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Review Article

Hydrogels Platforms Addressing the Multiple Applications in Medicinal and Drug Delivery: A Critical Review

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Abstract

Hydrogels are three-dimensional polymeric networks renowned for their remarkable water-absorbing capacity, tunable physicochemical properties, and high biocompatibility. This review comprehensively explores the synthesis, classification, and physicochemical and biological characteristics of both natural and synthetic hydrogels. Advances in crosslinking mechanisms, including ionic, chemical, and physical methods, are critically analyzed alongside their functional properties such as pH-, temperature-, and photo-responsiveness. Special emphasis is given to the role of hydrogels in drug delivery systems, including buccal, oral, vaginal, transdermal, ocular, and injectable formulations. Additionally, their applications in wound healing, tissue engineering, biosensing, and 3D cell cultures are examined. Limitations and challenges in clinical translation, regulatory concerns, scale-up processes, and strategies to enhance drug loading and controlled release are discussed. The review underscores the transformative potential of hydrogels in personalized and regenerative medicine and calls for further translational research to address current constraints and expand clinical applicability.

Keywords: Hydrogel, crosslinked hydrogel, drug delivery, polymerization

1. Introduction

Hydrogels are three-dimensional networks composed of synthetic or natural polymers, renowned for their exceptional ability to absorb and transmit water due to their porous structure. They're non-toxic, non-reactive, and safe for pharmaceutical use[1].

Lately, hydrogels have become a hot topic in drug delivery, particularly for oral administration. Their high water content allows them to carry hydrophilic drugs effectively, while offering excellent biocompatibility and a tissue-like feel. In diffusion-controlled delivery, drugs are loaded into hydrogels, protected from damage, and gradually released. However, hydrogels struggle with lipophilic drugs, which are poorly water-soluble—an issue, since over 40% of drugs fall into this category. Researchers are working on various strategies to overcome this limitation [2].

Hydrogels can be made from both natural and synthetic polymers, often blended to enhance their properties. Among natural polymers, polysaccharides are commonly used[3]. They've shown promise in many applications, such as scaffolds[4], absorbents[5], drug delivery[6], and cartilage replacements[7]. Common examples include pullulan, starch, dextran, chitosan, alginate, and cellulose, along with their derivatives[8,9].

Chemically, hydrogels are made using traditional methods like polymerization or more complex cross-linking techniques[9]. Their water-holding power comes from functional groups like hydroxyl, carboxyl, sulfonic, and amidic groups. Hydrogels can also respond to environmental changes—such as temperature, pH, light, or electric fields—by changing their physical state. How they respond depends on factors like cross-linking, charge density, and polymer type[10].

2. History of hydrogel in case of medicinal and drug delivery

The history of hydrogels in medicine and medication administration is extensive. Hydrogel was first

developed in the 19th century and attracted interest due to its biocompatibility, physical qualities that could be adjusted, and capacity to replicate real tissues. Below are some significant advancements in the development of hydrogel.

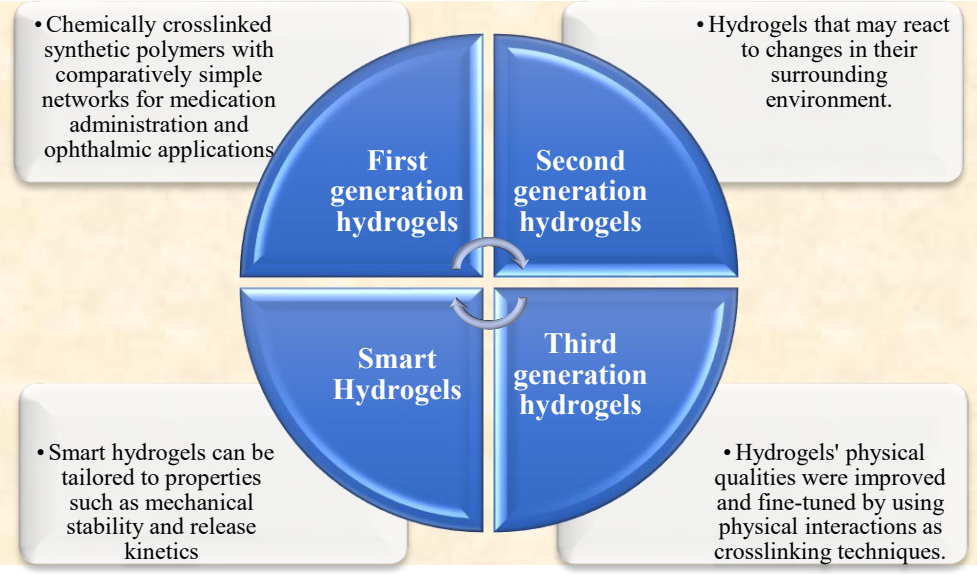

Figure 1 : Evolution of Hydrogels

2.1 Early Hydrogel Development

Around 1900, the word "Hydrogel" was originally employed to refer to an inorganic salt gel that is colloidal[11]. The first hydrogel for contact lenses(soft), poly (2-hydroxyethyl methacrylate) (pHEMA), was developed in 1960 by Wichterle and Lim[12]. Initially, hydrogel research concentrated on relatively basic networks of synthetic polymers that were chemically crosslinked, primarily for use in drug delivery and ophthalmology. Usually, monomers which are water soluble were polymerized with a multifunctional crosslinking agent present, or hydrophilic polymers were crosslinked to create these first-generation hydrogels[13]. Key polymers used in early hydrogels include pHEMA[14], poly vinyl alcohol(PVA)[15], and poly ethylene glycol(PEG)[16].

2.2 Second Generation Hydrogels: Stimuli-Responsive Materials

In the 1970s, hydrogel research began to concentrate on developing hydrogels that could respond to changes in the surrounding, such as temperature, pH and concentrations of biomolecules[17]. For in situ forming systems, hydrogels that are sensitive to temperature are desirable thus they can be administered as a fluid prior to gelling. Common polymers used in temperature-sensitive hydrogels include poly(ethylene glycol)-polyester block copolymers[18], poly(N-isopropyl acrylamide)[19] and poly(N-(2-hydroxypropyl) acrylamide)[20]. Acidic or basic groups in pH-sensitive hydrogels ionize at high or low pH levels, allowing for regulated release[21]. There are now hydrogels that react to the concentrations of biomolecules, such as glucose-sensitive hydrogels that use glucose oxidase to release insulin[22].

