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Review Article

Nanotechnology at Work: Hydrogel Drug Delivery Architectures

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Abstract

Hydrogels represent three-dimensional, interconnected networks known to absorb substantial amounts of H_2O but at the same time, being insoluble in the aforementioned solvent. Their exceptional hydrophilic nature, biocompatibility and diverse therapeutic potential position them as highly promising biomaterials within biological and biomedical fields. These materials, on account of their innoxious innate characteristics and safe utilization, have garnered widespread acceptance across tremendous and diverse biomedical applications ranging from traditional therapies to state-of-the-art advancements. This extensive review incorporates a spectrum of varied types of hydrogels, elaborating on both their chemical, physical aspects and also throws light on the rheological, analytical and spectroscopic tools employed for their characterization. It also continues to elaborate on the various mechanisms of gelation for facilitating a better understanding of the topic under discussion. The review also discusses the different strategies which are substantiated in recent times to expand the utilisation of hydrogels. The primary intent of this review is to render a comprehensive understanding of hydrogels as an ideal drug delivery system to undergraduates, graduates, biomedical students and researchers across the globe. It also targets to unravel the fundamental, applied and general aspects of hydrogels, offering valuable insights to help individuals associated with multidisciplinary research and application spheres.

Keywords: Gelation, Biocompatibility, Cross-linking, Smart hydrogels, Polymerization, Architecture, Polymer network

INTRODUCTION

Hydrogels are polymeric systems that are known to retain water and withstand dissolution. They are defined by their potential to swell while remaining insoluble in water. Both natural and synthetic materials comply with this definition. Synthetic hydrogels have gained prominence for their longevity, high water absorption and robustness, surpassing natural variants. Recent definitions focus on their two or multi-component structures, comprising polymer chains forming a 3D network with water filling the space between molecules. Swelling capacity relies on using water-soluble synthetic polymers. These hydrogels are synthesized through various chemical methods, allowing engineers to precisely control properties like degradation, strength and responsiveness to stimuli at a molecular level. Due to their inherent versatile characteristics, they can be used in association with novel delivery systems like liposomes, niosomes etc. These systems can also be fabricated as drug conjugates.

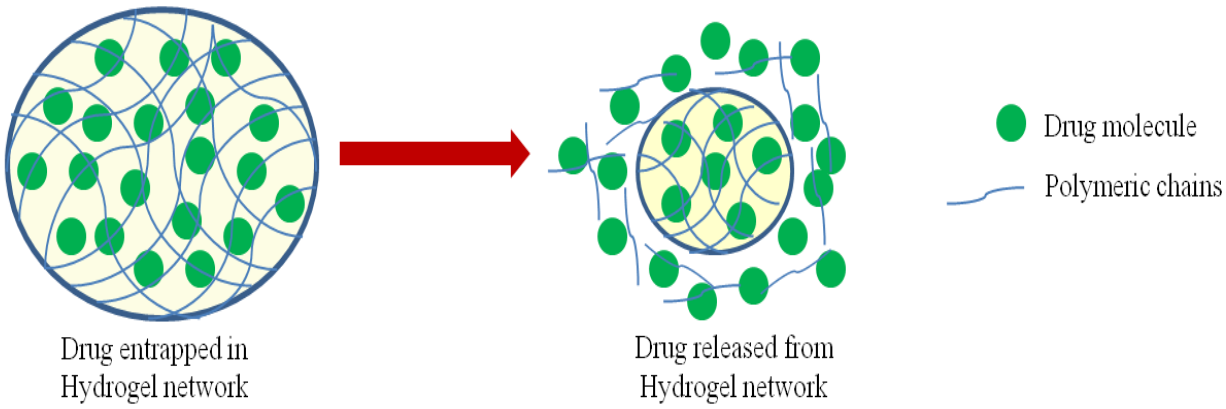

Figure 1: Drug release from Hydrogel matrix

MECHANISMS INVOLVED IN GEL FORMATION

Gelation refers to the interconnection of long molecular chain polymers, initially leading to increasingly larger and branched yet soluble polymers. This mixture of varied soluble branched polymers is termed a 'sol'. With the linking process persisting, the branched polymer's size grows, causing reduced solubility. This development leads to an 'infinite polymer' known as the 'gel' or 'network,' interspersed with defined branched polymers. The shift from a system possessing definite branched polymers to one with innumerable molecules is denoted as the 'sol-gel transition' or 'gelation' with the critical point marking the initial appearance of the gel termed the 'gel point'. Gelation can occur through physical linking (physical gelation) or chemical linking (chemical gelation).

Physical gels can be classified as strong or weak. Strong physical gels possess robust bonds between these polymeric chains, essentially enduring specific experimental conditions, much like chemical gels. Glassy nodules, lamellar microcrystals or double and triple spirals are prominent examples. Weak physical gels feature reversible links formed by short-term associations among chains, continually breaking and reforming. The temporary associations involve hydrogen bonds, block copolymer micelles and ionic associations. Conversely, chemical gelation involves the formation of covalent bonds, resulting consistently in a strong gel. The primary chemical gelation processes include condensation, vulcanization and addition polymerization[1].

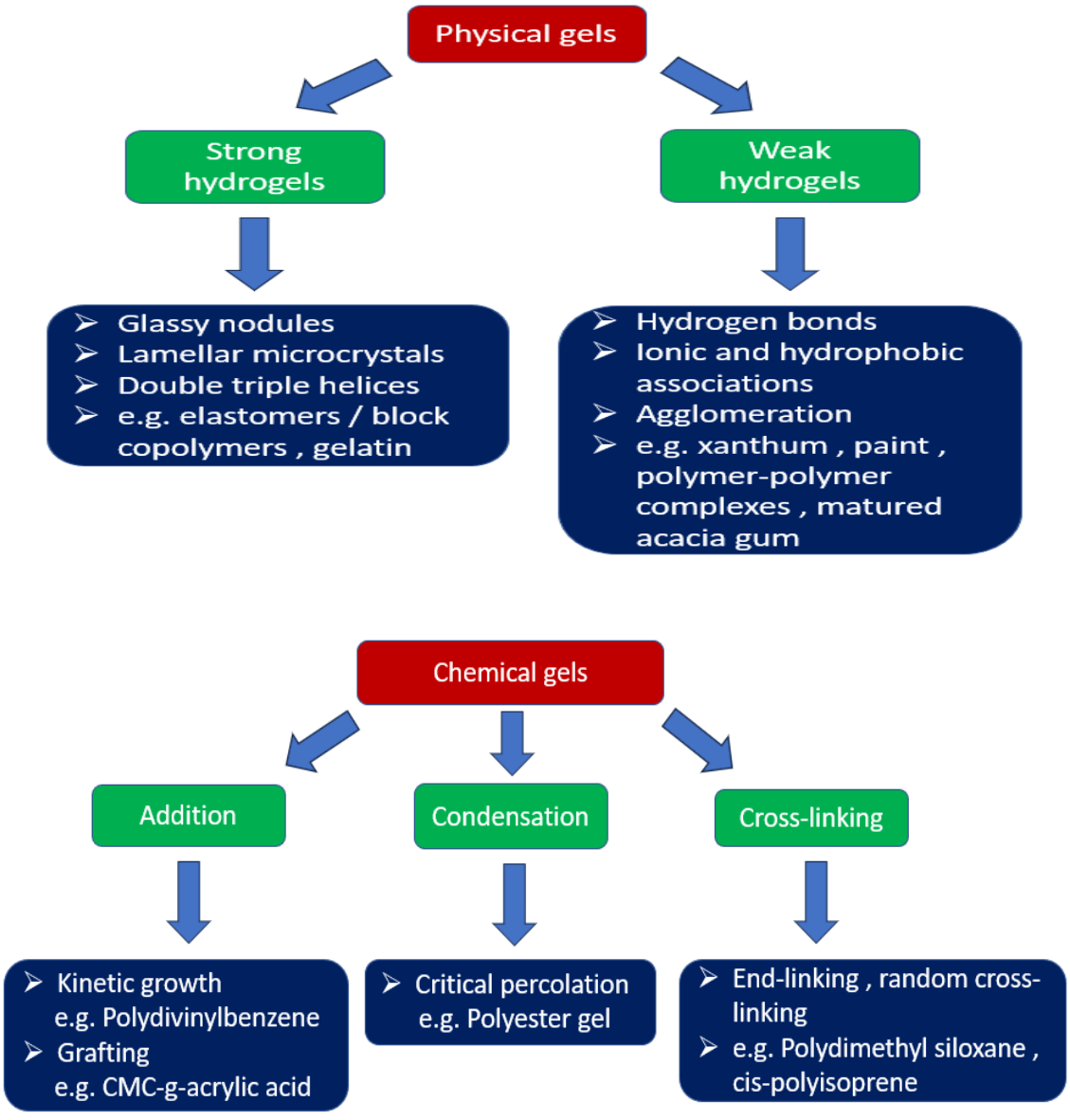

Figure 2: Mechanisms of gelation: Physical and chemical Gels

PROPERTIES OF HYDROGELS

Hydrogels, crafted from polymers with hydrophilic side chains, offer significant advantages in biomedical use. Their water-absorbing capacity and affinity for biological tissues like epithelial tissues and mucous membranes are notable. Fully swollen hydrogels possess viscoelasticity, softness and reduced interfacial angles with biological fluids, minimizing immune responses. Biocompatibility results from these properties. Degradation varies with crosslinker type. Hydrogels' responsiveness to stimuli and tunable properties makes them promising for diverse biomedical applications.

