydrogel's elasticity and flexibility, which may have an impact on its performance and biocompatibility.

Swelling Behaviour: In aquatic conditions, the degree of swelling is determined by the degree of crosslinking. Hydrogels with fewer crosslinks swell more quickly, enabling greater drug loading and quicker release rates. Highly crosslinked hydrogels, on the other hand, show less swelling, which results in a delayed drug diffusion and extended release.

Biodegradability: The density of crosslinking can also affect a hydrogel's capacity to break down naturally. For applications needing transitory drug delivery methods, hydrogels with lower crosslinking densities typically break down faster. Highly crosslinked hydrogels, on the other hand, break down more gradually, which makes them appropriate for long-term drug delivery applications.

10.3 Drug Interactions with Polymers

The way the drug interacts with the hydrogel matrix is another important factor that affects release kinetics. In comparison to drugs that are weakly bound, those that create strong interactions with the polymer matrix, such as ionic or hydrogen bonding, are released more slowly. The partition coefficient K can be used to describe these interactions:

$K = C_d / C_p$

Where:

- C_d is the concentration of the drug in the hydrogel,
- Cp is the concentration of the drug in the surrounding medium【140】.

Higher K values indicate stronger drug-polymer interactions and slower release rates.

10.3.1 Types of Drug-Polymer Interactions

Bonding of Hydrogen: Drug release can be considerably delayed by hydrogen bonds formed between the polymer matrix and drug molecules. Drugs that have functional groups (such as hydroxyl, carboxyl, and amine groups) that can establish hydrogen bonds diffuse through the hydrogel matrix more slowly.

Ionic Interactions: Charged drug molecules may interact electrostatically with oppositely charged polymer chains to further inhibit the release of the drug. These interactions are especially important when it comes to hydrogels made of polyelectrolytes.

Hydrophobic Interactions: Hydrophobic drugs may interact with hydrophobic regions within the polymer matrix, affecting their diffusion rates. Hydrophobic segments or monomers can be added to the hydrogel network to modify these interactions.

10.4 Non-Fickian Behavior

In addition to diffusion, hydrogels frequently display non-Fickian behaviour because of molecular relaxation processes. This suggests that the release mechanism is influenced by both the hydrogel's

swelling and the polymer chains' relaxing. A modified version of the diffusion equation can be used to describe non-Fickian diffusion:

$\partial C/\partial t = D(\partial^2 C/\partial x^2) + \partial R/\partial t$

Where C is the drug concentration, t is time, D is the diffusion coefficient, and R represents the relaxation term【142】.

10.4.1 Implications of Non-Fickian Behavior Release Kinetics:

Simple Fickian diffusion models are unable to capture the complex release kinetics caused by non-Fickian diffusion. Diffusion and polymer relaxation both have an impact on the release profile, which usually consists of an initial burst release and a continuous release phase.

Mathematical Modelling: Complex mathematical techniques that take into account both diffusion and relaxation processes are necessary to accurately represent non-Fickian behaviour. With the use of these models, hydrogel formulations for particular uses can be optimised and the drug release profile predicted.

Application in Smart Hydrogels: Non-Fickian behavior is particularly relevant for smart hydrogels that respond to environmental stimuli. These hydrogels can be engineered to release medication in reaction to pH, temperature, or other stimuli variations, enabling controlled and on-demand drug administration.

CHAPTER 9: ANALYSIS OF RECENT ADVANCES IN POLYSACCHARIDE-BASED HYDROGELS (2019-2023)

10.1 Overview

Research on polysaccharide-based hydrogels has increased significantly in the past few years, with a special emphasis on how these gels might be used in drug delivery systems. Many studies have been conducted between 2019 and 2023 to better understand the intricate interactions that exist between the kinetic properties, swelling behaviour, and structural features of polysaccharides. The objective of this chapter is to summarise and evaluate the results of these investigations, emphasising the major developments and continuing difficulties in the area.

10.2 Polysaccharide Versatility and Biocompatibility

Because of their various chemical functions, biocompatibility, and biodegradability, polysaccharides have attracted interest as possible biomaterials【143, 144】. These naturally occurring polymers present a good starting point for creating hydrogels that can satisfy the demanding specifications of biological applications. Since polysaccharides are naturally biocompatible, their use in drug delivery systems minimises immunological reaction and toxicity, which makes them perfect for long-term therapeutic applications.

10.3 Drug Release Kinetic Properties

The focus of current study has been on the kinetics of drug release from hydrogels based on polysaccharides. Many mathematical models have been used to clarify the mechanisms driving drug diffusion and release behaviour. These include the Higuchi, Korsmeyer-Peppas, zero-order, and first-order models. They all shed light on various facets of drug release kinetics【145, 146】.

10.3.1 Drug Release Mathematical Modelling

-Zero-Order Kinetics: This model explains a continuous release rate of the drug, regardless of the drug's concentration in the hydrogel. It is perfect for uses where the therapeutic substance must be released consistently and over time.

-First-Order Kinetics: According to this model, the rate of drug release decreases with time and is proportionate to the amount of drug still present in the hydrogel.

