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REVIEW ARTICLE

Hydrogel Based Drug Delivery System: A Novel Approach

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ABSTRACT
Hydrogels, composed of three-dimensional hydrophilic polymer networks, have emerged as highly versatile materials in biomedical applications due to their excellent water absorption capacity and tunable physicochemical properties. This review explores recent advancements in hydrogel development, highlighting their synthesis, characterization, and expanding roles in biomedical science. We detail the utilization of both synthetic (e.g., pHEMA, PEG, PVA) and natural polymers (e.g., collagen, chitosan, alginate), emphasizing their biocompatibility, cell viability, and structural diversity. Innovative cross-linking methods—ranging from physical interactions like hydrogen bonding and ionic contacts to chemical strategies such as enzymatic reactions and free-radical polymerization—are critically assessed for their roles in enhancing mechanical stability and functional performance. Key synthesis techniques, including bulk, solution, and suspension polymerization, are discussed alongside emerging eco-friendly methods. Application-wise, hydrogels are now used across a wide spectrum—from site-specific drug delivery and gene therapy to tissue engineering and wound healing. Furthermore, the review outlines essential evaluation criteria for hydrogel performance, including pH, rheology, spreadability, drug content, ex vivo skin permeation, and long-term stability. By integrating recent findings and technological improvements, this study offers a comprehensive overview of current trends and future directions in hydrogel research, supporting their optimization for clinical translation and next-generation therapeutic applications.
***Keywords**: Hydrogel, Polymers networks, Drug content, Drug delivery*

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INTRODUCTION

To meet specific requirements under various situations, hydrogels a class of water-swollen three-dimensional (3D) polymer networks—have customizable physicochemical properties. They have been widely used in the biomedical industry as a sort of promising material for anything from tissue regeneration and disease treatments to physiological and pathological mechanism investigations. [1–5] In general, the concentration and composition of the materials, the density and cross-linking techniques, and the construction techniques dictate the characteristics of hydrogel scaffolds as they are formed. Hydrogels based on collagen, gelatin, and polyethylene glycol (PEG) often have varied compositions that correlate to fibrous, microporous, and nanoporous architectures, respectively.[6] It is noteworthy that physical or chemical crosslinking techniques can also change the mechanical characteristics of hydrogels. For example, physical crosslinking, which is characterized by hydrogen bonds, hydrophobic interactions, polymerization entanglement, π–π stacking, etc., typically has low mechanical strength, whereas covalent Enzyme-induced cross-linking, free radical polymerization, and other forms of cross-linking will result in good mechanical characteristics. [7-9]

Numerous physiological processes (such as cell spreading, proliferation, migration, stemness, differentiation, etc.) and pathological processes (such as cell apoptosis, fibrosis, immunological rejection, etc.) are significantly impacted by the complex and dynamic interaction between cells and hydrogel. A thorough and in-depth understanding of the interaction between cells and hydrogels, particularly at the molecular level, is crucial in this regard as it aids in the future clinical translation of hydrogels and guides their logical design. When cells are exposed to an external hydrogel matrix, they often react to the hydrogels' static physicochemical cues (such as stiffness, pore size, viscoelasticity, microarchitecture,

degradability, and chemical surface, among others) and then convert them into biochemical signals to adjust their biology and homeostasis. [10-13]

Since hydrogels have different physicochemical, biological, and structural properties, they are now being investigated and utilized in a variety of biomedical applications. Among the most well-known sectors is cosmetic medicine, where a variety of commercial hydrogel solutions, including hyaluronic acid-based hydrogel, have been utilized as fillers.[14] Regarding clinical application, the Food and Drug Administration (FDA) has approved numerous facial corrective and cosmetic hydrogel-based products.[15,16] Hydrogel-based therapy has also been shown to be beneficial in a number of clinical trials, including those for advanced heart failure, type 2 diabetes, chronic renal disease, oral-maxillary and orthopedic trauma procedures, knee osteoarthritis, spinal fusion, and the spine.[17] Nevertheless, a number of problems and obstacles still need to be resolved for more comprehensive and effective biomedical applications, and further thought is required for clinical translation.