2.3 Advanced hydrogel systems

Hydrogels with enhanced mechanical characteristics and regulated degradation are produced by stereo-complexation between enantiomeric poly(lactides)[23]. To create supramolecular hydrogels, cyclodextrin inclusion complexes with polymers such as PEG are utilized. Hydrogels are also made from self-assembling proteins and peptides, which use natural building blocks to construct organized structures like β-sheets or coiled coils. Smart hydrogels include multi-component hydrogels, double-network hydrogels with combinations of ionic, covalent, or physical interactions, and in situ chemically cross-linkable hydrogels with low toxicity. Although there are stability restrictions, hydrogel synthesis uses enzymatic crosslinking with enzymes such as transglutaminase and horseradish peroxidase. In situ hydrogel creation frequently uses the Michael addition, a conjugation reaction between electrophilic olefins and nucleophiles. Click chemistry is a chemo-selective crosslinking technique for hydrogels, especially copper-free click chemistry. Initiators like potassium persulfate and N,N,N′,N′-tetramethyl ethylenediamine are employed in radical polymerization to crosslink macromers containing methacrylate or acrylate groups. Another technique for crosslinking natural polymers with (meth)acrylate groups is photopolymerization[24].

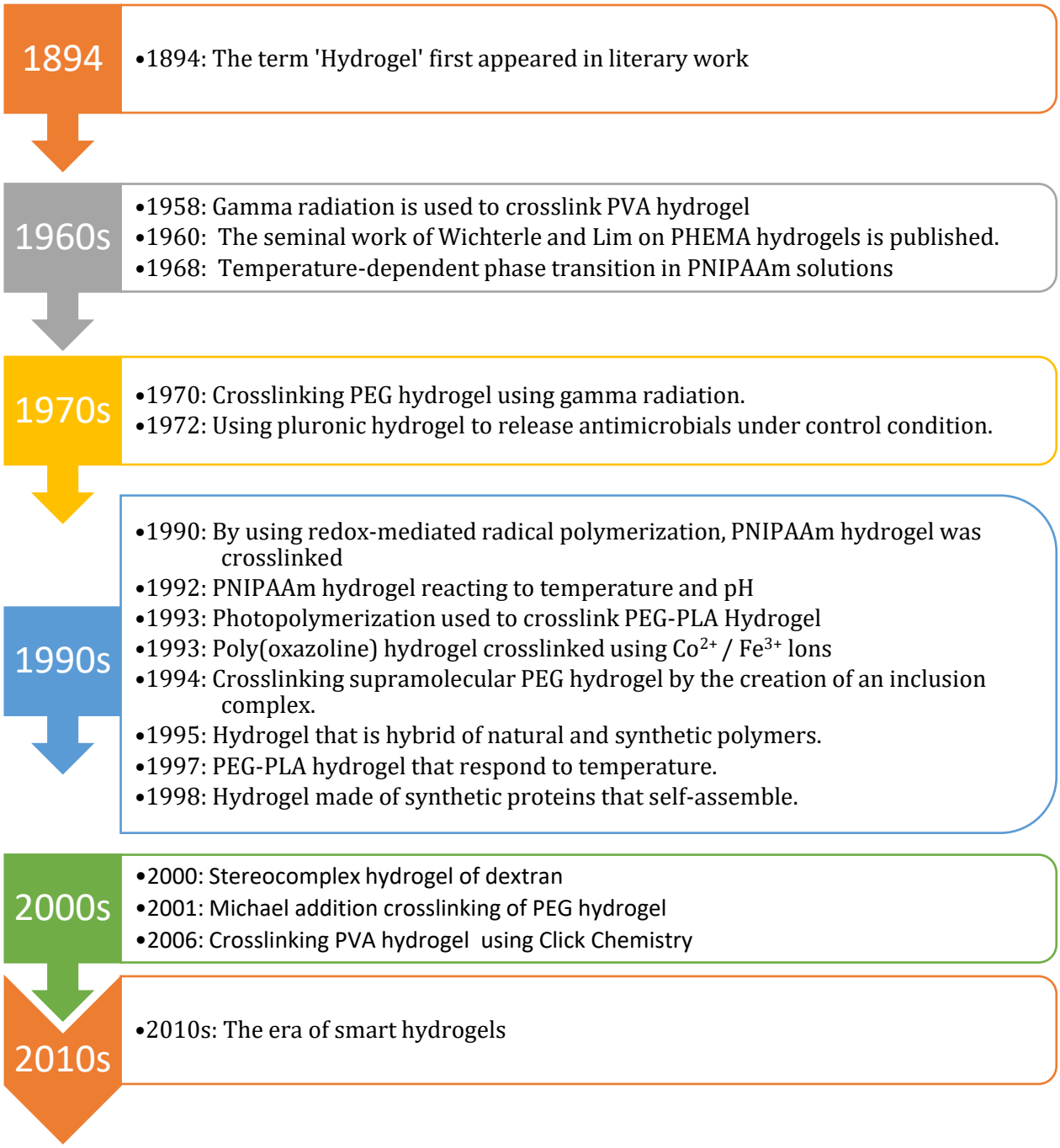

Figure 2: History of Hydrogels[25].

3. Properties of hydrogel

Hydrogels are extremely beneficial and adaptable in a variety of applications, especially in tissue engineering, drug administration, and medicine, because to their special combination of features. The categories of physical, chemical, and biological qualities include a variety of attributes. The following explains a few of them.

3.1. Physical Properties:

3.1.1 Swelling Behaviour*:* Because hydrogels are hydrophilic materials, they can swell dramatically in the presence of water. Three processes contribute to this swelling: the water diffusion into the hydrogel and the expansion of the hydrogel network leads to the relaxing of polymer chains.

3.1.2 Mechanical Properties*:* Hydrogels' mechanical strength is crucial, especially for biomedical uses like tissue engineering and drug delivery, requiring a balance between flexibility and durability. Strength can be tailored by adjusting polymer type and crosslinking. Mechanical properties are assessed using methods such as tension, compression, and frequency-based tests. Rheometers are commonly used for sinusoidal testing, where samples are placed on specific geometries to perform various sweep measurements.[26]

3.1.3 Thermal Stability*:* The degree of thermal stability exhibited by hydrogels varies based on their composition and crosslinking techniques. In order to preserve their

integrity under physiological settings, this stability is essential[27].

3.1.4 Degradation Rate: The selection of materials and crosslinking techniques can regulate the hydrogels' degradation; this is especially crucial for biomedical applications where a gradual degradation is frequently necessary.

3.2. Chemical Properties:

3.2.1 Crosslinking Mechanisms: Crosslinking can be done chemically or physically to create hydrogels. Physical hydrogels rely on weak interactions (like hydrogen bonds), while chemical hydrogels involve covalent bonds, which generally provide greater stability.

3.2.2 Stimulus-Responsive Behaviour: Hydrogels respond to various stimuli: physical (temperature, light), chemical (pH, ionic strength), and biological (enzymes). Physical stimuli are usually external, while chemical and biological ones are internal. Shape memory hydrogels are a special type that retain a permanent shape and can return to their original form using physical or chemical triggers.