Table 1: Properties of Hydrogels

Sr No.	Property	Description
1	Mechanical Properties[2–4]	Hydrogel strength is vital in biomedical fields, balancing elasticity and strength through crosslinking. Techniques like compression, tension analysis and rheometry assess these properties.
		Rheology studies material response to stress, seen in recent research like Jeong et al. and Lei et al., exploring how composition changes affect gel behaviour. For example, adding genipin crosslinkers to chitosan-based hydrogels enhanced elasticity and accelerated gelation.
		Novel compositions like sodium alginate and poly(acrylic acid) crosslinked by amorphous $CaCO_3$ show promise in prosthetics, with Khan et al. highlighting the role of carboxylic acid groups and metal cation interactions in mechanical strength.
		Understanding rheological properties guides hydrogel tailoring for specific applications by adjusting composition and crosslinking.
2	Biocompatibility [3,5,6]	Biocompatibility is crucial for biomaterials, especially hydrogels, in biomedical applications. Polysaccharides, known for non-toxicity and biocompatibility, are extensively studied and approved for dietary use.
		Research by Tokura et al. on self-degrading polysaccharides exhibited absence of acute toxicity in murine blood systems.
		Chan et al.'s work on chitosan-based complexes demonstrated around 90% cell viability.
		Synthetic polymers like poly glutamic acid and various hydrogels exhibited 90% cell viability on HeLa cells.
		For instance, polyaniline hydrogel improved cell morphology in rabbits and polypyrrole-conducting hydrogels accelerated neural stem cell differentiation for spinal cord injury treatment.
		Gan et al.'s work on conducting hydrogels highlighted applications in drug delivery and wound healing. Conducting hydrogels like polypyrrole and polyaniline hold promise due to biocompatibility across various biomedical uses, from wound healing to advanced electronic interfaces.
3	Biodegradability[3,7,8]	Biodegradable hydrogels are crucial in biomedicine, breaking down within living organisms through methods like hydrolysis, solubilization, bio-absorption and bio-erosion.
		Their degradation depends on composition, preparation techniques and factors like hydrophilicity, molecular weight, pH, temperature, oxygen content, water potential, polymer network structure, crystalline nature and linkages thereby influencing water absorption and dissolution.
		Biodegradable natural and synthetic polymers with hydrophilic properties absorb water, undergo significant swelling and eventually dissolve because of water absorption. Some polymers degrade via ester hydrolysis.
		Enzymes such as proteinases and glycosidases break down protein, polypeptide and polysaccharide hydrogels, like chitosan, which undergoes enzymatic degradation through reactions such as lysozyme-induced breakdown.
		Structural modifications in chitosan have limited impact on degradation rates, while differences in crosslinking affect degradation rates in various chitosan films under enzymatic degradation.
		Degradation, observed through weight changes over time, varies among materials like NSC/OCMC and NSC/PEG hybrids, demonstrating biodegradability under controlled conditions.
		Polysaccharides including starch, cellulose, dextran, alginate, pectin and natural gums exhibit similar biodegradability, while synthetic polymers degrade more slowly than natural ones.
		Studies on poly (acrylic acid) and poly (glutamic acid) derivatives show varied degradation rates in various pH buffer solutions with proteinases, linked to hydrophilicity or hydrophobicity.
4	Swelling Behaviour of Hydrogel[3,9,10]	Hydrogels' swelling behaviour, key for their diverse applications, responds dynamically to factors like solvent composition, pH, ionic concentration, temperature, light and electric fields. This behaviour, influenced by crosslinking, polymer chemistry, ionic strength and synthesis state, is quantified using the swelling ratio.
		Higher crosslinking reduces swelling, while the presence of either hydrophilic or hydrophobic groups on polymer chains significantly affects swelling, with more hydrophilic groups promoting greater swelling.
		pH-sensitive hydrogels swell owing to ionization changes in their lipophobic groups, disrupting secondary bonds between polymer chains.

		Hydrogel swelling involves water diffusion into the network, polymer chain relaxation and network expansion from a dehydrated glassy state to a swollen rubbery state. The process is governed by diffusion mechanisms.
		Studies on hydrogels like polyvinyl alcohol/ natural rubber/cassava starch-g-polyacrylic acid and karaya gum-g-poly (acrylic acid) and blend by Bashir et al. and Tanan et al. examined their swelling behaviour under varied pH and ionic conditions.
		Hydrogel swelling, impacted by diverse factors and responsive to environmental changes, significantly influences their suitability for various applications.
5	Rheology[3,11,12]	Rheology assesses a gel's flow behaviour, where temperature influences viscosity: - higher temperatures ease flow, while lower ones follow scaling laws.
		Shear storage modulus (G') and loss modulus (G") measure stiffness and liquid flow.
		Advancements in assessment methods include confocal rheometric assembly and particle tracking velocimetry, improving traditional assumptions. Guilia Fanesi et al. (2018) showcased a combined low-frequency magnetic resonance and rheology images for hydrogel characterization.
		Thixotropic nature of hydrogel systems which is driven by shear-dependent fracturing, makes them valuable as injectables. They provide a cell-friendly environment, reduce shear impact and provide nutrients during injection. These gels adapt to tissue spaces, aiding regeneration and excel in sustained drug delivery, ensuring prolonged drug presence.
6	Surface properties[3,13]	Hydrogel surfaces vary in roughness and structure, influencing cell fate akin to natural tissue extracellular matrices. Techniques like SEM, FTIR, STM and AFM determine these properties.
		Recent studies, like Unadkat et al. 's work introducing diverse surface features, explore how topographies impact cell behaviour, aiding tissue development and guiding osteogenic differentiation and proliferation of human mesenchymal stromal cells.

CLASSIFICATION OF HYDROGEL

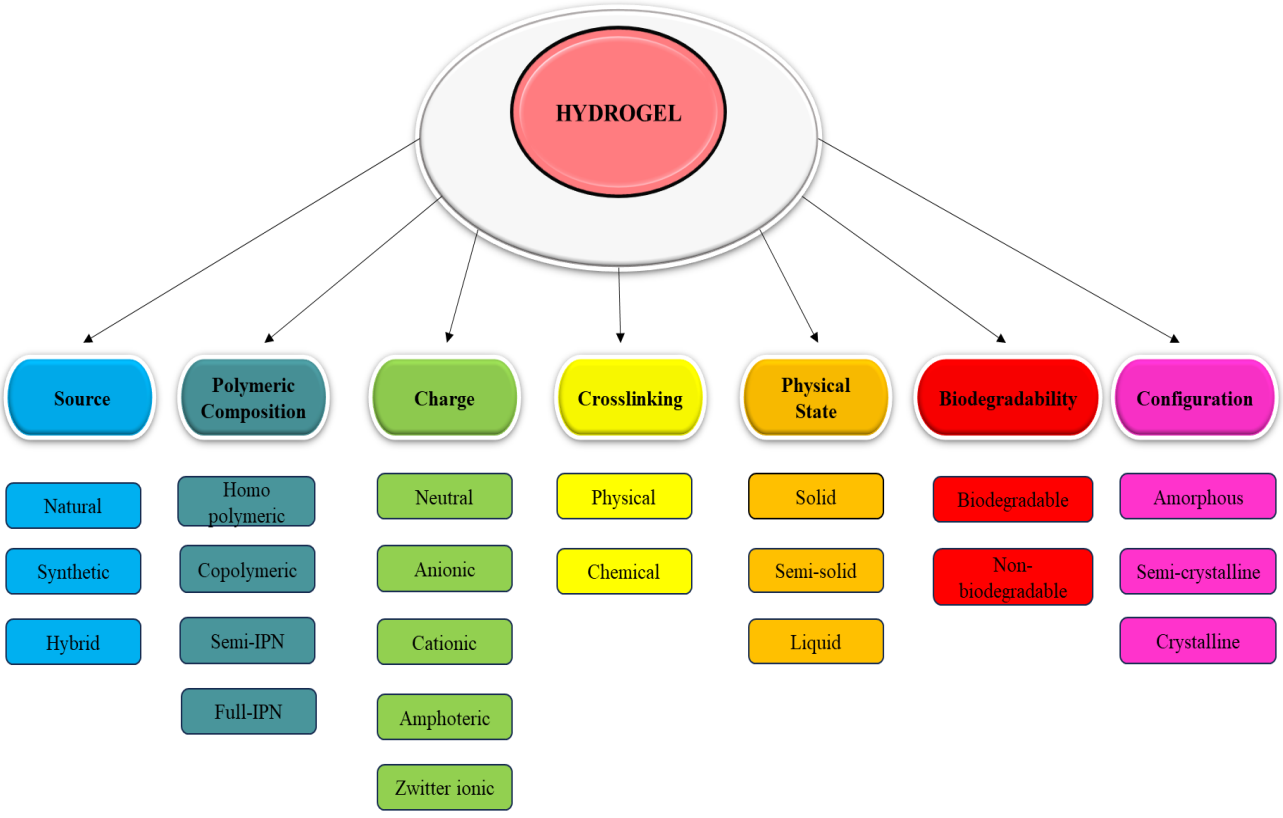

Figure 3: Diverse Classification of Hydrogel

A. Predicated on Source:

1. Natural Hydrogel: Hydrogels derived from naturally occurring polymers are referred to as natural hydrogels encompassing polysaccharides, polynucleotides and polypeptides. These naturally occuring polymers are sourced from decoctions derived from various animals and plants like chitosan, chitin, collagen, alginate, hyaluronic acid, cellulose and gelatin[14]. These polymers are easily available, abundant, cost-effective, non-toxic, biodegradable and exhibit distinct, huge structures formed through covalently linked monomeric units. Despite well-defined structures, they exhibit suboptimal mechanical properties and batch variability, posing challenges to reproducibility[15,16].

2. Synthetic Hydrogel: Synthetic hydrogels are composed of synthetic polymers like polyacrylic acid, polyacrylamide, PVA, polyethylene oxide and polypeptide. These hydrogels are manufactured on an industrial scale, subjected to chemical modifications and offer precise control. However, in contrast to naturally occurring hydrogels, their self-degradation and biosecurity are diminished because of incorporating crosslinking agents and initiators during the production procedure[14].