In this study, we collectively outlined and examined the most recent developments in hydrogel production for biomedical applications, as well as their relationships to biological reactions and associated signaling cascades.

The biomedical discipline has seen exponential growth in recent years in a number of areas, including tissue engineering (TE), medication delivery, and controlled wound healing. For instance, a major problem nowadays is the demand for and supply of organs and tissues for transplantation or tissue regeneration [18]. For the creation of these biomaterials, TE is a multidisciplinary discipline that blends engineering and biological science methodologies and principles. These biomaterials are good biological substitutes that can preserve, repair, or enhance the function of target tissues [19]. Thus, TE depends on the creation of scaffolds, which are extremely porous three-dimensional structures that, by offering the ideal conditions for cell growth &differentiation, might hasten the regeneration of injured tissues and organs. [20,21] These scaffolds need to be safe for the body's tissues and organs and biocompatible. They are typically packed with cells, growth factors, and medications because they can work in concert to greatly increase the rates of cell retention in the surrounding tissue. They also act as carriers for these substances. Furthermore, after scaffolds are implanted, they must satisfy the mechanical needs of the treated area [22-24].

In particular, the extracellular matrix (ECM) has long been a focus of scaffold fabrication research because of its great biodegradability and biological compatibility. An assortment of proteins, polysaccharides, and glycosaminoglycans make up the majority of the extracellular matrix. During the regeneration process, this complex combination regulates the surrounding cells' performance and provides them with sufficient biochemical and mechanical support [25,26].

Thus, this review's goal was to provide an overview of the most popular materials and synthesis techniques for hydrogel production, as well as various strengthening strategies like compositional changes, various cross-linking methods, and hybridisation, in order to update and summaries current trends in applications and advancements in hydrogel science.

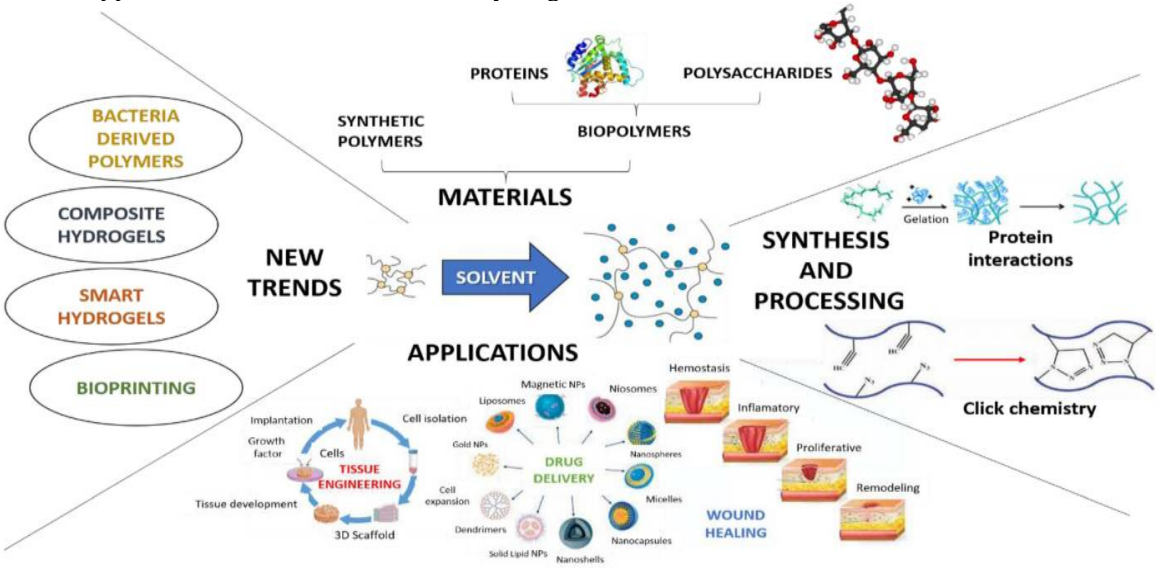

Figure 1. An overview of current and emerging developments in hydrogel research in the biomedical domain.[25]