3.3. Biological Properties:

3.3.1 Biocompatibility: Hydrogels are highly biocompatible, making them ideal for medical uses like drug delivery, wound healing, and tissue engineering. Their soft, tissue-like nature minimizes immune reactions. Natural polymer-based hydrogels, such as those made from chitosan or alginate, offer excellent biocompatibility and biodegradability, ensuring safe interaction with biological tissues.[26,27]

4. Classification of hydrogels:

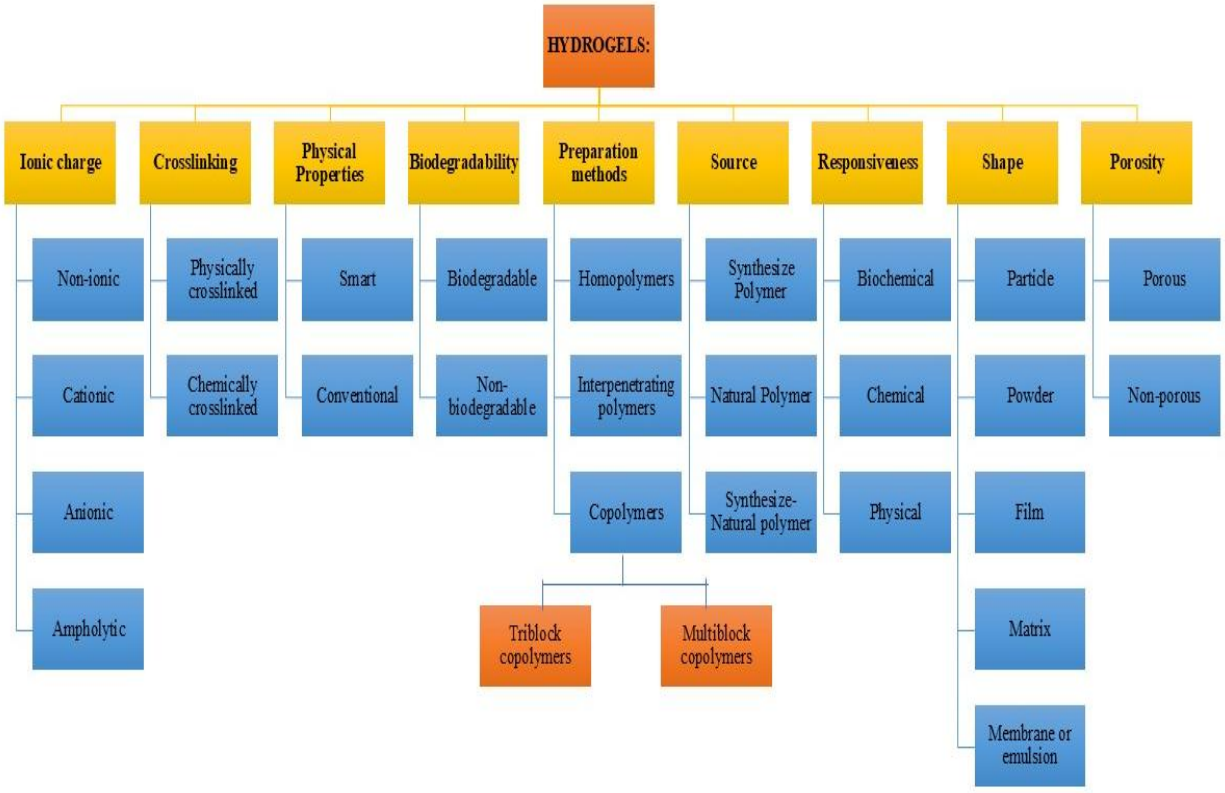

Figure 3: Classification of hydrogel

5. Methods of preparation of hydrogels:

Numerous techniques can be used to create hydrogels in order to obtain the appropriate mechanical, structural, and functional characteristics. These techniques can be roughly divided into groups according to the kind of crosslinking process, the makeup of the polymer, and the intended use. Here is a summary of the main techniques for making hydrogel.

5.1 Ionic crosslinking:

Ionic crosslinking is a widely used method for forming hydrogels, especially with polysaccharides like chitosan and alginate. It involves ionic interactions between multivalent cations and negatively charged polymer groups, creating stable gel networks. For example, Savić Gajić, Savić et al. (2023) prepared alginate hydrogels by mixing alginate with calcium chloride. The alginate solution was stirred for 24 hours, then added dropwise into a $CaCl_2$ solution using a syringe to form the hydrogel through ionic gelation.[28]

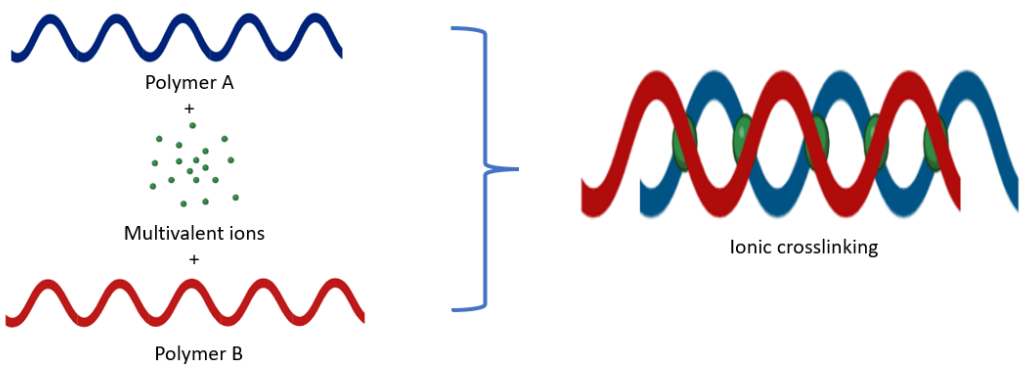

Figure 4: Mechanism of ionic crosslinking

5.2 Interpenetrating Polymer Network (IPN):

Interpenetrating polymer network (IPN) hydrogels consist of two or more interlaced polymer networks that are physically entangled but not covalently bonded. They are synthesized either simultaneously—where both networks form at the same time through separate mechanisms—or sequentially, where one network is formed first and the second is polymerized within it. This method allows precise control over hydrogel structure and properties. For instance, Matsumoto, Sakikawa et al. (2018) created an IPN hydrogel by polymerizing N-isopropylacrylamide with a crosslinker in the presence of sodium alginate, using a redox initiator system and final ionic crosslinking to form the network[29]

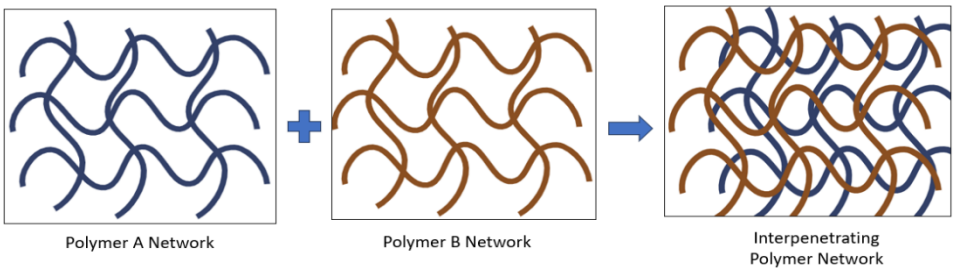

Figure 5: Mechanism of Interpenetrating polymer network hydrogel matrix

5.3 Chemical crosslinking:

Chemically crosslinked hydrogels are typically prepared by dissolving natural (e.g., chitosan, gelatin) or synthetic (e.g., PVA, PEG) polymers in a solvent, followed by adding a crosslinking agent like glutaraldehyde or carbodiimide. Conditions such as pH, temperature, and time are controlled, and initiators like heat or UV may be used. For example, Ali, Ranjha et al. prepared PVA/Gelatin hydrogels by dissolving PVA in water at 60°C and gelatin in 3% acetic acid at 37°C. The solutions were mixed, and chemical crosslinking was triggered using HCl and glutaraldehyde. [30].

