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Review Article

# A REVIEW ON RECENT ADVANCES IN HYDROGELS AS DRUG DELIVERY SYSTEM

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**ABSTRACT**

Hydrogels are hydrophilic three-dimensional polymeric networks which has the capability to absorb water or biological fluids. These polymeric network is formulated through chemical crosslinking or physical crosslinking mechanisms. Several polymers of synthetic and natural origin can be used to form hydrogels. Mechanical properties, swelling and biological properties are about the most significant hydrogels properties that can affect their morphology and structure. Hydrogels are promising biomaterials due to their significant properties as hydrophilicity, biodegradability, biocompatibility and non-toxicity. These characteristics make hydrogels appropriate for medical and pharmaceutical application. This review discusses the types of hydrogels, their properties, mechanism of preparation and applications of hydrogels as drug delivery system.

**Keywords:** Hydrogels, Networks, Hydrophilic, Drug targeting, Drug delivery, Crosslinking


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## INTRODUCTION

Hydrogels are three-dimensional networks of polymers that have the capability of absorbing high amounts of water or any biological fluids in the body, which utilized in various biomedical applications. Hydrogels have the ability to swell and preserve these fluids within its structure without being dissolved [1]. In general, hydrogels properties depend on their chemical composition that response to various stimuli for example, heating, light, pH, and chemicals. Moreover, due to the large amount of water that they can retain in their structure, they have a degree of flexibility that make them identical and analogue to natural tissue [2]. The absorption capacity of hydrogel rises from the hydrophilic functional groups that are linked to the main polymeric backbone. Among these hydrophilic functional groups are the hydroxyl (OH-), amine (NH2), carboxyl (COOH-) and sulfate (SO3H-) groups [3]. Hydrogel polymer hydrated to different degrees depending on the type of the aqueous surrounding fluids and polymer structure; the hydrophilic groups and the backbone. However, hydrogels display a swelling performance in the aqueous surroundings rather than being dissolved as a result of the critical crosslink's found between network chains [3]. There are two significant types of hydrogel crosslinks. The first type is the physical crosslink, such as, entanglements or crystallites and the second one is the chemical type that includes tie-points and junctions. These crosslinks within the polymer network arises from the presence of Vander Waals interactions, hydrogen bonds, covalent bonds or physical entanglements [4]. The first appearance of hydrogel was in 1960 when Wichterle and Lim suggested the usage of poly (2-hydroxyethyl methacrylate) hydrophilic networks in contact lenses. Subsequently, hydrogels use has spread to several pharmaceutical and biomedical applications [5]. A number of terms have been used for hydrogels, for instance intelligent gels and smart gels. Hydrogels take these terms because they can behave in intelligent and smart way in observing the predominant stimuli and responding to it by forming changes in their physical or chemical properties, causing the release of the drug entrapped inside it in a controlled mode [6].

In contrast to other artificial biomaterial technologies, hydrogels are closely similar to the biological tissues in their physical properties due to their somewhat high content of water and elastic consistency. Actually, Hydrogels are polymers which can preserve water many times their individual weight. They are carboxylic acids polymers. In water the acid groups ionize, so a several negative charge appears along the surface of the polymer. And this affects the hydrogel in two ways. First, the polymer is enforced to enlarge due to the repulsion forces of the negative charges. Second, the negative charges attracted the polar molecules of water, so the viscosity of the formed mixture will increase because the polymer chains now use more space and resist the solvent molecules flow around them. An equilibrium between the polymer and the water around it in now formed, but the distortion of this equilibrium can be happened in a different of ways. Increasing the ionic concentration of the solution by for example, the addition of salt, the ions of positive charge attached to the negative charged sites on the polymer surface, so charges neutralizing effectively occurs. As a result, the polymer collapse on itself again. As well, adding an alkali material eradicates the acid ions and causes the equilibrium position to move to the right; addition of acid has an opposite effect. There are numerous hydrogels that can expand or contract by varying the pH values, ionic concentrations and temperatures [7].

Furthermore, Hydrogels can be formed from natural polymers as chitosan, hyaluronic acid, cellulose, sodium alginate, albumin, dextran and gelatin. These hydrogels are biodegradable, biocompatible and support the activities of the cells. Through the past two decades, synthetic hydrogels replaced the natural hydrogels. Because synthetic hydrogels have long life stability, high water absorption capability, and strong gel texture. In addition to that synthetic hydrogels have well-defined structure which could be adjusted to enhance their properties and function [8]. Synthetic hydrogel polymers include polyvinyl pyrrolidone, polyurethane, polyvinyl alcohol, polyacrylate, poly hydroxyethyl methaacrylate, polyethylene glycol, polymidine and derivatives [9].

Recently, as a result of hydrogel properties as water absorption, biocompatibility, soft structure, low adsorption of protein because of low surface tension and similarity to biological structure, researchers have paid more attention for using hydrogels in various medical applications including release of therapeutic agents (drugs, proteins orgenes), contact lenses, tissue engineering and wound coverings.