POLYMERS USED IN PREPARATION OF HYDROGEL

The best materials for making hydrogels are hydrophilic polymers, both natural and manufactured, as was previously indicated. These polymers are distinguished by the presence of polar functional groups, such as carboxyl, hydroxyl, and amino groups, which cause them to swell (via absorption of water) or become soluble in water [27,28]. Table 1 lists the most widely used materials for hydrogel design and manufacture along with details on their cell viability and experimental status (to assess the biocompatibility of the systems based on these polymers).

Table 1. Types of polymers used in hydrogel

Type of polymer	Main polymer	Experimental stage	Cell viability %	References
Synthetic Polymer	pHEMA	*In Vitro* (Human), *In vivo*(mice & porcine)	>80	27
	PVA	*In vivo*(mice) Ex vivo(porcine)	>88	27
	PEG	*In vivo*(mice) Ex vivo(porcine)	>80	27
Natural Polymer	Collagen (COL)	In vitro(human) In vivo(mice) Ex vivo(human)	>80	27
	Elastin (EL)	In vivo(mice) Ex vivo(human)	>80	27
	Chitosan (CTS)	In vivo(mice) Ex vivo(human)	>80	27

Synthetic Polymer

Good controllability and superior mechanical capabilities are two of the most intriguing qualities of synthetic materials for hydrogel applications in biomedicine. But the primary difficulty with synthetic materials is that they don't have antibacterial activity and can't efficiently and rapidly stimulate the growth of new tissues after being implanted [29]. The most popular synthetic polymers will be discussed in this article, along with their benefits, issues, and solutions. Unfortunately, there is little commercial use for single pHEMA-based hydrogels, so many studies have been done to alter the structure of pHEMA in order to improve its properties. For instance, β-cyclodextrin-hyaluronan (β-CDcrHA) has been used to decrease tear protein absorption in a contact lens [129], and cross-linking agents like ethylene glycol Di methacrylate (EGDMA) [30] and tetra (ethylene glycol) diacrylate (TEGDA) [31,32] have been used to improve the mechanical properties of pHEMA.

PVA, or poly-vinyl alcohol. PVA is yet another intriguing option for creating TE hydrogels. This well-known hydrophilic polymer exhibits remarkable biocompatibility [33]. Moreover, PVA-based hydrogels are extensively employed in ophthalmologic and wound healing systems. [34] Furthermore, in vivo experiments using SD rats yielded encouraging outcomes, suggesting that this PEG-based hydrogel is a great option for biomedical uses [35]. This biomaterial was actually employed for ophthalmic purposes by Zhang et al. (2022), who tested it ex vivo using cadaveric pig eyes and in vitro using corneal epithelial cells. The results showed potential candidates with exceptional wound healing qualities following eye procedures.

Natural Polymer

Animals and plants are typically the source of biopolymers [36,37]. The production of tissues and the provision of molecules like signals for the human endocrine system are just two of the many roles these polymers play in the body [38]. Natural sources are therefore a great option for hydrogel production because of their well-known biological characteristics, even though these materials are frequently constrained by their difficult synthesis and processing, as well as their poor mechanical and stability qualities, which continue to be the most difficult aspects of these materials. Polypeptides and polysaccharides (PSAs) and nucleic acids, which comprise DNA and RNA, are the most common forms of biopolymers [39]. Due to its intriguing biodegradability and biocompatibility, bacteria-derived polymers are also increasingly being employed to compete with traditional polymeric materials in biomedical applications.