3. Hybrid Hydrogels: Hybrid hydrogels are formed by combining natural and synthetic polymers. Various naturally occurring polymers like dextran, collagen and chitosan are often merged with synthetic polymers such as poly(N-isopropylacrylamide) and polyvinyl alcohol to produce hybrid hydrogels. This strategic blending allows for the integration of desirable properties from both types of polymers in the resulting hydrogel[17].

B. Predicated on Polymeric Composition:

1. Homopolymeric Hydrogel: A homopolymeric hydrogel is formed exclusively from a sole type of monomer species, serving as the basic structural unit in a polymer network[18]. An instance is the cellulose hydrogel, formed through a one-step polymerization process using NaOH/urea solution and epichlorohydrin as a cross-linker. Another example is the poly(2-hydroxyethyl methacrylate) (poly HEMA) hydrogel, produced with polyethylene glycol dimethacrylate as a cross-linking agent and benzoin isobutyl ether as the UV-sensitive initiator[17].

2. Copolymeric Hydrogel: Co-polymeric hydrogels consist of two types of monomers with one being hydrophilic. In the context of drug delivery system development, Gong et al. engineered a biodegradable triblock poly(ethylene glycol)-poly(caprolactone)- poly (ethylene glycol) (PECE) co-polymeric hydrogel[19]. Another copolymeric hydrogel was synthesised through the polymerization of γ-benzyl L-glutamate (BLG) N-carboxy anhydride, initiated by diamine groups located at the ends of poly(ethylene oxide) chains of the poloxamer exhibited pH and temperature sensitivity[17].

3. Semi-Interpenetrating Network (semi-IPN) Hydrogels: A semi-IPN is produced by the penetration of one polymer, which is linear, into another polymer network that is cross-linked, without the formation of additional chemical linkages between them[20]. Polymer blends occur when the individual linear or branched polymers can be separated from the constituent polymer networks without disrupting the chemical bonds. Yang et al. prepared the promising protein drug delivery system i.e. semi-IPN hydrogels which are composed of poly (ethylene glycol) grafted on carboxymethyl chitosan and alginate for delivery of protein via oral route in the intestine[21].

4. Full-Interpenetrating Network (Full-IPN) Hydrogels: In the creation of semi-IPN hydrogels, enclosing a linear polymer within another matrix opens the possibility of forming a full-IPN. This involves selectively crosslinking a second, non-crosslinked polymer. Full-IPN hydrogel overcomes the thermodynamic incongruity, allows steady network formation and offers advantages like compact structures with enhanced mechanical sturdiness, adjustable characteristics and improved drug loading efficacy. The surface characteristics and size of pores of full-IPNs have the possibility of being manipulated to control release of drug and interaction with body tissue systems[3]. Dragan et al. demonstrated this with chitosan/polyacrylamide semi-IPN hydrogels and full-IPN hydrogels formed by selectively crosslinking chitosan with epichlorohydrin in an alkaline medium, confirmed by FTIR analysis[22].

C. Predicated on Charge:

Hydrogels are further subdivided based on the type of charges which are present in the closely associated polymeric network:

1.Neutral (Non-ionic) Hydrogel: Polymers do not have any charge on the backbone. Eg. Dextran.

2.Anionic Hydrogel: Polymers have acidic functional groups in their backbone. Eg. Carrageenan.

3.Cationic Hydrogel: Polymers have basic groups functional in their backbone. Eg. Chitosan.

4.Amphoteric Hydrogel: Polymers contain both acidic and basic functional moieties. Eg. Collagen.

5.Zwitterionic Hydrogel: Polymers contain both cationic and anionic functional groups. Eg. Polybetaines[17].

D. Predicated on Cross linking:

1. Physically Crosslinked Hydrogels: Physical hydrogels are 3D networks formed through noncovalent interactions between linear monomer molecules, resulting in the formation of concrete cross-linking intersections. These interactions include electrostatic interactions, hydrogen bonding, chain entanglement and hydrophobic interaction[23]. Physical hydrogels often demonstrate reversible sol-gel transitions as relatively low vitalities are needed to break the vital interactions between these molecules[24]. Their production does not require chemical reactions and the conditions involved are generally mild and rendering them well-suited for various biological applications.

2. Chemically Crosslinked Hydrogels: Chemical hydrogels result from irreversible chemical cross-linking between polymer molecules, providing stability, adjustable architectures and excellent mechanical properties. Unlike physical hydrogels, chemical crosslinked hydrogel networks are more stable and homogeneous, offering greater control over properties such as swelling behaviour, biodegradability and mechanical strength through covalent crosslinking[25].

E. Predicated on Physical state:

1. Solid Hydrogels: The solid hydrogels are agents cross-linked chemically and remain in a rigid state at room temperature, yet they have the ability to swell in aqueous environments including biological fluids, buffer solutions and aqueous systems. Due to their capability to mimic the physical, biological, electrical and chemical characteristics of various biological tissues, solid hydrogels find applications in biomedical, environmental and ecological fields. Mechanical properties can be enhanced by incorporating nanoparticles into the polymeric matrix, such as methacrylate gelatin with gelatin-collagen with bioactive glass nanoparticles and COOH-functionalized carbon nanotubes for cardiac tissue engineering[26,27].

2. Semisolid Hydrogels: The semisolid hydrogels are evaluated by their strong binding (adhesive) interactions involving interfacial forces like hydrogen bonds, van der Waals and electrostatic forces forming soft-tissue like network systems. Due to their bio adhesive nature, they are also referred to as bio adhesive or mucoadhesive hydrogels. These hydrogels are utilized in the field of biomedicals for prolonged drug administration and efficacious dosing. Examples include sterculia gum, poly(vinylpyrrolidone) hydrogels and a starch nanocrystal-based hydrogel for transdermal applications in the biomedical field[28].

3. Liquid Hydrogels: Liquid hydrogels exist as a liquid at room temperatures but exhibit a soft, tissue-like flexible phase with

suitable functionality at specific temperatures. They are injectable and widely used in biomedical applications. Examples include high mannuronic alginate hydrogels as wound dressing agents in cutaneous healing of wound, a smart injectable hydrogel composed of microbial transglutaminase (TG) and human-like collagen for skin tissue creation and keratin-silica hydrogel as a dressing material[26].

F. Predicated on Biodegradability:

1. Biodegradable Hydrogels: Hydrogels, including natural polymers like chitosan, fibrin and agar can exhibit biodegradability. Synthetic biodegradable polymers such as Poly(aldehyde guluronate), Polyanhydrides and poly(N-isopropyl acrylamide) also demonstrate the natural degradation capability of hydrogels[29].

2. Non-biodegradable Hydrogels: Non-biodegradable hydrogels are composed of varied vinylated monomeric units or macromeric units such as 2-hydroxyethyl methacrylate (HEMA), methoxy poly(ethylene glycol) (MPEG), acrylamide (AAm) and 2-hydroxypropyl methacrylate (HPMA). These polymers do not undergo natural degradation processes[29].

G. Predicated based on Configuration:

Hydrogels can be classified depending on their physical structure and chemical composition as follows:

1. Amorphous (non-crystalline).

2. Semicrystalline: A complex mixture of amorphous and crystalline phases.

3. Crystalline.

CURRENT TRENDS INVOLVED IN HYDROGELS

SMART HYDROGEL (Stimuli-responsive hydrogels)

Recent advancements in precision medicine and personalized pharmacotherapy have driven the development of stimuli-responsive hydrogels as smart biomaterials. These hydrogels, responsive to external stimuli such as pH, temperature, electrical and magnetic fields, light and biomolecule concentrations, enable controlled drug release. They exhibit rapid and reversible changes in physical properties with reproducible, intensity-scalable and predictable phase volume transitions. Smart hydrogels integrated into drug delivery systems offer advantages like reduced dosing frequency, maintenance of therapeutic concentration and minimized side effects.

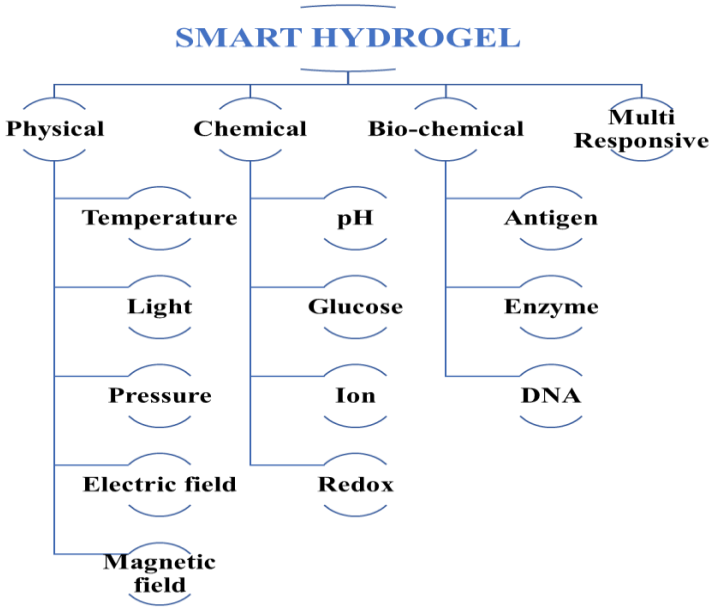

Figure 4: Classification of Smart Hydrogel

A. Physical Responsive Hydrogel:

1. Thermo/Temperature Responsive Hydrogel (TRHs):

Thermo-responsive hydrogels (TRHs) modulate drug release based on ambient temperature changes, typically undergoing a phase transition between dissolved and insoluble states. There are two main types of TRH: positive and negative. Positive TRHs have an upper critical solution temperature (UCST), swelling at higher temperatures and contracting at lower temperatures while negative TRHs possess a lower critical solution temperature (LCST), swelling at stunted temperatures and contracting at the temperatures above the LCST. TRHs are specific, biocompatible and enable controlled drug delivery for various categories such as antidiabetics, anticancer, hormones, proteins and peptides. Common TRHs include Poloxamer (Pluronic) and Tetronics, with Pluronic F127 exhibiting a phase transition from a liquid to a semi-solid gel around 27°C. Pluronic F127 can be used for burn treatment, sustained drug delivery after extravascular parenteral injection and topical administration of anti-cancer agents[30]. While poloxamer gels are suitable for short-term therapies like pain management and infection treatment, their delivery duration is limited to a few days[31].