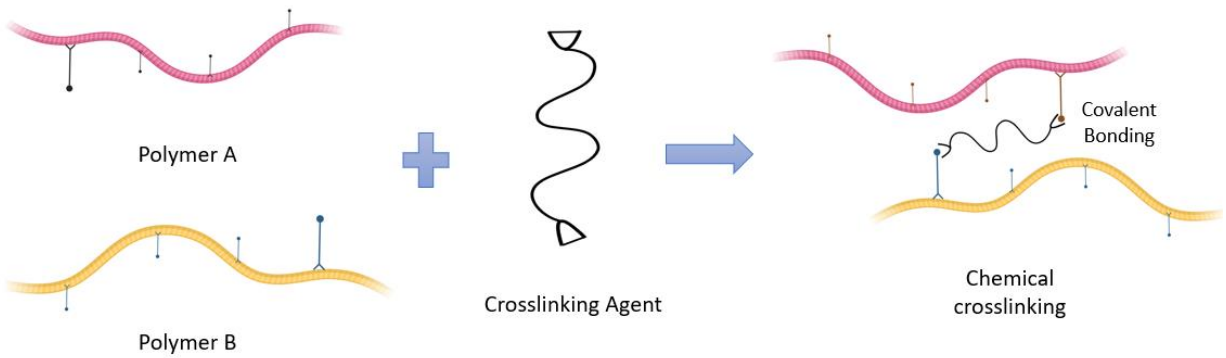

Figure 6: Mechanism of chemical crosslinking

5.4 Freez thraw method:

Freeze-thaw hydrogels are physically crosslinked networks formed by repeated freezing and thawing, promoting hydrogen bonding without toxic chemicals. Ding, Song et al. prepared hydrogels by dissolving PVA in distilled water, mixing it with Curdlan gel, and stirring for 2 hours. The mixture was poured into Petri dishes, frozen at -20°C for 12 hours, then thawed at room temperature for 4 hours. This freeze-thaw cycle was repeated four times to form stable hydrogels. [31].

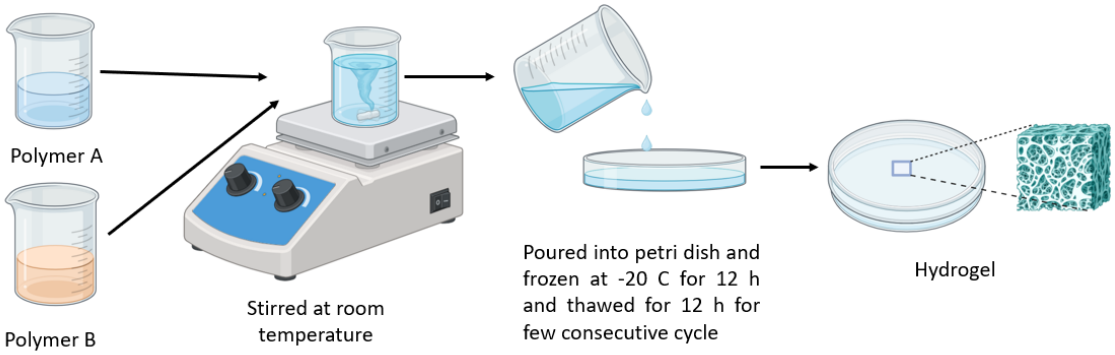

Figure 7: Mechanism of freez thrawing for hydrogel

5.5 Gamma Radiation induced polymerization:

Gamma radiation-induced hydrogels are formed using high-energy gamma rays (e.g., from cobalt-60) to initiate polymerization and crosslinking without chemical agents. This process creates free radicals in aqueous polymer solutions, forming covalent bonds[32].

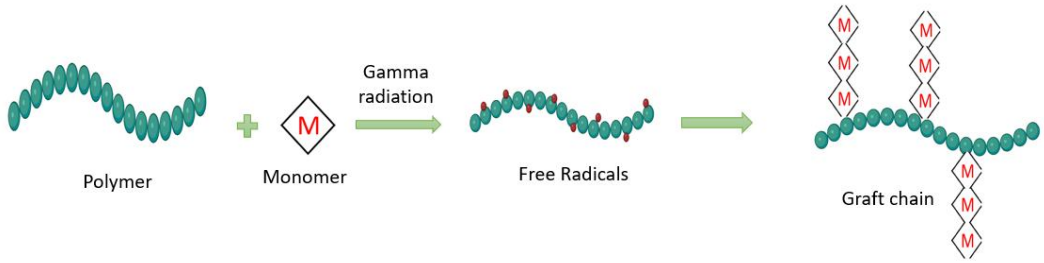

Figure 8: Mechanism of Gamma radiation-induced polymerization for hydrogel preparation

6. Medicinal application of hydrogel

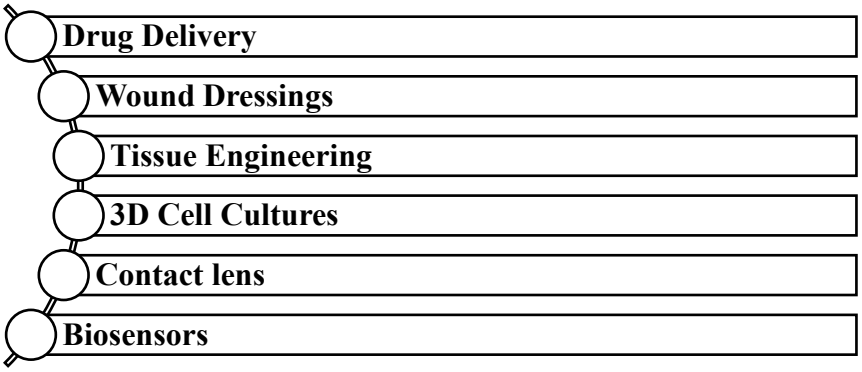

Figure 9: Various medicinal applications of hydrogel

6.1 Drug Delivery

Smart hydrogels, made from natural or synthetic polymers, are promising for targeted drug delivery due to their ability to respond to stimuli like temperature, pH, or magnetic fields by changing properties such as swelling or permeability[33]. While natural hydrogels are biocompatible, they often lack mechanical stability and are difficult to process[34]. Chemical modification can enhance their performance, but synthetic polymers are preferred for their easy tunability, hydrophilicity, and biodegradability, which also help reduce opsonization and phagocyte clearance[33].