-Higuchi Model: This model applies to systems where drug release is governed by diffusion through a porous matrix. This is especially important for hydrogels that have a lot of swelling.

-The Korsmeyer-Peppas Model is an empirical model that incorporates both diffusion and swelling effects to describe drug release from polymeric structures when the release mechanism is not well-defined.

10.4 Polysaccharide Structure's Effect on Drug Release

Studies have shown how important it is to modify drug release kinetics by taking into account factors such swelling behaviour, degree of crosslinking, molecular weight, and polysaccharide composition】147, 148】. The ability of polysaccharides to form networks, encapsulate medications, and regulate the release profile is influenced by their molecular structure.

-Composition: The distinct chemical structures of various polysaccharides, including hyaluronic acid, chitosan, and alginate, affect how well they gel and how they interact with medications.

-Molecular Weight: The polysaccharide's molecular weight affects the gel strength and viscosity, which in turn affects how quickly pharmaceuticals are encapsulated.

-Crosslinking Degree: The hydrogel matrix's porosity and mechanical strength are impacted by the degree of crosslinking, which in turn affects drug release rates. Highly crosslinked hydrogels have limited diffusion channels, which results in slower drug release.

-Swelling Behaviour: Hydrogels' ability to swell is essential to drug delivery since it controls how much the hydrogel expands and how the drug releases as a result.

10.5 Polysaccharide-Based Hydrogels' Swelling Behaviour

The swelling behaviour of hydrogels based on polysaccharides has drawn a lot of attention. Numerous environmental parameters, including pH, temperature, ionic strength, and solvent composition, have been studied in relation to hydrogel swelling【149, 150】. Comprehending these variables is crucial in order to tailor the characteristics of hydrogels for particular biomedical uses, such as tissue engineering, wound healing, and controlled drug delivery.

10.6 Synthesis and Characterization of Novel Hydrogels

The goal of research has been to create and characterise novel hydrogels based on polysaccharides that can have their kinetic properties customised. The objectives of these endeavours are to accomplish extended drug release profiles, augment drug loading capability, and elevate hydrogel stability【151, 152】.

Long-Term Drug Release: To slow down the release of drugs, functional groups that interact strongly with drug molecules can be included, and crosslinking density can be optimised.

Drug Loading Capacity: By altering the hydrogel matrix, active medicinal components are more effectively encapsulated, leading to improvements in drug loading.

Hydrogel Stability: Chemical alterations that strengthen hydrogels' resilience to deterioration under physiological settings lead to increased stability.

10.7 Stimulus-Responsive Polysaccharide-Based Hydrogels

Additionally, recent studies have explored the creation of hydrogels based on polysaccharides that respond to stimuli. These hydrogels are capable of changing their characteristics in reaction to outside stimuli, such as temperature, pH, or certain biomolecules【153, 154】. Stimulus-responsive hydrogels allow for precise control over drug release, making it possible to administer therapy on-demand in response to certain biological signals or alterations in the surrounding environment.

-pH-Responsive Hydrogels: These hydrogels can be used for targeted medication administration in areas of the body like the gastrointestinal system that have different pH levels because they can expand or contract in reaction to pH variations.

-Temperature-Responsive Hydrogels: These hydrogels undergo phase transitions at specific temperatures, allowing for temperature-regulated drug release, particularly useful in hyperthermia treatments.

Hydrogels that react to particular biomolecules: These hydrogels can deliver drugs selectively in response to metabolic products or illness indicators.

CONCLUSION

In summary, this comprehensive review highlights the exceptional properties, wide-ranging applications, and dynamic evolution of hydrogels across various scientific domains. From their categorization based on origin and manufacturing techniques to their critical mechanical attributes and roles in drug delivery, tissue engineering, and beyond, hydrogels have emerged as versatile biomaterials with significant potential for innovation and influence. Their biomimetic qualities, compatibility with biological systems, and adaptability render them indispensable tools for tackling intricate challenges in biomedicine, environmental science, and more.

The surge in research interest and expanding literature on hydrogels underscores their growing recognition as a promising platform for advanced applications, notably in drug delivery systems and regenerative medicine. By consolidating insights from diverse research articles and references, this review offers a comprehensive grasp of the capabilities and opportunities presented by hydrogels in the realm of science and technology. As researchers continue to explore novel synthesis approaches, fine-tune properties for specific applications, and unravel the intricate mechanisms governing drug release from hydrogel matrices, the horizon is brimming with exciting prospects for fully harnessing the potential of hydrogels to address pressing societal needs and push scientific boundaries.

In the pursuit of leveraging the unique attributes of hydrogels for transformative applications, collaboration, innovation, and interdisciplinary research will serve as pivotal catalysts for progress. By capitalizing on their versatility, compatibility with biological systems, and adaptable nature, researchers and scientists can chart a path towards groundbreaking advancements in drug delivery, tissue engineering, and environmental restoration. As the field of hydrogel science continues to advance, propelled by curiosity, ingenuity, and a thirst for knowledge, the prospect of hydrogels revolutionizing healthcare, biotechnology, and environmental sustainability remains an alluring and promising avenue for future exploration and discovery.

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