2. Photo/Light Responsive Hydrogel (LRHs):

Light-sensitive hydrogels incorporate photosensitive molecules that absorb UV or visible light, inducing temperature changes and modifying volume. They respond to either UV or visible light, with visible light preferred for its availability, safety, cleanliness and cost-effectiveness. UV-responsive hydrogels use bis(4-dimethylamino) phenyl methyl leucocyanide to generate cyanide ions upon UV exposure, elevating osmotic pressure and causing gel swelling[32]. Chromophores in these hydrogels dissipate heat during light absorption, leading to a temperature rise which is proportional to light intensity and chromophore concentration. Photoresponsive hydrogels have potential applications in

cartilage tissue engineering, in situ forming gels and the development of light-sensitive artificial muscles[33].

3. Pressure-Responsive Hydrogels:

Pressure-responsive hydrogels undergo volumetric phase changes in response to external pressure changes. Typically characterized by contraction at low pressure and swelling at high pressure, often with temperature sensitivity. These hydrogels exhibit a rise in lower critical solution temperature (LCST) under constant temperature conditions, leading to a swollen state. When used as drug carriers, pressure-sensitive hydrogels can target tissues subjected to dynamic mechanical environments like bone, blood vessels and muscles. For example, a pressure-responsive nanohydrogel developed by Hosseinifar et al. using modified β-cyclodextrin and alginate for drug delivery releases drugs in response to blood pressure stimulation. These controlled-release drug systems are compatible with various cells including small-volume colon cancer cells offering additional advantages[34].

4. Electric Field Responsive Hydrogels (ERHs):

Electric field-responsive hydrogels (ERHs) contain ionized groups like sulfonic, amide and sulfa groups within their network, a crucial requirement for responsiveness to electrical stimulation. Typically composed of polyelectrolytes, ERHs change shape or volume when exposed to an electric field in an electrolytic solution. These changes involve swelling elimination as well as bending and swelling deformation, enabling the conversion of electric energy into mechanical energy. ERHs are synthesized using various polymers including sulfonated polystyrene, vinyl sulfonic acid copolymer/acrylic acid, poly(sodium acrylate-co-sodium maleate)/PVA and combinations of natural and synthetic electrolytes such as chitosan/polyaniline, hyaluronic acid/ PVA and poly(methacrylic acid)/alginate[35].

5. Magnetic Field Responsive Hydrogels (MRHs):

Magnetic field-responsive hydrogels undergo volume changes, expanding and contracting when exposed to a magnetic field. Typically, these hydrogels incorporate inorganic magnetic nanoparticles within the gel structure, secured through chemical bonding or physical embedding. Exposure to a magnetic field causes rapid aggregation of magnetic particles, leading to hydrogel contraction and solvent expulsion, resulting in a swift change in shape. This property allows for guided drug movement within the body, directed by the environmental magnetic field. When loaded with concentrated drugs and affixed to pathological body tissues, these hydrogels achieve targeted controlled release. Hawkins et al. created a magnetic field-responsive hydrogel controlled-release system by embedding magnetic materials and a lysozyme drug model in a TRH system[36].

B. Chemical Responsive Hydrogel:

1. pH-Responsive Hydrogels (PRHs):

pH-responsive hydrogels (PRHs) are high molecular polymers that undergo a phase or volume transition in response to changes in the pH of the external medium. Typically derived from polyelectrolytes with weak acidic or basic functional groups, PRHs respond to pathological pH variations in body tissues through ionization, hydrogen bond dissociation and electrostatic interactions. Categorized into cationic and anionic hydrogels, they contain molecular chains with alkaline (e.g., –NH_2) and acidic groups (e.g., –COOH), respectively. Swelling in PRHs is influenced by the neighbouring medium's pH at the pKa and pKb values of the pendant acidic and basic groups. pH changes directly impact interactions between solvent molecules and polymer chains[37]. In the anionic type of PRHs, ionization occurs when the pH exceeds pKa value of acidic groups, forming negative and positive charges, while in cationic PRHs, ionization of basic groups happens when the pH is below the pKb value, causing the polymeric network to swell. Zwitterionic photo-responsive hydrogels, incorporating both acidic (e.g. carboxyl groups) and basic groups (e.g. amino groups), respond comprehensively to pH changes. Researchers have developed drug-loaded PLGA/Eudragit S100-coated stainless steel microneedles (MNs) for intelligent release of therapeutics based on pH levels of wound, aiming to improve the wound-healing process[38].

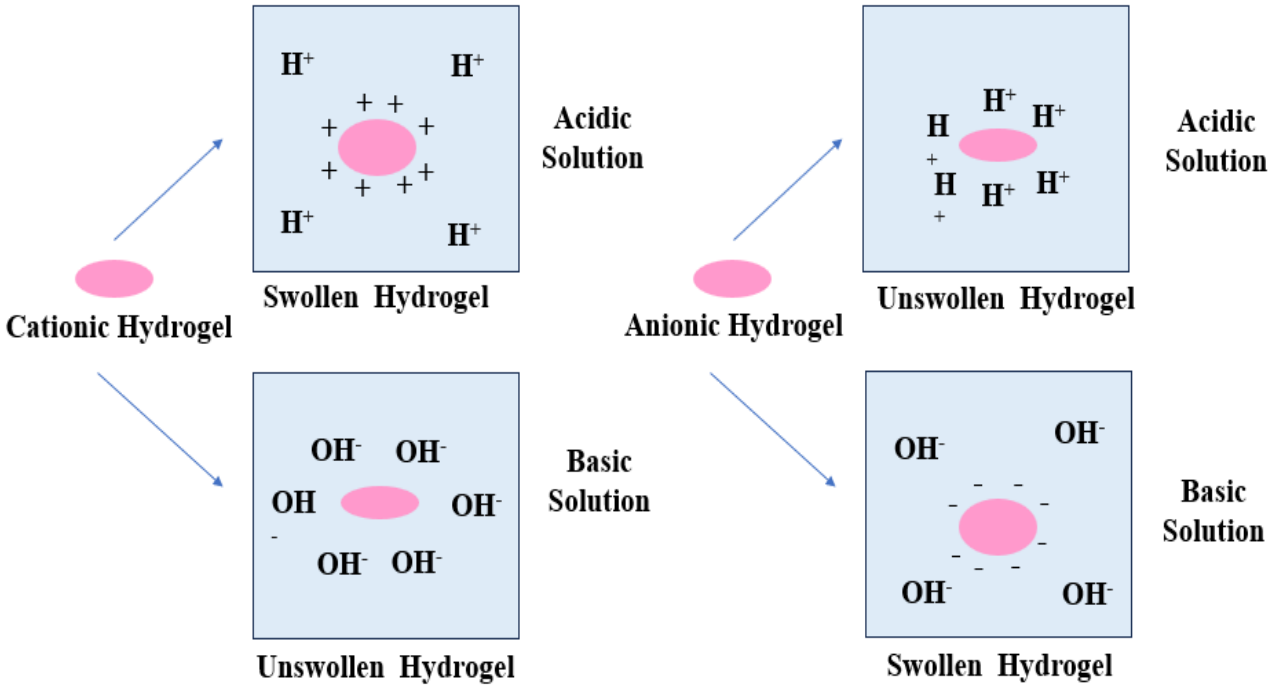

Figure 5: Mechanism of action of pH responsive Hydrogel

2. Glucose Responsive Hydrogel:

Automated devices for insulin delivery can utilize glucose-sensitive hydrogels which responds to blood glucose concentrations for insulin release. These hydrogels typically incorporate glucose oxidase for glucose sensing and fabrication. Glucose from the blood triggers oxidation by glucose oxidase, leading to gluconic acid production and an increase in pH, causing hydrogel swelling and insulin release. Loading insulin is achieved by adjusting the pH. The hydrogel's capability to swell and release insulin are controlled by varying glucose concentration in the surrounding medium. Altering the pH-sensitive hydrogel medium such as poly HEMA, enables the development of a glucose-responsive controlled insulin-release system, regulating blood glucose levels based on glucose concentration. A similar approach involving photopolymerization of 2-HEMA and 3-phenylboronic acrylamide acid creates a glucose-sensitive hydrogel that releases insulin depending on glucose concentration[39,40].

3. Ion Responsive Hydrogel:

Metal ions crucial for various physiological functions, regulate protein activity, nerve conduction, acid-base balance, muscle contraction, enzyme function and intracellular osmotic pressure in the human body. These activities involve macro metal elements like Na^{+}, Ca^{+2}, Mg^{+2}, K^{+} trace elements like Zn^{+2}, Fe^{+2} and ultra micro metal elements like Cr^{+3} , Mn^{+2} etc. Body fluids vary in metal ion types and concentrations and each organ has a specific ionic strength. Ion-sensitive hydrogels face challenges in low ion concentration situations, limiting counter ions' penetration and resulting in a low ionization degree of ionizable groups. As ion concentration increases, the gel's ionization degree rises, leading to enhanced swelling until reaching its maximum. In this point, ionic osmotic pressure reduction causes a decrease in gel swelling[41,42].