6.1.1 Thermo-responsive hydrogel-

Thermo-responsive hydrogels can expand or shrink with temperature changes, altering their volume, solubility, and structure. Despite these shifts, they can maintain their gel-like state across different temperatures.

Table 1: Examples of thermos-responsive hydrogel

Drug	Carrier	Key Features	Duration	Notes
Dexamethasone (anti-inflammatory)	N-2-hydroxypropyl methacrylamide (ProGel-Dex hydrogel)	- Liquid at 4 °C, forms gel at ≥30 °C- Injected into arthritic joints- Targets immune cells (synoviocytes)- Minimizes side effects	Slow release over 30 days	Small polymer size (~6.8 kDa) ensures fast clearance from the body[34]
Topotecan (anti-cancer)	Solid Lipid Nanoparticles (TPT-SLN) with Poloxamer 407/188	- Gelation above 31 °C- Used in colorectal cancer model- Better anti-cancer effect than pure topotecan- Fewer side effects	Lasts up to 28 days, stable for 6 months	Promising results, but longer-term studies still needed[35]
Lamivudine (3TC) + Zidovudine (AZT) (anti-HIV)	Nano co-crystal with Pluronic F-127	- Reduces dose frequency- Sustained drug release- Less toxicity than standard therapy	Releases >168 hours (~7 days)	Can improve adherence in HIV therapy[36]
Antibody-based therapy	PEGMA-based hydrogel	- PEG alternative- Controls protein release by adjusting PEGMA- Dissolves at 37 °C to release protein	Sustained release for 13 days	Potential for use as a sustained antibody delivery system[37]

6.1.2 PH-responsive hydrogel

pH-responsive hydrogels swell with pH changes, absorbing water and releasing drugs. When taken orally, they can target the gut or intestines for drug delivery[38]. They're also effective in cancer treatment, releasing medication in the acidic environment of tumors[39].

Table 2: Examples of pH responsive hydrogel

Drug	Material	Key Features	Effectiveness	Notes
Bortezomib (BTZ, anti-cancer) + Luteolin (LUL)	pH- and photo-responsive hydrogel (mPEG-LUL-BTZ)	- Releases BTZ at acidic pH (5.5)- Works up to 50 hours- Safe in normal animals- Boosted by photothermal agent ICG	Reduced tumor growth in rats	Combining with ICG (indocyanine green) enhances photothermal & photodynamic therapy[40]
Amifostine (radioprotective drug)	pH-responsive hydrogel (MAC-g-PCL)	- Gel formation at pH 1.2 (stomach)- Rapid release at pH 7.4 (intestine)- Protects Ami from stomach acid	Burst release in intestine; improved survival in mice	Suitable for oral delivery of drugs with low stomach stability or poor bioavailability[41]

6.1.3 Photo-responsive hydrogels

Photo-responsive hydrogels use light energy to change their characteristics. It is simple to manage the alteration by varying the durations of light stimulation and turning on and off the light in a specific wavelength[42].

Table 3: Examples of Photo responsive hydrogel

Drug	Material	Key Features	Effectiveness	Notes
Doxycycline (antibiotic)	Light-sensitive hydrogel with carboxylated spiropyran (SPCOOH)	- UV light triggers drug release- Reduces initial burst release- Allows controlled, sustained delivery	Up to 42 hours under UV light	Better control than non-photoresponsive hydrogels[43]
Insulin (for diabetes management)	Photoresponsive hydrogel with black phosphorus (BP) + pNIPAM in microneedles	- Light converts to heat (photothermal)- Triggers insulin release- Microneedles ensure painless skin penetration	Effective blood glucose control in mice	Promising for smart, responsive insulin delivery systems[44]

Table 4: Examples of Dual-responsive hydrogels

Drug	Material	Key Features	Effectiveness	Notes
Doxorubicin (DOX), Curcumin (CUR), Methotrexate (MTX)	pH-/thermo-responsive hydrogel (NIPAAm + DMAEMA)	- Dual responsiveness: pH (5.8/5.5) and temperature (40 °C)- Sustained release of DOX & CUR: 168h- MTX: 50h	DOX/CUR: 168h, MTX: 50h	Significantly improved cancer cell death vs. free drugs (colon & breast cancer models)[45]
Magnesium ions (for gut health / therapy)	pH-/redox-responsive hydrogel (PLP-CDE)	- Swells in acidic/reducing environments- Controlled Mg^{2+} release at pH 6.8- Enhanced with DTT- Minimal in pH 1.2 (stomach)	Mg^{2+} released up to 6 hours in intestines	Designed for oral delivery with intestinal targeting, especially for sensitive molecules or ions[46]

6.2 Wound Dressings

Hydrogels help heal wounds by absorbing excess exudate, creating a protective barrier, and maintaining a moist environment that supports recovery [47]. They're biocompatible, biodegradable, and mimic the natural extracellular matrix (ECM), offering features like antibacterial activity, blood clotting, and tissue regeneration[48]. Natural polymers like chitosan, hyaluronic acid, collagen, and cellulose contain bioactive agents, making them ideal for wound dressings. Modified in-situ collagen–hyaluronic acid hydrogels are especially effective for promoting natural wound healing.

Table 5: Examples of hydrogel for wound dressings

Hydrogel Composition	Bioactive Agents	Antibacterial Activity	Wound Healing Effect	Notes
Graphene–silk fibroin hydrogel	Ciprofloxacin	Effective against P. aeruginosa, S. aureus, and biofilms	Enhances fibroblast growth, supports burn wound healing	Combines antimicrobial and regenerative properties[49]
PVA hydrogel with κ-carrageenan and chitosan HCl	Cefotaxime sodium (CTX)	Active against S. aureus, E. coli, and P. aeruginosa	Improves granulation and re-epithelialization in diabetic burns	Good oxygen permeability[50]
pH-sensitive hydrogel with silver nanoparticles	Silver nanoparticles	Effective against biofilms of P. aeruginosa and S. epidermidis	Not yet studied in vivo	Needs more research for in-body effectiveness[51]
Injectable collagen–PEG hydrogel	Stem cell factor (SCF) from umbilical cords	Unclear	Promotes angiogenesis, reduces inflammation in diabetic wounds	Antibacterial effect not well studied[52]
Gelatin–PVA hydrogel	3-carboxy-phenylboronic acid, VAN-AgNCs, Nimesulide	Kills P. aeruginosa, S. aureus (dose-dependent)	Strong hemostasis, supports cell growth, aids chronic diabetic wound healing	Combines multiple functionalities: clotting, anti-inflammatory, antibacterial[53]
Carboxymethylcellulose (CMC) hydrogel	Plasma-derived exosomes	Not determined	Activates VEGF pathway, enhances regeneration and angiogenesis in diabetic wounds	pH-responsive delivery system[54]