Protein-Based hydrogel

Hydrogels made from pure proteins have the advantages of being highly biocompatible, easy to synthesize, and able to achieve comparatively homogenous network architectures [40]. The difficulty of protein extraction and the high expense of these procedures are two drawbacks, nevertheless, that need to be considered [41,42]. Several obstacles still need to be addressed for these hydrogels to have

beneficial biological outcomes, including comprehending the structure and how it may alter during hydrogel manufacturing or after being inserted into the body.

The protein collagen (COL). In vertebrate species, COL makes about 30% of the protein [43]. The triple-helix shape of this most prevalent protein in the extracellular matrix gives it exceptional tensile strength [44]. Different COL kinds exist, including types I, II, III, IV, and V, according on how they act in the body. [45]

This has led to the description of some of the most well-known protein materials, such as COL, GEL, and elastin. In comparison to cross-linked COL-based hydrogels and GEL, which is the partially denatured structure of COL that increases the random coil content and Favors the structure for gelation, it can be concluded that COL is the most limited protein for hydrogel fabrication due to its poor physicomechanical features and strong influence from gelation conditions.

Polysaccharide-Based (PSA) Hydrogel

Glycosidic bonds covalently bind the several unique monosaccharide units that comprise PSAs [46]. As structural components and energy sources, PSAs are crucial to the growth of many plants, microbes, and animals. Glycans are also essential for adhesion and other cellular contacts, differentiation, and signaling, among other cell functions[47,48]. Polysaccharide-based hydrogels still face a number of obstacles, such as shifting hydrogel synthesis towards more environmentally friendly techniques that use less harmful solvents and low energy use. CTS (chitosan). CTS is produced by partially deacetylating chitin, one of the most prevalent naturally occurring amino polysaccharides in the world, using a vigorous, high-temperature alkali treatment [49]. Acid hyaluronic (HA). This biopolymer's flexibility, biodegradability, bioactivity, biocompatibility, non-thrombogenicity, and non-immunogenicity have earned it a stellar reputation in the biomedical sector.

Alginate (ALG). A polysaccharide derived from brown algae serves as the basis for this widely utilized biopolymer [50]. Alginate is a widely accessible and plentiful biopolymer with a number of intriguing properties, including excellent water retention, outstanding porosity, amazing biocompatibility, and changeable viscosity, all of which make it a material that is especially well-suited for biomedical applications [51]

SYNTHESIS OF HYDROGELS

A solid nanostructured network is created by hydrolyzing and condensing the selected precursors, which is the typical synthesis method for a hydrogel [52]. Therefore, the majority of research on the synthesis of hydrogel focusses on physical and chemical cross-linking techniques (Figure 3). The current challenges in synthesis procedures are focused on obtaining structures with a higher cross-linking density for particular applications like hard-tissue engineering [53] or limbal stem cells [54], as well as the use of green alternative procedures, solvents, and cross-linking agents to evaluate effective hydrogel synthesis without compromising biological properties like cytotoxicity and biocompatibility [55].