4. Redox-Responsive Hydrogels:

The design of redox-responsive hydrogels is based on variations in redox potential between cancerous abrasions and normal tissues. Normal tissues have lower concentrations of reduced glutathione (GSH) compared to cancer cells, which exhibit approximately four times the GSH concentration. This difference, with normal tissues in a reduced state and cancer cells in an oxidized state, has inspired research into leveraging these conditions for targeted therapies.[14] They are stable in an oxidizing environment but disulfide bonds fracture and reduce to sulfhydryl groups (–SH) in a reducing environment. For instance, Chen et al. developed a redox-responsive hydrogel sensitive to both reactive oxygen species (ROS) and GSH, achieved by using the antioxidant lipoic acid (LA) for the synthesis of ketal oligomers forming disulfide bonds, enabling the hydrogel to respond to distinct redox conditions[43].

C. Biological/Biochemical-Responsive Hydrogels:

Bio responsive hydrogels designed with biological functionalities, interact with the biological environment using antigens, enzymes or ligands for crosslinking. Their in vivo applicability enhances their appeal, offering a versatile approach to engage with biological systems[44].

1. Antigen-Sensitive Hydrogels:

Antigen-sensitive hydrogels are based on the principle of Ag-Ab interaction. This involves grafting an antigen(Ag) and antibody(Ab) onto varied distinct crosslinking points, forming a semi-IPN. Crosslinking is initiated when a specific antibody identifies a specific antigen. An example of this approach is a pharmaceutical hydrogel system developed using the Fab fragment of a polymerizable antibody derived from the monoclonal anti-fluorescein BDC1 antibody (IgG2a). Copolymerization with the polymerizable Fab fragment, N,N-methylene bis(acrylamide) and N-isopropyl acrylamide (NIPAAm) resulted in hydrogels that demonstrated reversible alterations in volume upon exposure to antigens like fluorescein (FL) and Poly amidoamine dendrimer (PAMAM)-fluorescein (FD). The sensitivity of these hydrogels to antigens dependent on factors such as temperature, Fab content and pH[45,46].

2. Enzyme-Sensitive Hydrogels:

Enzyme-sensitive hydrogels, incorporating polymers which are biodegradable, function like sensors for diagnostic purposes and targeted delivery systems. These hydrogels undergo degradation through the digestion or breakdown of peptide building blocks by specific enzymes. In applications like colon-targeted drug delivery, enzyme-specific hydrogels are commonly used. For example, dextran hydrogels exhibit controlled-release patterns in the colon due to the presence of dextranase enzymes in colonic microbiota[47]. Both naturally derived biodegradable polymers (e.g. alginate, amylose, gellan gum, chitosan, pectin , dextran and chondroitin sulfate) and synthetic nonbiodegradable polymeric systems (eg, poly(2-HEMA), poly(N-isopropyl acrylamide) and PEG/poly(ethylene oxide)) capable of enzyme cleavage enable site-specific delivery through enzymatic breakdown are prominent[48,49].

3. DNA-Hydrogels:

Hybrid bionanomaterials can be created using DNA as a foundational building block, forming predictable 2D or 3D structures. Complementary DNA interactions result in highly structured networks and in an aqueous environment, these structures undergo swelling and form hydrogels. Key attributes include high solubility, bio-compatibility, versatility and responsiveness. They can be labelled for effective tracking in in vitro biological studies. In cancer immunotherapy, drug-loaded cytosine-phosphate-guanine (CpG)-DNA hydrogels induce immune responses. CpG-DNA hydrogels with CpG nucleotides stimulate innate immunity through Toll-like receptor 9 and enhance immune responses to comprised adjuvants like ovalbumin (OVA). The employment of CpG-DNA hydrogel significantly reduces adverse reactions compared to conventional adjuvants[50].

D. Multi-Responsive Hydrogels:

Scientists are developing intelligent hydrogels with multiple response capabilities within a single drug carrier to address the complexities of the human physiological environment and diverse lesion site conditions. This innovative approach allows the hydrogel to adapt its response based on environmental characteristics, offering significant development potential[51].[51] Researchers have successfully developed slow-release hydrogel complexes with dual and triple responsive properties. For instance, Chen et al. designed a pH/temperature dual-responsive hydrogel-controlled drug release system using UV light-induced poly(N-isopropylacrylamide), arginine branch and carboxymethyl chitosan (CMCT) crosslinking [52].[52] Another example involves Mahdavini et al., who incorporated magnetite nanoparticles into a hydrogel system which are made from sodium alginate and carrageenan, resulting in a magnetic/pH dual-responsive hydrogel-controlled drug release system[53].

TECHNIQUES EMPLOYED FOR FABRICATION OF HYDROGELS

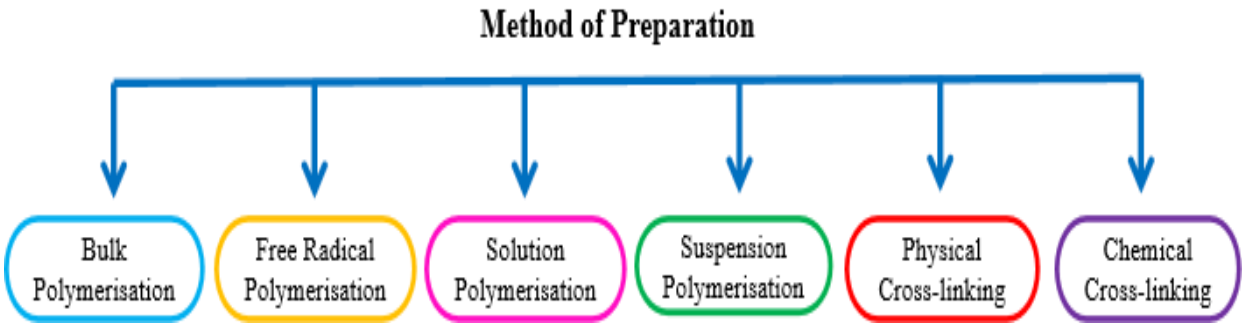

Figure 6: Fabrication techniques involved in hydrogel synthesis

1. Bulk Polymerisation: Hydrogels are made from vinyl monomers, often incorporating various types for versatility. A small quantity of any cross-linking agent is added to the formulation. Polymerization is then initiated by radiation, UV light, or chemical catalysts, selected based on monomer and solvent types. Resulting hydrogels can take forms like rods, particles, films, membranes, or emulsions[17,20].

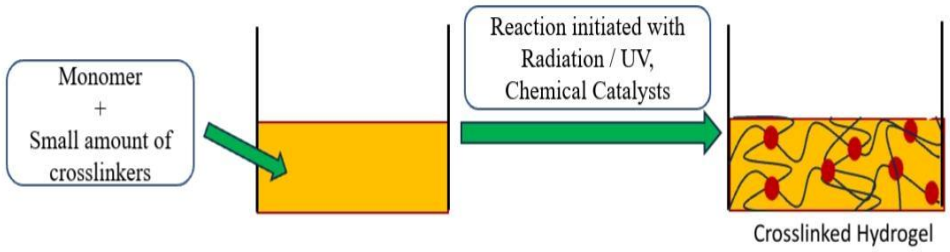

Figure 7: Bulk polymerization

2. Free Radical Polymerisation: Hydrogel preparation primarily involves acrylates, vinyl lactams and amides as key monomers, often with functional groups or modified with radically polymerizable groups. The process mirrors free-radical polymerization, encompassing initiation, propagation, chain transfer and termination steps. Various initiators like thermal, UV, visible and redox agents generate radicals, activating monomers into reactive forms for polymerization[17,54].

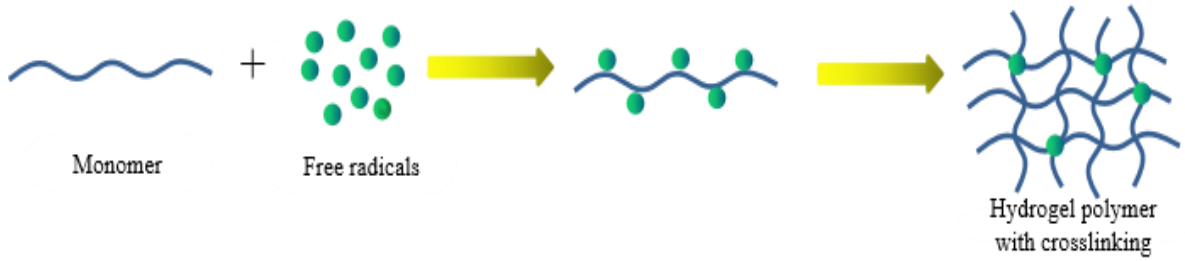

Figure 8: Free radical polymerization

3. Solution Polymerisation: Ionic/neutral monomers are combined with multifunctional crosslinking agents and polymerized using thermal, UV or redox initiators. Solution polymerization offers an advantage over bulk polymerization due to the presence of a solvent acting as a heat sink. Post-polymerization, hydrogels are washed with distilled H_2O to eliminate initiators, soluble monomers, oligomers, crosslinking agents, extractable polymers and impurities. Vehicles like water, ethanol, water–ethanol mixtures and benzyl alcohol are commonly used for this purification process[17,55].

4. Suspension Polymerisation: This method yields products in powder or microsphere form, eliminating the need for grinding. Employing a water-in-oil (W/O) process, known as 'inverse suspension,' differs from the common oil-in-water (O/W) technique. Monomers and initiators are distributed in the hydrocarbon phase as a homogeneous mix. Controlling resin particle size and shape dictates monomer solution viscosity, rotor design, speed of agitation and the type of dispersant used. Continuous agitation and addition of a low hydrophilic–lipophilic-balance (HLB) suspending agent are essential due to the dispersion's thermodynamic instability[17,56].