Various available methods for *in vivo* administration of drugs using hydrogel which are based on the pathological condition and localization, such as topical subcutaneous, oral, orthotopic, intraperitoneal, rectal and ocular [10].

For this review paper, the key phrases employed in the literature search were 'Hydrogels', 'Hydrophilic polymers', 'Hydrophobic polymers', 'Crosslinking', 'Hydrogels preparation', 'Hydrogels properties and characteristics' and 'Drug targeting using hydrogels', using 'Pubmed', 'Google search engine', 'Cross references', 'Science direct', 'Scopus' and 'Google Scholar'. Since 1998 and by initial peer-review of the obtained articles some of them which contained the specified keywords have been involved in this review article.

The primary objective of this review article is to discuss one of the main subjects of biomaterials research, which is hydrogels. This article will focus in hydrogels definition, properties, methods of preparation and their application in drug delivery and various medical fields.

**Types of hydrogels**

**Based on the mechanism of cross-linking**

Hydrogels can be categorized into two groups based on the nature of cross-linking reaction. The first type is the permanent hydrogel as it formed from covalent bonds among its polymeric chains. The second type formed as a result of physical interactions among the polymeric chains of the hydrogel, these interaction includes ionic interaction, molecular entanglement and hydrogen bonding. This type called physical hydrogels. However, this type of crosslinking may not be permeant junction, its only sufficient to preserve the hydrogel from being dissolved in an aqueous media [10].

**Based on polymer type**

Furthermore, based on polymer type, hydrogels are distributed into two categories: synthetic and natural hydrogels. Hydrogels formulated using natural or synthetic polymers. Natural polymers like chitosan, proteins as gelatin, lysozyme, collagen, fibrin and fibrin, or polysaccharides as alginate and hyaluronic acid. However synthetic hydrogels are formulated through polymerization of monomers chemically. They have a wide-ranging of chemical and mechanical properties. Synthetic polymers include poly vinyl alcohol, poly acrylamide, poly ethylene glycol and poly N-isopropyl acrylamide. These polymers should be biodegradable and biocompatible [11].

**Based on stimuli-response method**

Moreover, Hydrogels may be classified into conventional or stimuli-responsive hydrogels. Conventional hydrogels may not be affected by any change in the temperature, pH or electric field of the environment surrounding them because they are chains of cross-linked polymer which absorb water and swollen and reversibly release water solutions when placed in an aqueous media [12].

On the other hand, the stimuli responsive hydrogels also called smart hydrogels are sensitive to various stimuli as physical, chemical or biological and have the advantage of controlling drug release from hydrogel system in response to external or internal selected triggers [13].

These hydrogels undergo notable alterations in their permeability, network structure and swelling behavior. Any external stimuli as electric field and light have been applied using stimuli producing devices, whereas internal stimuli arise from the intrinsic body environment. Features such as hydrophobic and hydrophilic balance, monomers type, confirmation of chemical groups, cross-link density or osmotic pressure, also affect the way gels response to the stimuli [14].

Numerous chemical, physical and biological stimuli have been used to prompt several responses to the hydrogel delivery systems as shown in fig. 1.

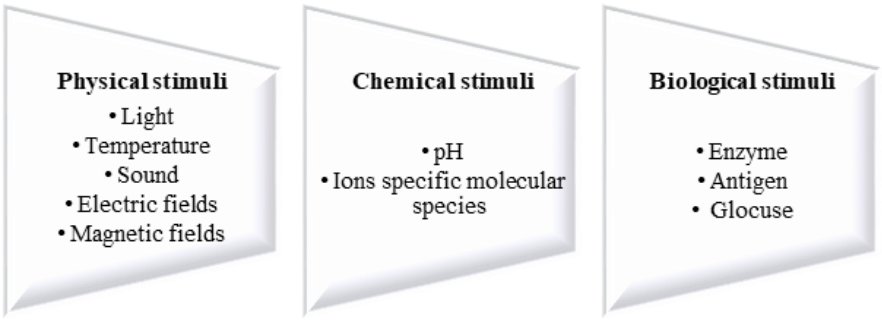


**Fig. 1: Different factors that can stimulate and affect hydrogels**

**Hydrogel properties**

**Porosity**

Hydrogels pore size and extent control drug loading and release through diffusion-controlled mechanism [15] which obeys the first law of Fickian diffusion [16, 17]. Hydrogel porosity also affects the tissue engineering process and is related inversely to the stiffness of the scaffold decreasing [18].

According to pore size, hydrogels are classified into four different classes; nano-porous, micro-porous, macro-porous and super-porous hydrogels [19]. Nano-porous hydrogels have small-sized pores between 1 to 10 nm. This tiny pore size is due to the dense polymer chains of these hydrogels and leads low loading and diffusion capacities, which restrict their use in effective drug delivery [19, 20]. In contrast, The pore size of micro, macro, and super porous hydrogels allows solute diffusion and water convection in the pores to diverse extents [19, 21, 22].