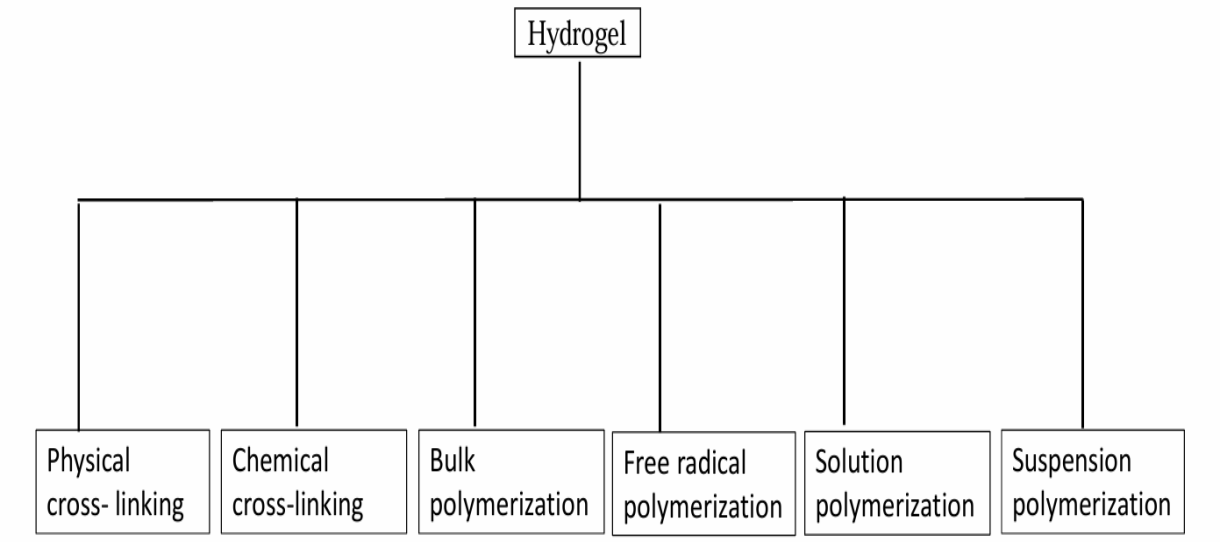

Figure 2. Schematic overview of the different physical and chemical cross-linking methods of synthesis of hydrogels.

Physical Cross-Linked Hydrogels

When a liquid phase changes into a gel due to an environmental change (such as a change in pH, temperature, mixing two components, or ionic concentration), physical hydrogels are produced. The lack of cross-linking agents in the synthesis is what primarily interests them. Figure 3 schematically illustrates how physically cross-linked networks are formed, identifying the interaction that makes up the structures specified for each of the four cross-link types that produce physical hydrogels, as shown in Figure 2 [56]. hydrogen bonding. The foundation of this cross-linking technique is the creation of hydrogen bonds between the polymeric chains, which results in a nanostructured network [57]. However, Jing et al. . (2022) shown that the gel's pH has a significant impact on this type of relationship. During their examination, they found chitosan and alginate that respond to pH.

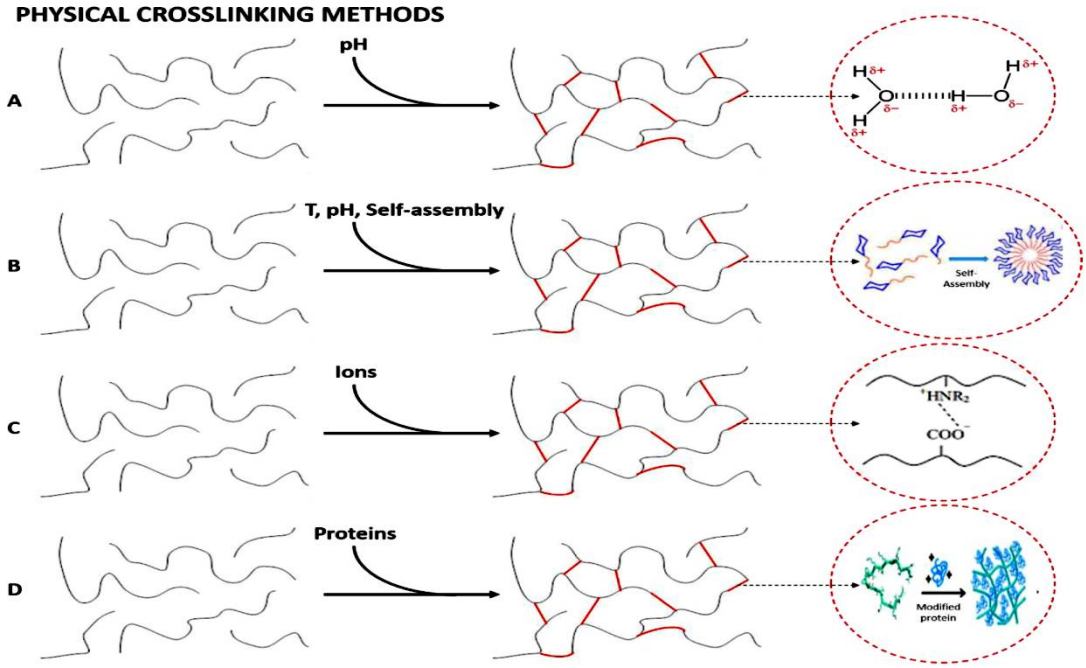

Figure 3. The following procedures are used to produce physically cross-linked hydrogels in (A) hydrogen bonding; (B) amphiphilic grafts and block polymers; (C) ionic contacts; and (D) protein interactions.[57]