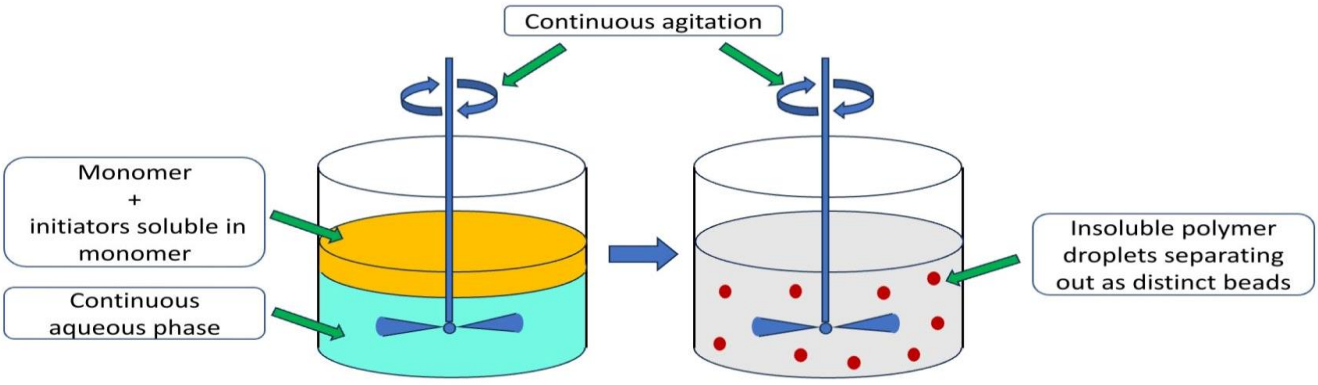

Figure 9: Suspension polymerisation

5. Physical Cross-Linking Methods:

Physical crosslinking methods in polymer-based hydrogels utilize interactions such as ionic, hydrophobic, stereo complex, hydrogen bonding and protein-polysaccharide interactions to form hydrogels. The lack of cross-linkers maintains low toxicity and enhances biocompatibility. Physical crosslinking yields reversible hydrogels, but structural imperfections or inhomogeneities may arise from free chain ends.

A. Ionic Cross-Linking or Ionic-Interaction: Ionic polysaccharide like sodium alginate can be cross-linked with calcium ions under mild conditions, at physiological pH and ambient temperature. Despite its advantages, controlling the gelation rate poses challenges, leading to nonuniform structures. Kuo et al. used calcium carbonate ($CaCO_3$), calcium chloride dihydrate ($CaCl_2.2H_2O$), calcium sulphate dihydrate ($CaSO_4.2H_2O$) and D-glucono-δ-lactone to prepare alginate hydrogel. Lower alginate concentration, higher counterion concentration and temperature increased gelation rate. Slower gelation resulted in mechanically stronger gels with a uniform structure[57].

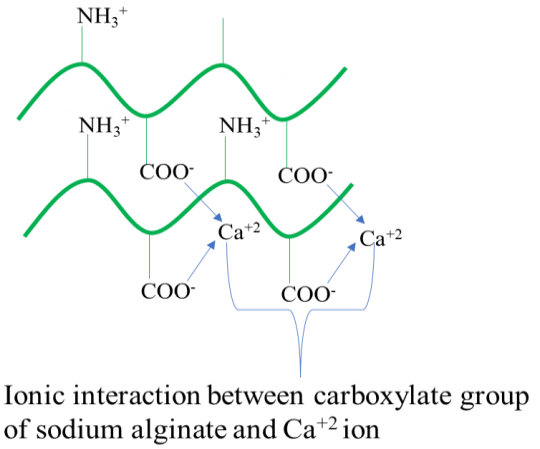

Figure 10: Mechanism of Ionic interaction

B. Hydrophobic Interaction: Polymers with hydrophobic regions can undergo reverse thermal gelation known as "sol–gel" chemistry, in an aqueous environment. In an amphiphilic polymer solution at higher temperatures, initially soluble polymers become insoluble as hydrophobic domains aggregate to reduce contact with water molecules. This aggregation increases solvent entropy, particularly with larger hydrophobic segments, enhancing hydrophobic interactions and reducing the gelation temperature[58].

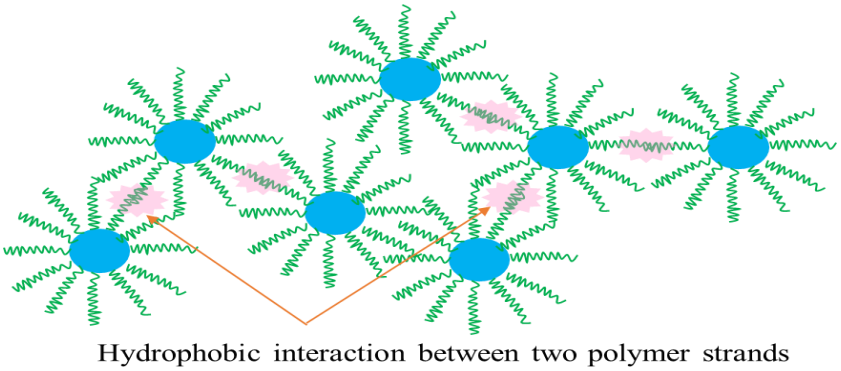

Figure 11: Hydrophobic interaction

C. Thermoreversible Gelation: Polysaccharides such as carrageenan or gelatin undergo physical cross-linking upon cooling, leading to hydrogel formation. Gelation occurs through helix formation, helical association and the creation of junction zones. Above their transition temperature, carrageenans exist as a random coil, transforming into rigid helical rods upon cooling. The presence of salt ions (Na^+, K^+, etc.) induces stable gel formation through the repulsion of sulfonic groups (SO^{-3}), resulting in aggregated structures[59].

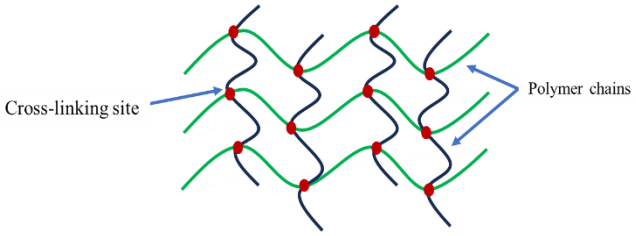

Figure 12: Thermoreversible Gel (Crosslinking junction by cooling)

D. Complex Coacervation: Mixing polycationic polyanionic polymers results in the formation of complex coacervate gels. This technique relies on oppositely charged polymers aggregating to form complexes with outcomes dependent on the pH and solution concentration. Lalevee et al. demonstrated a highly stretchable hydrogel based on hyaluronic acid and chitosan through complex coacervation. Mechanical properties shift from fragile (at pH close to chitosan's pKa, amine groups) to stretchable and strong (at pH close to hyaluronic acid's pKa, carboxylic groups). Similarly, proteins below their isoelectric point exist as positively charged, associating with anionic polysaccharides to form coacervate complex hydrogels[60].

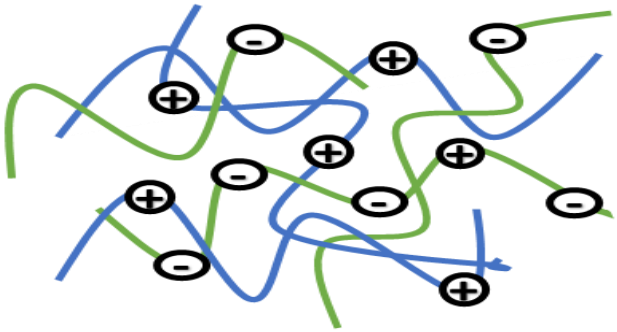

Figure 13: Complex Coacervation

E. Hydrogen Bonding: Lowering the pH of a polymer solution containing carboxyl groups enables the creation of a hydrogen-bonded hydrogel. Takigami et al. developed a carboxymethyl cellulose (CMC) based hydrogel by dispersing it in a 0.1 M HCl solution. In acidic conditions, sodium ions were replaced by hydrogen ions, promoting hydrogen bonding and decreasing the solubility of CMC, resulting in an elastic hydrogel. Similarly, polyacrylic and polymethacrylic acid form a hydrogel with polyethylene glycol at low pH, facilitated by hydrogen bonding interactions between the acidic groups (−COOH) of acrylate and the hydroxyl groups (−OH) of PEG[61].

F. Freeze Thawing: The freeze-thaw methodology is a promising approach for polysaccharide-based gels known for their documented compatibility with bodily systems and appropriate safety. This process involves freezing a polymer solution at low temperatures (-20 to -80 °C) followed by melting at room temperature. Hydrogel properties can be adjusted by controlling pH, freezing duration, temperature, thawing rate and the number of thawing cycles. Giannouli et al. reported cryogelation of xanthan gum, where freeze-thawing aligned xanthan gum chains through the conversion of water to ice crystals, forming a cryogel network. Mechanical strength can be enhanced by subjecting the gels to additional freeze-thaw cycles or by decreasing the temperature (to -80 °C)[62].

6. Chemical Cross-Linking Methods:

Physically cross-linked hydrogels offer advantages like cross-linking without agents but face limitations in mechanical strength. In contrast, chemically cross-linked hydrogels exhibit enhanced mechanical strength, resist matrix dilution and prevent hydrogel diffusion. Chemical cross-linking involves modifying polymer chains chemically or using cross-linking agents, with grafting and cross-linking as key techniques.

A. Grafting: The grafting technique includes addition of a monomer onto the backbone of a preformed polymer or polymerization, such as polysaccharides. Functional monomers are grafted onto activated polymer chains, leading to branching and subsequent cross-linking. Starch grafted with water-loving monomers like acrylic acid, acrylonitrile and acrylamide creates superabsorbent hydrogels with increased water absorption capacity. Chemical grafting uses initiators like benzoyl peroxide or potassium persulfate, while radiation grafting involves high-intensity radiation (e.g., γ-radiation) as a source of initiator [63].