Porosity can be measured by different techniques some of them are traditional as unit cube analysis, Archimedes method, mass technique, liquid displacement method, and other modern and more accurate technique such as: using electronic microscopy, micro-CT, also it is called X-ray micro-tomography [23].

Many studies (table 1) tend to increase pore size for different purposes, it was reported that gas foaming, freeze drying, solvent casting, and phase separation can be used to made controlled macroporous hydrogels [24–27].

Although increasing hydrogel pore size leads usually to increase the extent and rate of drug loading and release, it decreases the mechanical strength of hydrogels which is a serious challenge especially for super-porous hydrogels [22, 28]. Researchers (table 1) reported that this problem can be solved by controlling many factors especially the amount and type of crosslinking agent as increasing the crosslinking agent amount enhances the mechanical strength of hydrogels and super-porous hydrogels [20, 28].

**Hydrogel swelling capacity**

Hydrogels have an amazing ability for swelling. In water, hydrogels are able to absorb from 10-20% up to thousands of times of their dry weight [23]. when hydrogels contact with a thermodynamically compatible solvent (water and water-soluble materials)the solvent penetrates into the polymeric network through the pores by the capillary and convection force and lead to hydrogel swelling [19, 22, 29]. Particularly, this swelling is responsible for the rubbery and soft properties of hydrogel which is similar to the soft tissue and also have a role in dug loading and release [30].

Drug loading volume can be enhanced by increasing swelling ability of hydrogels. Though, it is unfavorable in many circumstances,

mainly in biomedical applications as soft actuating, internal wound closure, tissue engineering, bioelectronics, and others. This is because of hydrogel swelling frequently leads to a volume expansion, which resulted in deteriorate of the mechanical characteristics of the hydrogel and when applied *in vivo* it will resulted in undesirable oppression on the adjacent tissues. In contrast, hydrogels with anti-swelling property are almost not adjust their volume when subjected to an aqueous environment, consequently preserving its original mechanical performance, size-stability and facilitating their potential application [31].

However, physical and chemical crosslinks restricted the control on hydrogels swelling [32].

Swelling is controlled mainly with two forces: osmotic force and elasticity force, when a balance between these two forces is achieved, the equilibrium is reached and no additional swelling occur and the network structure is maintained against any deformities [19]. The understanding of hydrogel swelling behavior is important especially for controlling drug loading and release. Swelling-controlled drug release occur when the rate of drug diffusion is faster than the rate of hydrogel swelling [33, 34], in such model of release the higher the rate of hydrogel swelling leads higher rate of drug release [17].

The swelling rate and nature are affected by internal and external factors.

The internal factors include:

- The pores number and size [19, 23], super porous hydrogels are capable of rapid swelling and shrinking [29, 35].
- The crosslinking extent [23, 32, 36], increasing crosslinks increases the hydrogel stiffness and rigidity and restrict the movement of polymer chain leading to a limit swelling and shrinking ability [32].
- Polymer content and type [36], swelling can be decreased by reducing the average molecular weight of the polymer segments among crosslinks [37], also increasing hydrophobic polymer limits the swelling extent [23, 32].
- The repulsive and attractive interactions which exist between the networks will highly influence hydrogel volume, intra and inter molecular-interactions as Van der Waals attractions and hydrogen bonding, as well as the hydrophobic interactions also affect the degree of swelling in the hydrogel [38].

While the external factors that affect swelling rate and extent are:

- Medium pH [37, 38], pH effect is dependent on hydrogel composition, for example, in a study on natural polymers hydrogels, the swelling and release were higher in acidic medium (pH 3.9) compared to that once in (pH 7.1) [39], while other study reported that The water uptake increased with increasing pH in their designed hydrogel [40].
- Medium temperature [32], swelling weight and volume may decreased by decreasing the medium temperature of temperature-sensitive hydrogels [36].
- Photo irradiation and pressure showed marked ability to affect hydrogel swelling [36].

**Flexibility, stretching and mechanical strength**

Swelling of hydrogels requires a degree of flexibility which is often inversely proportion to the hydrogel mechanical strength, hydrogels low mechanical strength and rupturing ability is a strong cause to limit hydrogels use, hydrogels have a few energy dissipation mechanisms to slow crack propagation and have irregularly distributed crosslinking points and polymer chains of varying lengths between those points. This uneven distribution of stress among the polymer chains makes it easy for cracks to form. Researchers (table 1) have made numerous attempts to enhance the mechanical strength of hydrogels [41]. A number of methods have been developed in order to enhance hydrogel mechanical strength and thermal stability.

Below is a summary for two promising modern methods for enhancing mechanical strength:

Double network (DN) hydrogels, DN hydrogels have been proven to exhibit remarkable mechanical strength. These gels can withstand strain of 92% and fracture compressive stress of 17.2 MPa, as well as strain of 1000-2000% and fracture tensile stress of 1-10 MPa. Additionally, they also demonstrate great mechanical toughness with tearing fracture energy of 102-103 J $m^2$ [42].