Chemical Cross-linked Hydrogels

The techniques listed below can be used to create covalent connections during the irreversible process of chemical cross-linking [58]. Because of its strong mechanical resistance following cross-linking, this particular form of hydrogel is particularly interesting. Figure 4 illustrates the precise interactions and prerequisites for the production of the cross-linked structures. There are basically five ways to promote chemical cross-linking for these hydrogels (Figure 2). Enzyme-mediated processes. Enzymes must be utilised as reactants in enzymatic cross-linking to lower the possible toxicity of the chemical reagents that are typically used.

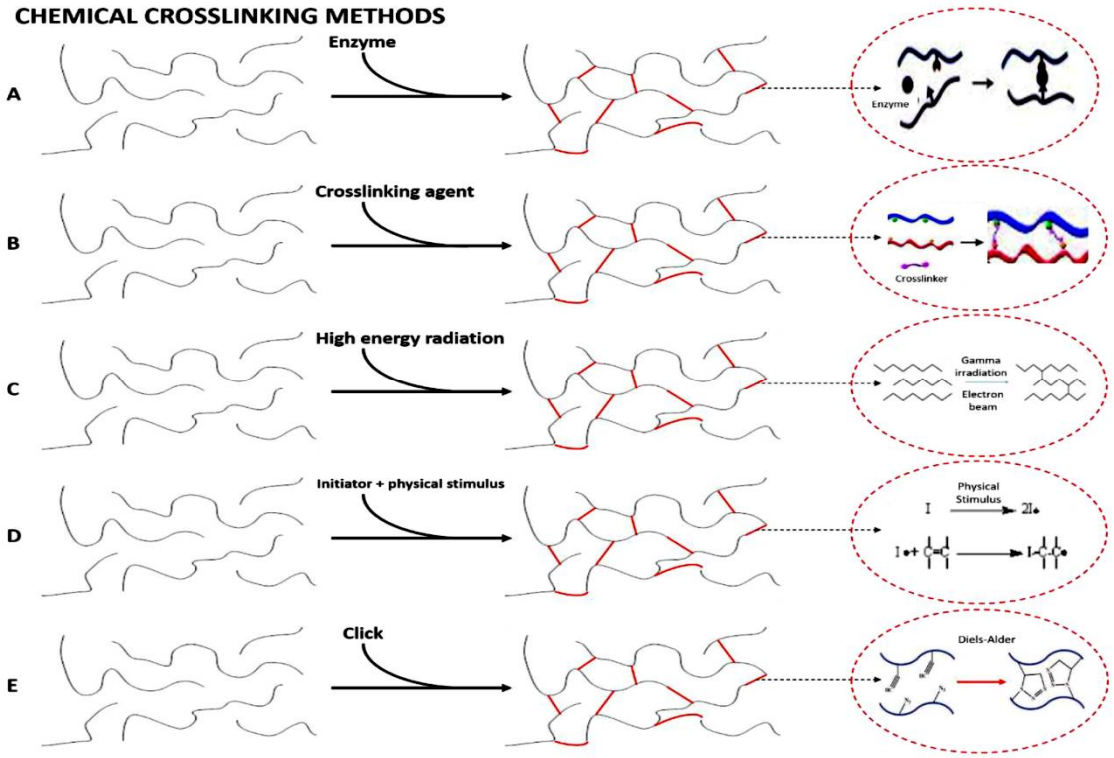

Figure 4. Forms chemically cross-linked hydrogels, (A) enzymatic processes, (B) chemical reactions aided by a cross-linking agent, (C) high-energy radiation, (D) free-radical polymerization, and (E) click reactions.[58]