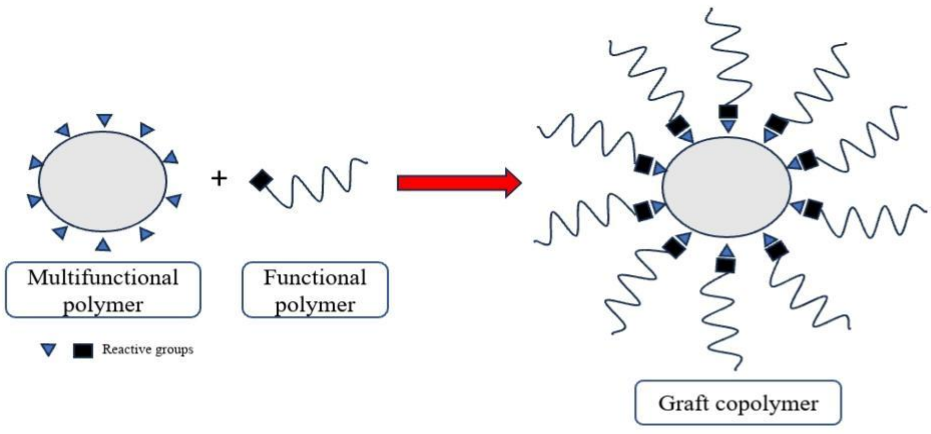

Figure 14: Grafting

B. Cross-Linking: Chemical cross-linkers like glutaraldehyde, PEG, glyoxal and epichlorohydrin in situ generated cross-linkers are common in formation of hydrogel, involving the incorporation of a reactive molecule between chains of polymer. Glutaraldehyde's toxicity limits its applications, leading to the emergence of biocompatible in situ generated cross-linkers, particularly using oxidized polysaccharides (e.g., alginate, hyaluronic acid, chitosan) as a base material. Jayakrishnan et al. explored this approach for biodegradable hydrogel preparation. Other methods include radiation cross-linking, enzyme cross-linking (e.g., microbial transglutaminase, mushroom tyrosinase), providing a useful tool for natural polysaccharides intolerant to harsh chemical conditions[64].

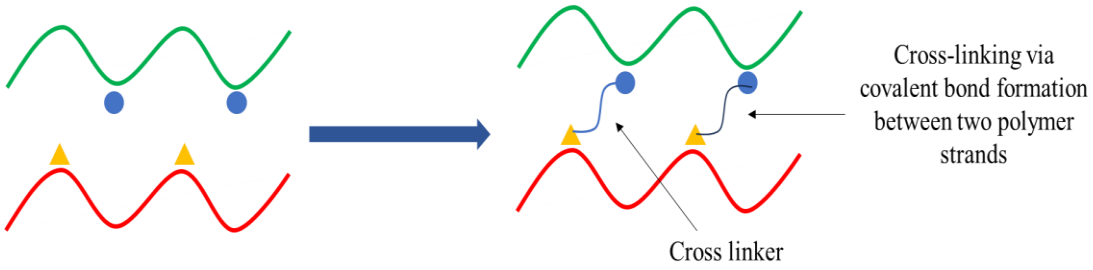

Fig. 15: Cross-linking between two polymer strands

CHARACTERISATION OF HYDROGELS:

Hydrogels undergo characterization based on several criteria such as their biocompatibility, biodegradability, bioadhesion, dielectric relaxation and properties related to mass transport.

Table 2: Characterisation of hydrogels

Sr No.	Characterization parameters	Description
A	Biocompatibility[44,65–67]	When integrating biosensors, drug release devices, or neuronal prostheses into living organisms, the risk of unwanted host-device interactions is a primary concern.
		Addressing this involves molecularly engineering hydrogels for improved compatibility with the host's immune system. For instance, materials like PEG resist protein adsorption, known to trigger immune responses. Other hydrogel types, such as poly (HEMA)-based ones, mimic body tissues' water content and elasticity to enhance compatibility.
		A study using a hyaluronic acid (HA)-based hydrogel film revealed structural shifts from featureless to porous microstructures upon hydration, observed via scanning electron microscopy (SEM).
		Evaluating hydrogel morphology also provides insights into transparency alterations, often observed using digital microscopes.
B	Thermal behaviour[44,65,68]	Differential scanning calorimetry characterizes hydrogel responses to thermal shifts. A pre-drying cycle is crucial to avoid broad water peaks in samples. A heating rate of about 10°C/min is common, allowing analysis between 0 and 200°C.
C	Responsiveness to pH[44,65]	Hydrogels used in wound dressings respond to varying wound pH levels. Research on their swelling behaviour in the pH range of 5–9 indicates a correlation between GAN quantity (an acid-responsive component) and swelling capacity. Higher GAN levels show consistent swelling in neutral and alkaline pH but decreased water absorption in acidic conditions.
D	Swelling studies[44,65,69]	Hydrogel swelling, measured as a percentage, involves weighing 1 cm^2 gel films, submerging them in water for five hours, periodically drying to prevent surface water interference, then reweighing to calculate swelling using the formula: % Swelling = (Final mass − Initial Mass) / Initial Mass Methylene blue loading and release indicate swelling. Dry gel films are immersed in methylene blue for 1 to 24 hours and UV–vis analysis at 664 nm measures concentration changes before and after interaction, evaluating loading characteristics.
E	Crosslinking degree[44,65,69]	ATR–Fourier transform infrared (FTIR) spectroscopy assesses polymer film crosslinking. It records IR spectra at room temperature via multiple scans. Comparisons analyse interactions within the hydrogel and involving GAN, highlighting covalent and non-covalent interactions. Observed changes in the IR spectrum reveal anhydride group emergence, new ester group formation and broader GAN peaks.
F	Porosity and Permeation[44,70]	The hydrogel film's pore network differs in size, distribution and interconnections, shaping its matrix and structure. 'Tortuosity' explains these pore traits which are influenced by the gel's composition and crosslink

		density.
G	Invitro microbiological assessment[44,65]	Biofilm materials can trigger pathogenic infections within the body because bacteria have ability to adhere to hydrogel surfaces which can lead to resistance to the host's immune defenses. In labs, evaluating hydrogel resistance ability includes estimating their anti-adhesive properties by exposing them to bacterial inoculums over incubation periods to prevent potential infections in vitro.
H	Spectroscopic studies[71]	Spectroscopic techniques like NMR, UV–vis, FT-IR, Raman spectroscopy and CD are essential for evaluating supramolecular hydrogels. They offer elaborate understanding of their atomic and molecular structures. They unveil dynamics at the gel-solution interface which are crucial for understanding gel formation and their stability which include host–guest chemistries. Particularly, CD spectroscopy is essential for observing chirality which is important in material functionality design. Techniques like DLS and DWS are also crucial for characterization of supramolecular hydrogels.
I	Scanning Electron Microscopy[1]	SEM (Scanning Electron Microscopy) is fundamental for studying a sample's surface topography, composition and aspects like electrical conductivity. Its magnification ranges from 10 to 500,000 times which offer accurate views of the 'network' structure observed in hydrogel system.
J	Sol-gel analysis[1]	Sol-gel analysis is critical in radiation cross-linking, evaluating specifications like cross-linking and degradation yields, gelation dose and correlating these parameters with particular physical and chemical properties.
K	DSC and TGA[1]	Differential scanning calorimetry (DSC) is important for estimating free and bound water in hydrogels. The procedure evaluates the melting of free water during heating which indicates the amount of free water in sample. Bound water content is assessed by subtracting free water content from the total calculated water content. Furthermore, thermogravimetric analysis validates the development of cross-linked network structures in hydrogels system.

CONTEMPORARY APPLICATIONS OF HYDROGELS IN TARGETED DRUG DELIVERY

FOR DISTINCT THERAPEUTIC AREAS:

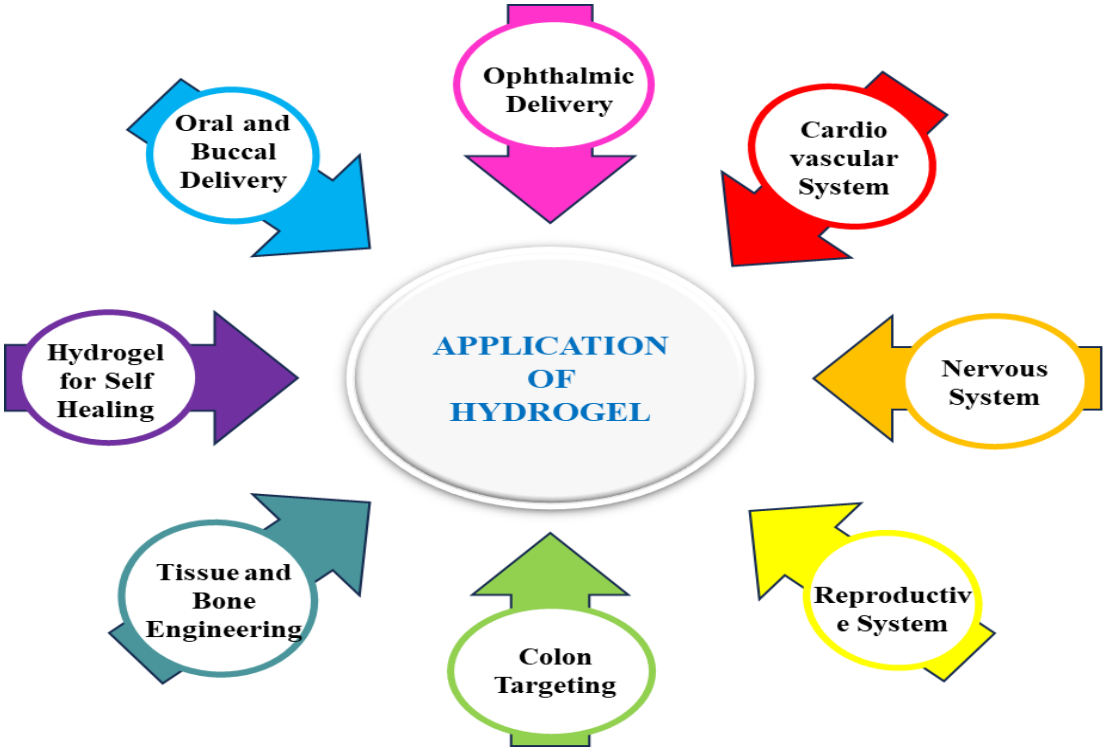

Figure 16: Application of Hydrogel in numerous drug delivery routes

1. Oral and buccal delivery:

Gastroretentive drug delivery systems (GRDDS) increase the drug bioavailability in the proximal GI tract. Using muco-adhesion, buoyancy modification and increased swelling, polyionic complex hydrogels like ring-opened PVP (Polyvinyl pyrrolidone) and chitosan enable controlled release of alendronate for osteoporosis treatment. These hydrogels show enhanced muco-adhesion, minimal irritation, delayed clearance, slower release and improved bioavailability. In vivo experiments demonstrate optimized pharmacokinetics which maintains the therapeutic drug levels. Another example include

a complexation hydrogel of poly(methacrylic acid-g-ethylene glycol) (P(MAA-g-EG)) with octa arginine peptide which enables specific insulin delivery to the intestine with ideal targeting, immediate release upon absorption and absorption[72].