DN hydrogels have significantly enhanced mechanical properties, which are likely due to their distinctive contrasting network structure and tough network entanglement, the principles for preparing tough chemically linked DN hydrogels can be summarized as follows [42]: first, use a hard and brittle polyelectrolyte as the first network, and the second network is a soft and ductile neutral polymer. Second, ensure that the molar concentration of the second network is 20-30 times that of the first network. Finally, tightly crosslink the first network while the second network is loosely cross-linked to achieve a strong asymmetric gel structure [43–45]. With these design principles in mind, the two-step polymerization method has been shown to be feasible for producing different tough DN hydrogels [46].

Although the high mechanical strength of DN hydrogels they also can hold a high water content (~90wt%) [42], so DN hydrogels can work as a stable carriers to release and deliver therapeutic drugs or biomolecules in a precise manner [46]. These advances have also led to new designs of biocompatible DN hydrogels for tissues regeneration as cartilage [47].

Nano composite hydrogels, these systems are distinguished by their unique network structure. They can be defined as hydrated polymeric networks, covalently or physically cross-linked with one another and/or with nanoparticles [48]. nanoparticles incorporation in hydrogels structure is a hopeful alternative to overcome the weak mechanical strength of traditional hydrogels, some results displayed that the nanocomposite hydrogel strength in distilled water and 0.9 wt% NaCl solution can reach 198.85 and 204.23 mJ/g, respectively, which were 13 times larger compared with the gel strength of matrix so it can withstand deformation such as elongation and torsion, it also behave free in swelling and deswelling [49, 50]. In addition, nanocomposite hydrogels are shown to be multi-responsive with improved physical, mechanical, and biological properties that may be obtained.

These nanoparticles that can be incorporated with hydrogels include inorganic nanoparticles as clay, graphene, hydroxyapatite, and metallic nanoparticles and organic/polymeric nanoparticles, which could be used as fillers to strengthen the hydrogel matrix and bring the hydrogel new functionalities as well [51].

**Mechanism of hydrogel formation**

Hydrogels are networks of polymers having hydrophilic nature. Generally, hydrogels are formed using hydrophilic monomers. However, hydrophobic monomers are sometimes used in preparation of hydrogel. Either natural or synthetic polymers could be used in preparation of hydrogels [10]. The synthetic polymers have hydrophobic properties and chemically stronger compared to natural polymers. Because of their mechanical strength the degradation rate of synthetic polymers is slow, but this mechanical strength enhances their stability as well. A balance between these two opposed properties should be achieved to prepare an optimum hydrogel design. Moreover, Natural polymers could be used in the preparation of hydrogels provided that these polymers have appropriate functional groups [66].

Hydrogels can be formulated by choosing the monomer or polymer type and the kind of hydrogel formation techniques. Hydrogels are designed by two methods either chemical crosslinking or physical crosslinking.

**Table 1: Classification of studies that aimed to improve hydrogel properties according to the improved property and the improvement method**

| Property | First author | Property improvement method | References |
|---|---|---|---|
| Porosity | K. Kabiri | Control the addition time and sequence, and shorten the gelation time of the porosity generators (Acetone and sodium bicarbonate). | [52] |
| | Maya Ovadia | Synthesis of polys high internal phase emulsions which are extremely porous polymers and control their compositions. | [40] |
| | HV Chavda | Addition of low crosslinker concentrations led to a better porous structure. | [53] |
| | Kourosh Kabiri | Foaming conducted in the course of polymerization and dewatering of the as-synthesized gels. | [54] |
| | Nasim Annabi | Utilizing high-pressure CO2 to prepareα-elastin porous hydrogels. | [55] |
| | Manisha Pandey | Using solubilized bacterial cellulose in hydrogel synthesis. | [56] |
| | N. Vishal Gupta | Polymerization of crosslinking agent and using gas blowing method, Ac-Di-Sol as a stabilizer and bicarbonate as a foaming agent to produce the porous structure. | [57] |
| Mechanical strength | Jian Ping Gong | Synthesis of double-network gels to have both great water content and large toughness and mechanical strength. | [42] |
| | Haque Md Anamul | | [58] |
| | Xuefeng Li | | [59] |
| | Rakesh K. Mishra | Increasing the PVP content in the hydrogel membranes. | [60] |
| | Swati Sharma | Using cuminaldehyde and chitosan for gel preparation by covalent bonding between free carbonyl and amino group of cuminaldehyde and chitosan, respectively. | [61] |
| Absorption | Ali Pourjavadi | Optimizing a number of variables of the implant copolymerization (i. e. the initiator, the monomer, and the crosslinker concentration) to attain a hydrogel with improved swelling capacity. | [62] |
| | Qandeel Zahra | Adding Acrylamide-2-methyl propane sulfonic acid to enhance the swelling of hydrogels because of its polyelectrolyte nature. | [63] |
| | Maria Lazaridou | Synthesis chitosan copolymers (CS-g-SBMA) grafted with [2-(methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide in different molar ratios. | [64] |
| | Manisha Pandey | Graft polymerization of acrylamide on bacterial cellulose solubilized in an NaOH/urea solvent system and crosslinked by *N*,*N*′-methylenebisacrylamide under microwave irradiation. | [56] |
| | Swati Sharma | Using cuminaldehyde and chitosan for gel preparation by covalent bonding between free carbonyl and amino group of cuminaldehyde and chitosan, respectively. | [61] |
| Release | Baoqi Cai | Synthesis\hydrogel based on dynamic covalent bond, composed of 3-acrylamidophenyl boronic acid copolymerized with 2-lactobionamidoethyl methacrylate (p(APBA-*b*-LAMA)) by means of the association of boronic acid with diols. | [65] |