Pluronic F127 hydrogel	Stem cell exosomes (umbilical cords)	Not determined	Promotes VEGF, TGFβ-1, cell proliferation	Encouraging results for chronic wound healing, antibacterial effects need more study[55]
Thermoresponsive hydrogel (PEG, PPG, PDMS)	Lignin (antioxidant)	Inhibits C. lipolytica, L. monocytogenes, S. aureus	Enhances cell growth, supports wound healing	Lignin gives both antioxidant and antibacterial benefits[56]
Alginate–polylysine–hyaluronic acid hydrogel	Curcumin, epigallocatechin gallate	Binds/inhibits E. coli, S. aureus	Reduces oxidative stress, fights inflammation, boosts blood vessel growth	Suitable for radiation-damaged skin[57]
Polydopamine-based hydrogel	Silver nanoparticles (generated in situ from silver nitrate)	Inhibits S. aureus, E. coli	Not fully evaluated in vivo	Needs more research on wound healing impact[58]

6.3 Tissue Engineering

An interesting but challenging therapeutic option for individuals with permanent tissue damage and functional failure.[59] It aims to promote tissue regeneration by producing a platform that mimics the extracellular matrix present in vivo. Because of their biodegradability, biocompatibility, mechanical strength and similar extracellular matrix found in vivo.[60]

Table 6: Examples of hydrogel for tissue engineering

Hydrogel Composition	Application Area	Outcomes	Animal Model or Notes
3D-printed chitosan-collagen	Nerve regeneration (peripheral)	Reduces cavity/scar formation, promotes nerve fiber renewal and functional recovery	Demonstrated in animal model[61]
Alginate + Fibrin + Hyaluronic acid (HA)	Peripheral nerve regeneration	Used as 3D printing additive for nerve scaffolds	Application in regenerative biofabrication[62]
HA–cellulose hydrogel	Central nervous system	Supports central nerve healing	Focus on brain and spinal cord repair[63]
Gelation hydrogel (crosslinked w/ horseradish peroxidase + choline oxidase) + mMSCs	Traumatic brain injury	Enhances neurotrophic secretion, neural differentiation, and cell viability; promotes neuro-repair	Tested in rats with brain injury[64]
Not specified	Intervertebral disc regeneration	Hydrogel supports hBMSC differentiation into nucleus pulposus cells	Key for spinal disc therapy[65]
PEG–fibrinogen microsphere hydrogel + hiPSCs	Heart regeneration	Supports cardiac differentiation, generates cardiomyocytes	Useful in injection-based regenerative therapy[66]
Alginate/Silk Sericin w/ lamellar coating (ASS@L) + ADSCs	Heart (myocardial infarction)	Injectable system improves heart healing post-heart attack	Demonstrated effectiveness in acute myocardial infarction model[67]
Silk fibroin	Cardiac pacemaker therapy	Enables pacemaker cells to mimic real sinoatrial node cells in structure and function	Silk-fibroin-based pacemaker cells successfully functioned in rats as in situ heart pacemakers[68]

6.4 3D Cell Cultures

In the body, cells grow in a 3D environment shaped by the ECM, which guides how they behave. 3D lab platforms mimic this setup better than 2D ones, helping us study cells more realistically. [69]Hydrogels provide a soft, moist 3D space like the natural ECM, making them a popular choice for 3D cell cultures.[70] Made from natural or synthetic polymers, hydrogels have unique properties that make them great for 3D cell cultures.[69]

Table 7: Natural, synthetic, and semi-synthetic hydrogels for 3D cell cultures.

Type	Material	Application	Key Findings
Natural	Collagen(Type I & II)[71]	Chondrocyte culture, cartilage regeneration	Supports chondrogenesis, maintains chondrocyte phenotype, enhanced with silk fibroin for stability
	Hyaluronic Acid (HA)[72]	Neural, cardiac, cartilage regeneration; cancer 3D models	Promotes stem cell differentiation, cancer cell proliferation, angiogenesis; RGD-modified HA enhances neural differentiation
	Fibrin[73]	Cardiomyocyte, adipose-derived stem cell culture, bone, vascular modeling	Simulates ECM, supports vascularization, osteogenesis, oocyte maturation; tunable stiffness enhances specific cell functions
	Alginate[74]	Neural retina, neuron networks, cancer 3D culture	RGD/collagen-modified alginate promotes adhesion, neural differentiation, and neuron network development
Synthetic	PVA (Polyvinyl Alcohol)[75]	Cancer modeling (glioma, breast, pancreatic), mHSC culture	Enhances stem cell growth, promotes tumor spheroid formation, reduces apoptosis in cancer cells
	PEG (Polyethylene Glycol)[76]	Tumor spheroids, stem cells, cartilage regeneration	Biocompatible, encapsulates drugs, tunable stiffness; supports chondrocyte and mMSC development
Semi-synthetic	HA-PEG, PEG-alginate-RGD[77]	Hepatocytes, endothelial cells, osteogenesis	Improves mimicry of in vivo ECM, enhances osteogenesis, supports capillary sprouting and fibroblast proliferation

6.5 Contact lens

The first corneal lens, was created in 1948 [78]. Over time, efforts to improve contact lenses grew, but a major breakthrough came when Otto Wichterle developed soft lenses using HEMA, despite doubts from his superiors. [79] Since the early days of contact lenses, the need for more breathable, lightweight materials has been clear to improve eye comfort and health. A major step forward came in 1974 with the addition of silicone to Poly(methyl methacrylate), creating silicone acrylates. Later, silicone hydrogel lenses entered the U.S. market in 2001 and quickly gained popularity, making up 73% of soft lens prescriptions by 2014. [80]

Hydrogels in contact lenses must transmit at least 91% of light, but temperature changes can cause cloudiness by separating water—so proper storage is key [81]. Their comfort, strength, and flexibility depend on mechanical properties, which are hard to measure accurately because hydrogels are so water-rich and respond to deformation.[82] Strength affects handling, while a low elastic modulus means the lens is softer and more comfortable. Surface traits like friction, wettability, and lubrication are also crucial—wetting agents are often added to improve comfort by reducing friction[83]. Studies show people prefer lenses that are softer, have higher water content, and allow better oxygen flow to the eye.[84] Siloxane hydrogels are introduced to combine the high oxygen permeability of fluorosiloxanes with the wettability, softness, and comfort of traditional hydrogels.[85].

6.6 Biosensors

Biosensors offer fast, real-time, and accurate detection. Hydrogels act as a bridge between biomolecules and the physical sensor components, often containing hydrophilic molecules for binding. Common materials include alginate, alginic acid, and blends with N-isopropyl acrylamide, acrylamide, or chitosan[86]. Devadhasan and Kim developed a hydrogel-based pH sensor using a CMOS image sensor. The hydrogel changes color across pH 1–14, and the sensor captures this for precise analysis—useful for detecting hazardous chemicals on-site [87].

7. Formulation and drug delivery application of hydrogel

Hydrogels are widely employed as drug delivery vehicles and are widely used in drug delivery. The commercial drug delivery products are mentioned in paragraph according to administration route.