Bulk polymerization

Vinyl monomers are the most common monomers used in the creation of bulk hydrogels, while other types can also be used. In most hydrogel formulations, a minor amount of cross-linking agent is included. The polymerization reaction is started by radiation, ultraviolet light, or chemical catalysts. The type of monomers and solvents being utilized determines the choice of initiator. There are numerous ways to create the polymerized hydrogel, such as rods, particles, films and membranes, and emulsions [59]

Free radical polymerization

Acrylates, vinyl lactams, and amides are the primary monomers utilized in this process to create hydrogels. These polymers are functionalized with radically different functional groups or have appropriate functional groups. groups that are polymerizable. The chemistry of common free-radical polymerizations, including the processes of propagation, chain transfer, initiation, and termination, is used in this process. A large range of heat, UV, visible, and redox initiators can be used for the radical formation in the initiation stage. The radicals react with the monomers to transform them into active forms.[60]

Solution polymerization

The multifunctional crosslinking agent is used with these ionic or neutral monomers. UV light or a redox initiator device can thermally start the polymerization process. The solvent acting as a heat sink is the main benefit of solution polymerization versus bulk polymerization. The hydrogels that are prepared are cleaned using distilled water to get rid of the extractable polymer, cross-linking agent, soluble monomers, oligomers, initiator, and other contaminants. Water, ethanol, benzyl alcohol, and water–ethanol combinations were employed as solvents. [61]

Suspension Polymerization

This technique creates spherical hydrogel microparticles that range in size from 1µm to 1mm. This technique disperses the monomer solution in a non-solvent to create a tiny droplet that is stabilized by a stabilizer. the polymerization brought on by the free radical's thermal breakdown. The produced microparticle was cleansed to eliminate any cross-linking reagent and initiator for reactive monomers.[62]

Application of hydrogel

Application	Hydrogel Type / Composition	Delivery Route	Mechanism / Key Feature
Colon-specific delivery	Dextran (cross-linked with diisocyanate or poly-HEMA), glycogen-PNIPAM, guar gum, starch	Oral	Enzyme/pH-triggered breakdown in colon by dextranase or colonic microflora [63]
GI- tract site specific	Chitosan-alginate, dextrin-poly (HEMA)	Oral	pH-sensitive swelling, enzyme response.
Modified dosage (insulin)	Poly(methacrylamide-co-itaconic acid-co-NVP)	Oral	pH-responsive mesh shielding insulin [64]
Rectal delivery	Ascorbylpalmitate, methylcellulose/polyacrylate blends	Rectal enema	Temperature-sensitive gelation; bioadhesive; enzyme-triggered release in inflamed tissue
Protein delivery	Chitosan/PAA; cyclodextrin-chitosan; DNA hydrogel	Oral, Injection	Swelling, thermo- or pH-responsive, barrier & controlled release
Transdermal & wound healing	Gelatin/PVA, alginate, peptide hydrogels	Topical / Wound dressing	Swelling, thermo- or pH-responsive, barrier & controlled release
Subcutaneous delivery	PEG-DPCA, biodegradable polysaccharide implants	Injection / Implant	Biodegradable matrix; sustained release; avoids surgery
Cosmetic implants	Hydroxyl propyl cellulose gel with silicone shell	Implant	Biocompatible, polysaccharide-based filler
Gene (nucleic acid) delivery	Modified polysaccharide / DNA hydrogels	Injection	Responsivedegradation; encapsulation of DNA/RNA
Wound/cartilage repair	Gelatine, PVA, collagen-like peptide hydrogels	Topical / Implant	ECM-mimicking scaffold; tissue regeneration support
Topical drug delivery	Hydrogels loaded with desonide or corticosteroids	Topical cream/hydrogel	Hydrated matrix improves adherence and release [65-66]