**Chemical cross-linking**

Chemical crosslinking is a method that is often employed to create hydrogels. This process entails the use of polymer chains possessing functional groups that can form covalent bonds, which are cross-linked using multifunctional molecules or ions [67]. One such example is the creation of alginate hydrogels through ionic interactions between alginate polymer chains and divalent cations [68]. This interaction helps to stabilize the hydrogel structure, preventing it from dissolving in water and physiological fluids. Compared to physical hydrogels, chemically crosslinked hydrogel networks offer greater control, as their synthesis and applications are not solely reliant on pH. Chemical crosslinking provides the ability to modify the physical characteristics of the hydrogel [69]. The cross-linking process involved the use of small cross-linker molecules, photosensitive agents, polymer-polymer conjugation or enzyme-catalyzed reactions.

Small molecule crosslinking, the easiest method for producing hydrogels using small-molecule cross-linking is to mix a polymer, a small-molecule cross-linker, and an appropriate solvent. These substances, known as cross-linkers, are made up of at least two active functional groups that facilitate the formation of bonds between polymer chains [70]. Examples of these small molecules include formaldehyde, genipin, glutaraldehyde, diethyl squarate, blocked di-isocyanates and ethylene glycol diglycidyl ether [71].

Enzymatic cross-linking, it is a gentle and practical approach for in-situ hydrogel formation as it is a cytocompatible process, because no exogenous substances are used. Most of the enzymes used in hydrogel cross-linking are like those found in our bodies that catalyze biological processes. Several enzymes have been involved in this process, including lysyl oxidase, plasma amine oxidase, Transglutaminases TG, peroxidases, tyrosinase, phosphopantetheinyl transferase, Horseradish peroxidase, Laccase and phosphatases [72]. This process can take place under minor conditions as physiological temperature, an aqueous medium and neutral pH, which are compatible with body cells. The main advantage of this method is enzyme specificity as toxicity could be avoided, and no cytotoxicity may be generated. Moreover, the on-site creation of covalently bound hydrogels without the need of cross-linker molecules is another advantage of Enzymatic-based hydrogels. However, this method is expensive and difficult to produce [73].

Photo cross-linking, formation of hydrogels through photo-crosslinking relies on the presence of photo-sensitive functional groups. These groups are attached to a polymer, allowing it to form cross-links when exposed to specific wavelengths of light as UV light. This method offers spatiotemporal control over the reaction, fast cross-linking, preservation of the shape of hydrogels and room temperature environments. However, the light intensity, duration of exposure and concentration of photo-initiator are critical parameters which can cause cell damage. UV light (290–320 nm) could be replaced by visible light such as green (505 nm) and blue (405 nm) lights, as their intensity is relatively similar to that of UV, and they do not harm the cells. Chitosan, PEG and gelatin have been extensively studied for this purpose [67]. This technique can be applied to encapsulate bioactive molecules, like growth factors, for a variety of purposes, including wound healing [74].

Polymer-Polymer cross-linking (hybrid polymer networks), this process involves the interaction between a building block of one polymer chain and a building block of a different polymer chain with distinct characteristics. Consequently, before the cross-linking process, the polymers need to be modified by incorporating specific reactive functional groups. The choice of covalent connections can be tailored to control the cross-linking speed, select the desired reactive functional groups, and determine the biodegradability of the resultant compound [75].

For more details, (table 2) summarizes the advantages and disadvantages of each of the above methods.

**Physical cross-linking**

Hydrogels can be formulated using reversible or physical cross-linked networks. Molecular entanglements, supramolecular chemistry or physicochemical interactions such as hydrophobic interactions, hydrogen bonds, charge condensation, are responsible for holding physically cross-linked hydrogels together. The interest in physical or reversible gels has grown due to their simple production process and the absence of cross-linking agents so the primary benefit of physical crosslinking methods is their biomedical safety, as they do not involve the use of chemical crosslinking agents that may be cytotoxic [70]. The choice of hydrocolloid type, concentration, and pH is vital in achieving various gel textures. Many techniques have been

documented for the synthesis of physically cross-linked hydrogel [67].

Several methods have been documented for creating physically cross-linked hydrogels (table 3) shows some of them.