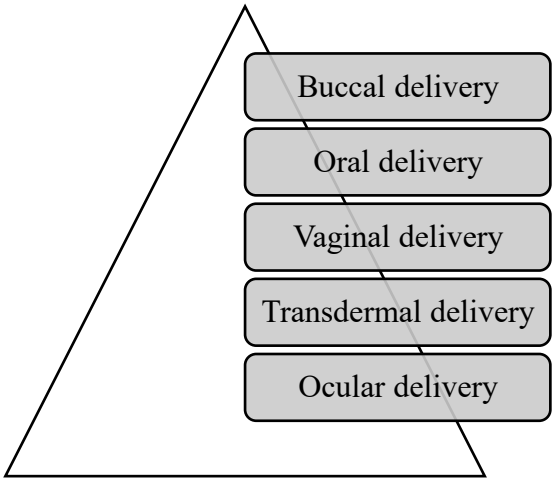

Figure 10: Different routes of drug delivery through hydrogel

7.1 Buccal delivery

The oral cavity, covered by100 cm^2 of mucus-lined epithelium, includes the floor (sublingual delivery), cheeks (buccal route), and gums (gingival route) for medication administration.[88] The oral cavity is ideal for drug delivery due to easy administration and avoidance of first-pass metabolism and GI tract degradation.[89]

Polymer having good adhesion are used for buccal mucosa, good spreadability, wetness, swelling, and viscoelasticity mechanical qualities[90], low cost, biodegradability, and bioadhesive qualities in both liquid and dry states characteristics, non-toxic breakdown products, and it can't act as a conduit for secondary infections as dental caries[91]. Use of Cellulose or acryl polymers high adhesion for extended hours, with high drug content. Hydrogel-based mucoadhesive tablets can control the release profile of the drug it depending on the hydration.

Hydrogels used in these applications are: polyacrylic (PA) resins, carboxymethyl cellulose (CMC), hydroxyethyl cellulose (HEC), polyvinyl alcohol (PVA), hydroxypropyl methyl cellulose (HPMC), chitosan, hydroxypropyl cellulose (HPC).[88]Even with a high drug concentration, the use of cellulosic or acrylic polymers typically provides nearly instantaneous, strong adhesion performance for extended periods of time.

Marketed formulations

- Mouthwashes, oral gels, and sprays all contain Lubrajel™ BA (by Ashland) oral moisturizing hydrogel, a mouth moisturizing solution.
- Hydrogel 15% (by Honest O3) is a sunflower seed oil-infused oral gel that contains ozone. This specially designed mucoadhesive hydrogel cleanses and nourishes the mouth for optimum health.

7.2 Oral delivery

Oral delivery is convenient for treating chronic diseases but works best for small molecules. Large molecules like proteins and peptides face challenges such as degradation by stomach acid and enzymes, low intestinal permeability, and poor bioavailability[92]. As molecular weight rises above 500–700 Da, absorption drops significantly, and most large, hydrophilic drugs lack the lipophilicity needed to pass through the intestinal barrier[93]. one of the major challenges is to deliver big molecules orally[94.]To improve oral delivery of proteins and peptides, innovative strategies like hydrogel encapsulation are used to protect them from stomach acid[95]. These hydrogels stay compact in acidic environments, preventing early drug release. Natural polymers with anionic groups are ideal, as they remain protonated in low pH[96]. pH sensitivity is often achieved by grafting natural polymers with acrylic acid derivatives[97]. Known as "stimuli-responsive hydrogels," these materials adjust drug release based on changes in their environment, responding to physical (e.g., temperature, light) or chemical (e.g., pH, ionic strength) stimuli[95.]

Liu et al. published review on the polymeric network design of hydrogels to address response and mechanical properties.[98]

Oral drug delivery often uses two hydrogel-based systems: matrix and reservoir. In matrix systems, the drug is mixed into the polymer, swells upon contact with fluids, and releases as it diffuses through the gel while the matrix slowly erodes. In reservoir systems, a drug core is enclosed by a polymer shell, with release controlled by the shell's properties and the drug's characteristics.[99]

Here are some commercially available hydrogel-based oral drug delivery systems.

- Sanofi Aventis's Suprax® is a patented antibiotic (since 1979) that treats bacterial infections by binding to penicillin-binding proteins, disrupting peptidoglycan synthesis, and damaging the bacterial cell wall.
- Pfizer's Lopid® is a lipid-regulating drug that increases HDL cholesterol and reduces serum triglycerides and VLDL cholesterol.

7.3 Vaginal delivery

The vagina is prone to infections like vaginitis, making it a common site for delivering antimicrobial drugs. However, factors like hormonal changes, menstrual cycles, and age-related variations in vaginal fluid can affect drug absorption and retention. Despite challenges like rapid physiological clearance, various solid, semi-solid, and liquid formulations are used for vaginal drug delivery.

Two main methods to overcome this restriction are using mucoadhesive formulations to prolong vaginal retention and applying stimulus-responsive gels that undergo sol-gel transitions in the vaginal cavity[100]. Mucoadhesive properties enhance vaginal surface contact and prolong residence time, involving hydration, wetting, and

diffusion during adhesion.[101]Excipients or polymers typically provide these properties. Commonly used in vaginal formulations are hydrogels like polyacrylates, chitosan, cellulose derivatives (e.g., HPMC, CMC), hyaluronic acid, and Carbopol, valued for their strong hydration and bioadhesive properties.[102] Alginate and gelatin are suitable for vaginal delivery due to their moisture retention and biocompatibility. Thermo-sensitive hydrogels are the most common environment-responsive gels, undergoing reversible sol-gel transitions in response to temperature changes, driven by mechanisms like micelle packing, hydrophobic interactions, and coil-to-helix transitions.[102]

Marketed products based vaginal applications listed below

- Replens® Moisturizer adheres to dry cells, providing continuous hydration until they naturally renew.
- Hydeal-D® and Hyalo Gyn®, both HA derivatives, act as moisturizers by adhering to the vaginal cavity, extending residence time, and providing hydration and protection.

7.4 Transdermal delivery

Transdermal delivery is a great alternative to pills, especially for drugs that don't absorb well or for people who can't handle injections.[103]The first transdermal system, using scopolamine for motion sickness, was approved in the U.S. in 1979. A decade later, nicotine patches became the first major transdermal success, boosting patient compliance and patch awareness.[104]

Hydrogels are used in transdermal delivery as creams and patches, offering hydration that enhances drug solubility. They also help stabilize and boost delivery systems like micelles, nanoparticles, and liposomes.[105]

Marketed products based transdermal delivery are listed below

- The special mix of Clean & Clear® Persa-Gel® 10 Acne Medication starts working right away, release medication deeper in pore from where pimple begin.
- Many ingredients in a cosmetic uses hydrogel to regulate passage through skin are delivered by Johnson & Johnson's Neutrogena® family.