The buccal route is preferred for drug delivery due to rapid onset, easy emergency removal and minimal side effects. It is non-painful, causing little irritation and the highly vascular buccal mucosa enhances permeability and improves patient compliance. Mucoadhesive hydrogels, using polymers like chitosan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), carboxymethyl cellulose (CMC) and polyacrylic (PA) resins are commonly employed for efficient buccal drug delivery systems[73].

Table 3: Commercial hydrogel-based buccal DDS available in market

Product Name	Company Name	Description
Nicorette and Nicotinell®	Johnson & Johnson and GlaxoSmithKline	Nicotine-containing chewing gums or sprays for smoking cessation, utilizing HPMC-hydrogels.
Zilactin-B Gel®	Innovative Pharmaceuticals	Relief for toothache and mouth sores, incorporating an HPC-based buccal film.
Imdur®	Key Pharmaceuticals	Used for angina prophylaxis, featuring HPMC and HPC-buccal hydrogel.
Buccastem M® buccal tablets	Alliance	Xanthan gum-based hydrogels with prochlorperazine, designed for managing nausea and vomiting associated with migraines.
Gengigel®	Oraldent Ltd	Hyaluronan-based mouth and gum care solution, used for treating mouth ulcers.

2. Ophthalmic Delivery:

Hydrogels play a vital role in ocular applications, serving in controlled drug delivery, tissue engineering and regenerative medicine. Derived from natural or synthetic polymers, these hydrogels offer a 3D network structure with stimuli-responsive behaviour. Dextenza by Ocular Therapeutix, an FDA-approved hydrogel for post-surgical ocular pain, showcasing innovation in drug delivery through intracanalicular implants is a prominent example. Gel-forming polymers like xyloglucan are employed for sustained delivery of drugs such as pilocarpine and timolol[74]. Hydrogels containing N,N-dimethyl acrylamide, poly-HEMA and 2- (N-thyl per fluorooctane sulphonamide) ethyl acrylate achieve complete corneal absorption for ocular delivery. HyloR Gel, a viscous hydrogel eye drop with sodium hyaluronate, provides prolonged lubrication for dryness treatment. Intravitreal preparations like Lacrisert R and Vitrasert, with hydroxypropyl cellulose, address dryness and cytomegalovirus-associated retinitis in AIDS patients, respectively. A thermo-responsive polymer blend, poly(acrylic acid-graft-N-isopropyl acryl amide) (PAAc-graft-PNIPAAm) with epinephrine, enhances in vitro ophthalmic drug release, extending intraocular pressure reduction from 8 to 36 hours - a controlled method for ophthalmic drug delivery[75].

3. Cardiovascular System:

In vascular tissue engineering, hydrogels offer potential for cardiovascular disease treatment, addressing toxicity and biodegradability issues. Focus is on bone defect repair, angiogenesis regulation and enhancing vascularization. Li et al. developed an injectable method, covalently linking heparin to gelatine and introducing vascular endothelial growth factor (VEGF), demonstrating successful angiogenesis induction in mice as an excellent model for soft-tissue regeneration[76]. Hydrogels are promising for treating myocardial infarction, entering clinical trials. Biological mechanisms include promoting angiogenesis, reducing necrosis, facilitating stem cell homing and inhibiting infarct area expansion. Chen et al.'s hydrogel formulation with curcumin and nitric oxide demonstrated enhanced efficacy in reducing myocytic apoptotic death and decreasing collagen deposition in mouse models of myocardial infarction[77].

4. Nervous System:

The nervous system plays a crucial role in regulation of body functions and disorders like Parkinson's, insomnia and Alzheimer's are significant threats. Current treatments for nerve injuries include surgery, gene therapy, drug therapy and tissue engineering. Hydrogels, especially those made from silk fibroin (SF), fibrin and collagen, are promising for nerve repair. Hopkins et al. found that SF hydrogels outperformed fibrin and collagen as carriers for cultivating chick embryonic dorsal root ganglia, promoting growth[78]. Ren et al. developed an injectable chitosan-gelatine hydrogel for Parkinson's disease, incorporating dopamine and metronidazole. The hydrogel demonstrated stable mechanical attributes, commendable biodegradability and biocompatibility, suggesting potential as a sustained-release drug delivery system for Parkinson's treatment[79].

5. Reproductive system:

Hydrogels are less common for male reproductive system diseases but find broader applications in treating female reproductive system issues. In female reproductive health, nanometer silver antibacterial hydrogel shows therapeutic effects in treating vaginitis, caused by fungal infections, with a notable slow-release effect[80]. Hyaluronic acid hydrogel is effective for preventing uterine adhesions after cavity surgery. A chitosan-heparin hydrogel loaded with recombinant human stromal cell-derived factor-1α (SDF-1α) shows potential for repairing injury of endometrium and preventing uterine adhesions[81]. Hydrogels also offer a contraceptive method such as styrene-maleic anhydride inserted in a biodegradable hydrogel, inhibiting sperm and preventing egg cell formation. This provides additional contraceptive choices for women, potentially reducing side effects associated with existing options[82].

6. Colon Targeting:

Hydrogels designed for targeted drug delivery to the colon address conditions like colon cancer, ulcerative colitis and Crohn's disease. Colon-specific hydrogels, altered by enzymatic activity or pH, enable tissue-specific drug release. A crosslinked guar gum hydrogel with glutaraldehyde, for instance, achieves controlled release of ibuprofen specifically in the colon[83].

Researchers, including Shabina Mahmood et al. and Muhammad Suhail, Yu-Fang Shao et al., have synthesized pH-responsive hydrogels for colonic delivery of Losartan Potassium and 5-aminosalicylic acid. These hydrogels enable targeted drug delivery to the colon, providing precision in therapeutic interventions[84].

7. Tissue and Bone engineering:

Hydrogel matrices, incorporating cells and growth factors, hold promise for repairing bone defects and cartilage tissue. Their 3D structure fosters cellular growth crucial for effective regeneration. These scaffolds mimic the extracellular matrix of cartilage, aiding repair by encapsulating stem cells and promoting differentiation. Injectable hydrogels excel in three-dimensional cell cultures for bone and cartilage tissue engineering, showing significant potential. Liu et al. in 2017 emphasized the considerable suitability of hydrogels for various applications, attributing it to their high H_2O content, resemblance to the natural extracellular matrix (ECM), porous structure encouraging cell proliferation, minimally invasive characteristics and ability to adapt to misshapen defects[44,67].

8. Hydrogels for Self-healing:

Hydrogels, intricate polymer networks, are pivotal in biomedical fields for tissue repair. They self-heal by forming new bonds when damaged, adapting to surroundings. They are split into robust (for durable applications like biosensors) and soft (for delicate tasks like drug delivery). These versatile gels aid wound healing, 3D printing and drug delivery and smart hydrogels show promise in managing conditions like myocardial infarction, enhancing vasculogenesis when encapsulating endothelial progenitor cells in ischemic myocardium. In a 2015 study, Gaffey et al. demonstrated a self-healing hydrogel created by host-guest interactions. When injected into an ischemic myocardium and encapsulating the endothelial progenitor cells (EPCs), it notably boosted vasculogenesis[44,85–88].

Conclusion and Future prospective:

Polymeric hydrogels possess extraordinary qualities that render them irreplaceable across diverse fields like biomedical, agricultural, industrial and environmental sectors. Continuous amendments and reformations have propelled their usefulness and application scope. This review comprehensively explores the newer generations of polymeric hydrogels and their technical applications. The review comprehensively includes various categories of hydrogels, including smart hydrogels. It throws light on their versatile applications as well.

Future studies should focus on meeting specific requirements for advanced drug delivery systems. Cross-linked architectures of monomers, pre-polymers and polymers are expected to remain crucial in this sector. An inclination towards environmentally friendly "green" approaches, utilising safe solvents or no solvents and low-energy processing for hydrogel systems is predicted. Injectable hydrogels formed within the body without the need for surgical intervention for targeted drug release or tissue engineering are seen as a suitable option.

Simplifying hydrogel formulations aiding their utilisation in diverse spheres will be a key goal in the years to come. Current extensive research focuses to provide newer versatile hydrogels to cater to future requirements. Innovative conceptual integration in hydrogel preparation could lead to tailored properties, expanding their applications across various fields. Ultimately, an economically viable approach to enhance the efficacy of hydrogel systems is of paramount importance and high demand.

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Authors Contribution

All authors have contributed equally to this review article.

Conflict of Interest

The authors do not have any conflicts of interest.

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