**Table 2: Advantages and this advantage of chemical crosslinking method**

| Methods | Advantages | Disadvantages | References |
|---|---|---|---|
| Small molecule crosslinking | Mild conditions<br>Fast gelation<br>Good mechanical properties<br>Spontaneous reaction | The possible toxicity of unreacted residual cross-linker agents *in vivo*. | [71] |
| Enzymatic crosslinking | No exogenous reagents.<br>Specificity<br>Spontaneous reaction.<br>Fast gelation<br>Control over the reaction.<br>Mild conditions | The change of activity during stock solution storage.<br>The enzyme costs are additional costs. | [72] |
| Photo-crosslinking | Fast gelation.<br>Stabilization of weak cross-linked hydrogels<br>Room temperature conditions.<br>Spatiotemporal control of the reaction. | Light irradiation may affect cells. Needs precise regulation of photo-initiator, light intensity and duration of exposure. | [74] |
| Polymer-Polymer crosslinking | Biological inert gel<br>Rapid formation of gel.<br>Flexibility in multiple bonds types formation. | Multi-step purification and preparation | [75] |

**Table 3: Summary of physically cross linking method for hydrogel preparation**

| Method | Description | Method of hydrogel formation | Example | References |
|---|---|---|---|---|
| Crystallization | Involves creating a strong and extremely elastic hydrogel by freezing-thawing process. | The highly elastic gel is produced by subjecting the aqueous polymer solution to a repeated freeze–thaw process. | Freeze-thawing of xanthan and polyvinyl alcohol. | [70] |
| Hydrophobic interaction | Polymers undergo hydrophobic interaction must have both hydrophobic and hydrophilic domain, which is called amphiphilic. | This method involves increasing the temperature of the copolymers to the critical micelle temperature then they aggregate to form spherical micelles. These micelles composed of an outer layer of hydrated swollen hydrophilic chains with dehydrated hydrophobic blocks in the core. | Hydrogel made from polysaccharides such as dextran, chitosan and pullulan. | [76] |
| Ionic interactions | Hydrogels cross-linked using specific ions. | Cross-linking of Hydrogel is done using suitable ions under gentle conditions at physiological pH and at room temperature. | Alginate could cross-linked through calcium ions. | [69] |
| Polyelectrolyte complexes (PECs) | PECs are prepared by electrostatic interactions in an aqueous solution, between two polyelectrolytes with opposite charged. | Oppositely charged polymers will stick together forming soluble and insoluble complexes dependent on the pH and concentration of the particular solutions. | Polyatomic chitosan with polyanionic xanthan. | [76] |
| Hydrogen bonding interaction | Hydrogen bonded hydrogel of polymers carrying carboxyl groups. | Hydrogen bonded hydrogel could be obtained by dropping the pH of aqueous solution of polymers carrying carboxyl groups by dispersing the polymer into 0.1M HCl. | Hydrogen-binding of carboxy methyl cellulose polymer. | [69] |
| Stereo complexation | A synergistic interaction among polymer chains or small molecules with same chemical composition, but different stereochemistry. | Stereo complexation does not require harsh organic solvents or chemical cross-linkers. | Hydrogel prepared via crosslinking of lactic acid oligomers with opposite chirality. | [72] |

**Applications of hydrogels as a drug delivery system**

Drug delivery systems play significant role in improving drugs therapeutic efficacy by overcoming the limitations of the traditional drug preparations. Some of these limitations are poor solubility, low bioavailability and short half-life, which considerably can influence the efficacy of the drug and require a frequent dosing [77]. Conversely, controlled drug delivery systems, like polymer-based hydrogels, display a hopeful solution for these limitations by permitting continued drug release for a long time period. This sustained and controlled release property assists in the maintenance of drug concentrations in the target site within the required range as well as avoiding any unexpected decrease or increase in blood-drug concentration that can result in suboptimal treatment results. As a result of extending the duration of drug release, the drug bioavailability will be enhanced using the polymer-based hydrogel systems as well as the frequency of drug dosing will be reduced which will support patient convenience and compliance [78]. Furthermore, hydrogels drug delivery systems have the advantage of delivering the drug to the target tissues or organs. Targeting drug delivery could be achieved by incorporating directing ligands or by altering the properties of hydrogel's. This approach will minimize the drug systemic exposure and diminishes the possible side effects, as well as enhancing the therapeutic efficiency at the intended site.

Furthermore, hydrogel drug delivery systems could be designed to accommodate various active ingredients with diverse physicochemical properties. In particular, these hydrogel systems offer flexibility in drug release and loading mechanisms, which allows for the delivery of numerous drug types as peptides, proteins and nucleic acids [79].

Hydrogels have been generally used for the preparation of controlled drug delivery systems for long time period. Once the hydrogel system that bears a drug comes in contact with an aqueous medium, the water will penetrate into the hydrogel system and the drug will be dissolved. Mainly, Diffusion phenomena occurs when the drug that is dissolved diffuses to the surrounding aqueous medium and gets out of the hydrogel delivery system [80].

Particularly, all of these distinctive properties makes the polymer-based hydrogels an attractive and promising technology for drug delivery and the current research in this area is predicted to result in preparation of novel and advanced drug delivery systems.