Evaluation of hydrogel

pH determination

For pH measurement, 5 g of each sample was put in a beaker, and dissolver 100 ml of solvent the surface of pH was measured using a digital pH meter. Three parallel measurements were performed at room temperature. [67]

Spreadability test

One ml of the produced hydrogel was injected onto the glass plate using a sterile syringe. A calibrated plate was placed over the formulation, and weights ranging in mass from 20 to 50 to 200 to 300 to 400 to 500 to 600 g were placed on its surface. Twenty seconds after the subsequent weight was placed, the gels' radii were measured. The acquired data made it possible to compute the area occupied by the created hydrogels using the formula:

$$P=\pi r2$$

where P is the hydrogel's surface area occupied (m2) and r is its radius (cm).

Three separate tests of the new hydrogel's spreadability were conducted at room temperature. [68]

Rheology measurement

The rheological parameters of the prepared hydrogel formulations were assayed using Brookfield viscometers are rotational viscometers that operates various speeds (RPMs) and with different spindle types. Rheology measurements of hydrogel formulations were carried out in six repetitions at 25 ± 0.5 °C. [68]

Determination of drug content

After dissolving the prepared gel in 100 ml of solvent, it was agitated for two hours. The goal of this action is to guarantee the best possible medication solubility while mechanically shaking. After the solution was purified, it was examined using a UV spectrophotometer. [69-70]

Ex- vivo skin permeation experiment

Vertical diffusion Franz cells with an effective permeation diameter of 0.636 cm were used in skin penetration tests utilizing a Franz Cell diffusion equipment. Samples of pork skin were acquired from a

nearby slaughterhouse. The skin was cleared of subcutaneous hair and fat. Skin pieces measuring 1.1 cm by 1.1 cm were placed in diffusion cells at 37.0 ± 0.2 °C after being cleaned with a 0.9% NaCl solution until an absorbance of A < 0.02 was achieved. A 0.2g hydrogel sample was then applied to the donor compartment's skin, facing the stratum corneum. As an acceptor fluid, a 40:60 v/v mixture of 96% v/v ethanol and PBS was utilized in a 5 mL volume [71]. Acceptor solution in a volume of 2 mL was drawn through the Franz diffusion cell's sampling port at predefined intervals (after 1, 2, 4, 8, 12, and 24 hours), and the same volume of new acceptor solution was supplied. A UV spectrophotometer was used to measure the samples' absorbance at a specified wavelength. Every formulation underwent six tests. Remaining hydrogels were removed from the skin, cleaned several times with 3 mL PBS, and then wiped four times with ethanol-soaked paper and filter paper to measure the amount of API still present in the skin. To remove the API residue, the skin was cleaned, sliced into small pieces, filled with 5 mL of ethanol, and shaken on the Compact Shaker for 4 hours. In the same manner as treated skin, an untreated skin blank was created. The validity of such a washing technique was validated in control studies conducted earlier, when the skin was extracted with ethanol and the q hydrogel formulations were removed immediately after application. [72]

Stability Test

For 28 days, the formulations were stored in plastic boxes between 2 and 8 degrees Celsius. Following this, the hydrogel samples were examined for formulation appearance and chemical and physical stability (color, pH, spreadability, texture, and viscosity) as well as API concentration.[73]

CONCLUSION

Hydrogel science's latest developments for biomedical applications are covered in this review article. Researchers are investigating new materials, synthesis methods, and crosslinking strategies to improve the properties of hydrogels, which has led to significant advancements in the field. Interpenetrating polymeric networks and the combination of metallic and non-metallic nanoparticles have improved the physicochemical and biological properties. Although these developments have increased the uses of hydrogel, there are still significant obstacles. More in vivo research is required to evaluate biological interactions, and environmentally friendly synthesis techniques that eschew hazardous solvents and cross-linkers to improve biocompatibility are two key issues.

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