7.5 Ocular delivery

From an anatomical and physiological perspective, the eye is a very unique organ since it has several distinct structures, each of which performs a very specific role. This is why scientists have always found it so difficult to build and optimize ocular medication delivery devices.[106]

Hydrogels offer several advantages over traditional materials like implants or colloidal systems, especially in eye treatments. Their high-water content and gentle preparation help preserve delicate molecules like proteins and peptides. Plus, some types—like temperature-sensitive or in situ forming hydrogels—can be applied with less invasive methods than long-term implants.[107]

The global market for eye-related biopharmaceuticals topped $8 billion in 2016 and is expected to grow quickly, reaching around $35.7 billion by 2025.[108]

Marketed products based ocular delivery are listed below

- For the treatment of severe, persistent dry eyes, Hylo® Gel (by Candorpharm Inc.) guarantees a thorough and delayed lubrication of the ocular surface.
- SYSTANE® Gel Drops offer long-lasting relief from irritation caused by dry eyes. These eye drops have a thicker formulation that covers the eyes like a shield.

8. Patents of hydrogel

Table 8: The patents on hydrogel drug delivery system.[109]

Sr. No	US Patent number	Title	Inventor	Publication Year	Assignee
1	12110879	Artificial muscle actuators	Marcio Dias Lima, Yang Yang, Luis Plata, Marilu Guerrero, Franklin Le, Randy Allen	October 8, 2024	LINTEC OF AMERICA, INC.
2	12053527	Compositions with permeation enhancers for drug delivery	Daniel S. Kohane, Rong Yang, Lily Yun Lin	August 6, 2024	Children's Medical Center Corporation, Massachusetts Institute of Technology
4	11903384	Hydrogels as rheology modifiers and methods	Danny Brown, Christine Colby, Lillian Magidow, Megan Barta	February 20, 2024	WinField Solutions, LLC

5	11866636	Embedded treatment fluid additives for use in subterranean formation operations	Dipti Singh, Aaron Michael Beuterbaugh, Enrique Antonio Reyes	January 9, 2024	Halliburton Energy Services, Inc.
6	11739174	Cationic cyclic amine and amphipathic transfection reagents	Nicholas A. A. Rossi, Anatoly Pinchuk, Karen Neder, James Ludtke, Laura Juckem	August 29, 2023	Mirus Bio LLC
7	11578176	Silicone hydrogel contact lenses having non-uniform morphology	Azaam Alli, Donald E. Riederer, Alexander Guzman, Bernardo Santa Maria	February 14, 2023	Johnson & Johnson Vision Care, Inc
8	11555127	Curable film-forming compositions comprising catalyst associated with a carrier and methods for coating a substrate	Scott J. Moravek, Davina J. Schwartzmiller	January 17, 2023	PPG Industries Ohio, Inc.
9	8968764	Nerve regeneration employing keratin biomaterials	Mark E. Van Dyke	March 3, 2015	Wake Forest University Health Sciences

9. Future prospect of hydrogel

9.1 Limitation of hydrogel:

Hydrogels face limitations in applicability, sustainability, and clinical use. Many natural and synthetic types, like Pluronic and poly (N-isopropyl acrylamide) and poly (phosphazene), are liquid at cool temperatures but form gels at body temperature. Though promising, they require further research. Poly(ester)-based copolymers may help overcome these issues. PEG and poly(ester)-based hydrogels are less effective for long-term therapy and unsuitable for nasal or oral delivery, despite FDA approval for implants. Challenges remain, including chemical interactions, structural compatibility, burst release with charged proteins, and effectiveness in injectable systems for protein and peptide delivery.[13] Enzymatic stimuli-responsive systems often use harmful catalysts and cross-linkers that can damage sensitive proteins, cells, or drugs. Challenges also include uneven encapsulation, low loading efficiency, and premature drug release.[110]

9.2 Challenges in Injectable Formulation

Injectable hydrogels (IHs) raise concerns that require further research. Crosslinking must protect sensitive molecules like proteins, peptides, and DNA while supporting cell viability. Understanding interactions with cells and tissues helps prevent cytotoxicity and inflammation. Key factors like structure definition, reproducibility, degradation time, release kinetics, gelation, injection viscosity, and post-gelation strength must be carefully considered.[111]. IHs should be designed with application-specific features, ensuring biocompatibility and chemical-physical crosslinking tailored to specific diseases or medical conditions.[112]

9.3 Loading and Release of Therapeutic Agents

Injectable hydrogels (IHs) can carry and release treatments like proteins, small drug molecules, or even living cells, depending on their size, interaction, and compatibility with the gel. Microparticle depot systems, such as lidocaine-based hydrogels, are already used in clinics, though lidocaine tends to release quickly. Other hydrogels, like those with hyaluronic acid, are approved for facial treatments. To better control drug release—especially for wounds—more drugs need to be tested in hydrogel formulations.[113] To slow down drug release and extend its effect, hydrogel mesh size can be reduced using physical or chemical crosslinking, or by increasing the drug's affinity to the gel.[114]

9.4 Hydrogel Bioactivity

For tissue regeneration, hydrogels need to be able to absorb, adapt, and gradually break down. Bioactive materials like gelatin, fibrin, or hyaluronic acid help cells or growth factors stick and work effectively like in clinical trials for kidney and heart repair. Non-adhesive polymers, such as PEG or polyacrylamide, often need to be modified with sticky molecules to support cell growth. However, some hydrogels, like TraceIT®, degrade too quickly. So, longer-lasting hydrogels that break down over weeks or months are better suited for healing.[115]

9.5 Technological Challenges

Clinical translation of hydrogel delivery faces major challenges, including chemistry, GMP compliance, practical use, and regulatory clarity. Development costs are estimated between USD 50 million and 800 million.

9.6 Scale-Up Strategies and GMP Processes

cGMP standards are essential for scaling up biomaterial-based hydrogels, as most are developed at small pilot scales during preclinical phases. Large-scale production must address issues like consistency, safety, and

reproducibility. Additionally, the highwater content of hydrogels complicates synthesis, storage, sterilization, and overall process optimization.

9.7 Regulatory Approvals

Regulatory approval and USFDA clearance for injectable hydrogels is a lengthy process, complicated by their diverse structures, crosslinking methods, and biomaterials.[113]

10. Conclusion

Hydrogels have emerged as versatile biomaterials with broad applications in drug delivery and regenerative medicine due to their biocompatibility, tunable physicochemical properties, and responsiveness to environmental stimuli. This review highlights their critical roles across diverse biomedical platforms, including drug carriers, wound dressings, tissue scaffolds, and biosensors. Despite their promising therapeutic utility, several challenges persist—such as premature drug release, limited stability in physiological conditions, and scalability issues—which hinder their full-scale clinical adoption. Addressing these limitations through innovative crosslinking strategies, stimuli-responsiveness enhancement, and bioactive material integration is essential. Furthermore, rigorous investigations into regulatory pathways, biocompatibility, and long-term efficacy are crucial for the successful translation of hydrogel-based technologies from bench to bedside. With continued advancements in polymer chemistry and biomedical engineering, hydrogels hold immense promise for the future of precision medicine and next-generation therapeutics.

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