The following are some of the hydrogels applications as drug delivery system:

**Controlled drug release**

Polymer-based hydrogels can be utilized to control and adjust the release of drugs by altering the behavior of hydrogel swelling. This can be achieved by modifying the chemical structure or by adjustment of hydrogel crosslinking density [81].

**Targeted drug delivery**

Polymer-based hydrogels could be formulated to precisely target definite cell, tissue or organ. By combining targeting moieties for instance peptides or antibodies into the hydrogel, the drug could be targeted to a precise site inside the body [82].

**Oral drug delivery**

The oral bioavailability of drugs could be improved using polymer-based hydrogels. The drug will be protected from degradation and released in a controlled manner in the gastrointestinal tract [83].

**Transdermal drug delivery**

Transdermal delivery is a painless way of administration drugs systemically by applying a drug preparation onto healthy skin [84, 85]. Polymer-based hydrogels could be also used for drug delivery trough transdermal route. The drug is incorporated inside the hydrogel matrix and the hydrogel system then applied topically to the skin. The drug release will be in an organized manner over time [85].

**Implantable drug delivery systems**

Polymer-based hydrogels can be employed as implantable drug delivery systems, in which the hydrogel is applied inside the body and the drug is released over long period of time. In particular, these systems are utilized for chronic diseases therapy or in delivering long-acting drugs [86].

**Gene delivery**

The genetic material as DNA or RNA could be delivered to the intended site using polymer-based hydrogels. The genetic material is incorporated into the hydrogel matrix. Mainly, this will protect the genetic material from degradation and enforce its delivery to the target site [87].

Hydrogels success as drug delivery systems can be judged by a number of marketed formulations (table 4).

**Table 4: Some of hydrogel-based products on the market**

| Active ingredient | Product | Hydrogel based product | Polymer system | Remarks of hydrogel based product | References |
|---|---|---|---|---|---|
| Diltiazem | Cardizem® | Diltiazem SQZ Gel™ | Chitosan and polyethylene glycol | pH-Sensitive, provides less-frequent administrations than a traditional tablet product thus enhances patient compliance as it once a-day tablet of diltiazem hydrochloride. | [88] |
| Metronidazole | MetroGel Vaginal ® | Hycore-V™ and Hycore-R™ | Not disclosed | Localized delivery of metronidazole for vaginal and rectal infections, respectively. Thus minimize its side effects. | [89] |
| Dexamethasone | Maxidex® | DEXTENZA™ | PEG | Post-operative inflammation, allergic conjunctivitis providing coverage up to 30 d of sustained steroid release. | [90] |
| Morphine sulfate | Oramorph® | Moraxen ® | PU (PEG-diol) | Improved bioavailability of morphine. | [91] |
| Dinoprostone | Dinoglandin® | Propess® | PU (PEG-diol) | Induction of labor,the vagina pessary stays for 24 h and slowly releasing the hormone. | [92] |
| Histrelin acetate | - | Supprelin® LA | 2-Hydroxyethyl/propyl methacrylate, trimethylolpropane trimethacrylate | Treatment of children with central precocious puberty, provides sustained release for 12 mo | [93] |

## CONCLUSION

Hydrogels became a core of many studies due to their flexible structure, the capacity to hold a large amount of active ingredients, and their ability to respond to different stimuli. Studies and research about hydrogels started in 1960, and many trials to include hydrogels in dosage forms have been performed. However, hydrogel use in pharmaceutical technology is limited due to many obstacles that affect its quality. Many studies have attempted to overcome different limitations and make the better hydrogel formulation, which shows that hydrogels are on their way to becoming a milestone in many dosage forms.

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Nil

## AUTHORS CONTRIBUTIONS

Dr. Aya M. Ghanem (1st author, Corresponding author): Study the concept, design of the manuscript, review of literature and paper writing. Dr. Sondos Ahmad Ashour (2nd author): Data collection, review of literature, data interpretation and paper writing. Dr. Ruaa M Hussien (3rd author): Review of literature, planning and conceptualization.

## CONFLICT OF INTERESTS

The authors declare no conflict of interest

## REFERENCES

1. Ahmed EM. Hydrogel: preparation characterization and applications: a review. J Adv Res. 2015 Mar;6(2):105-21. doi: 10.1016/j.jare.2013.07.006, PMID 25750745.
2. Chamkouri H. A review of hydrogels their properties and applications in medicine. AJBSR. 2021 Feb 3;11(6):485-93. doi: 10.34297/AJBSR.2021.11.001682.
3. Sanchez Cid P, Jimenez Rosado M, Romero A, Perez Puyana V. Novel trends in hydrogel development for biomedical applications: a review. Polymers. 2022 Jul 26;14(15):3023. doi: 10.3390/polym14153023, PMID 35893984.
4. Giordano S, Gallo E, Diaferia C, Rosa E, Carrese B, Borbone N. Multicomponent peptide based hydrogels containing chemical functional groups as innovative platforms for biotechnological applications. Gels. 2023 Nov 15;9(11):903. doi: 10.3390/gels9110903, PMID 37998993.
5. Karoyo AH, Wilson LD. A review on the design and hydration properties of natural polymer based hydrogels. Materials (Basel). 2021 Feb 26;14(5):1095. doi: 10.3390/ma14051095, PMID 33652859.
6. Cao H, Duan L, Zhang Y, Cao J, Zhang K. Current hydrogel advances in physicochemical and biological response driven biomedical application diversity. Signal Transduct Target Ther. 2021 Dec 16;6(1):426. doi: 10.1038/s41392-021-00830-x, PMID 34916490.
7. HO TC, Chang CC, Chan HP, Chung TW, Shu CW, Chuang KP. Hydrogels: properties and applications in biomedicine. Molecules. 2022 May 2;27(9):2902. doi: 10.3390/molecules27092902.
8. Cai MH, Chen XY, FU LQ, DU WL, Yang X, Mou XZ. Design and development of hybrid hydrogels for biomedical applications: recent trends in anticancer drug delivery and tissue engineering. Front Bioeng Biotechnol. 2021 Feb 17;9:630943. doi: 10.3389/fbioe.2021.630943, PMID 33681168.
9. Catoira MC, Fusaro L, DI Francesco D, Ramella M, Boccafoschi F. Overview of natural hydrogels for regenerative medicine

applications. J Mater Sci Mater Med. 2019 Oct 10;30(10):115. doi: 10.1007/s10856-019-6318-7, PMID 31599365.
10. LU L, Yuan S, Wang J, Shen Y, Deng S, Xie L. The formation mechanism of hydrogels. Curr Stem Cell Res Ther. 2018;13(7):490-6. doi: 10.2174/1574888X12666170612102706, PMID 28606044.
11. Peng W, LI D, Dai K, Wang Y, Song P, LI H. Recent progress of collagen chitosan alginate and other hydrogels in skin repair and wound dressing applications. Int J Biol Macromol. 2022 May 31;208:400-8. doi: 10.1016/j.ijbiomac.2022.03.002, PMID 35248609.
12. Chen M, Wang Y, Zhang J, Peng Y, LI S, Han D. Stimuli responsive DNA based hydrogels for biosensing applications. J Nanobiotechnology. 2022 Jan 21;20(1):40. doi: 10.1186/s12951-022-01242-x, PMID 35062945.
13. Jiang Y, Wang Y, LI Q, YU C, Chu W. Natural polymer based stimuli responsive hydrogels. Curr Med Chem. 2020;27(16):2631-57. doi: 10.2174/0929867326666191122144916, PMID 31755377.
14. Wang C, Zhang J. Recent advances in stimuli responsive DNA based hydrogels. ACS Appl Bio Mater. 2022 May 16;5(5):1934-53. doi: 10.1021/acsabm.1c01197, PMID 35138079.
15. Das S, Kumar V, Tiwari R, Singh L, Singh S. Recent advances in hydrogels for biomedical applications. Asian J Pharm Clin Res. 2018 Nov;11(11):62-8. doi: 10.22159/ajpcr.2018.v11i11.27921.
16. Amsden B. Solute diffusion within hydrogels. Mechanisms and models. Macromolecules. 1998 Nov 1;31(23):8382-95. doi: 10.1021/ma980765f.
17. Ghasemiyeh P, Mohammadi Samani S. Hydrogels as drug delivery systems; pros and cons. Trends Pharmacol Sci. 2019 Mar 1;5(1):7-24.
18. Gerecht S, Townsend SA, Pressler H, Zhu H, Nijst CL, Bruggeman JP. A porous photocurable elastomer for cell encapsulation and culture. Biomaterials. 2007;28(32):4826-35. doi: 10.1016/j.biomaterials.2007.07.039, PMID 17692371.
19. Ganji F, Vasheghani FS, Vasheghani FE. Theoretical description of hydrogel swelling: a review. Iranian Polymer Journal. 2010;19(5):375-98.
20. Yin L, Fei L, Cui F, Tang C, Yin C. Superporous hydrogels containing poly(acrylic acid-co-acrylamide)/O-carboxymethyl chitosan interpenetrating polymer networks. Biomaterials. 2007 Feb 1;28(6):1258-66. doi: 10.1016/j.biomaterials.2006.11.008, PMID 17118443.
21. Lima CS, Balogh TS, Varca JP, Varca GH, Lugao AB, A Camacho Cruz L. An updated review of macro micro and nanostructured hydrogels for biomedical and pharmaceutical applications. Pharmaceutics. 2020 Oct;12(10):970. doi: 10.3390/pharmaceutics12100970, PMID 33076231.
22. Hafezi Moghaddam R, Dadfarnia S, Shabani AM, Moghaddam ZH, Tavakol M. Electron beam irradiation synthesis of porous and non porous pectin based hydrogels for a tetracycline drug delivery system. Mater Sci Eng C Mater Biol Appl. 2019 Sep 1;102:391-404. doi: 10.1016/j.msec.2019.04.071, PMID 31147010.
23. Garg S, Garg A. Hydrogel: classification properties preparation and technical features. Asian J Biomater Res. 2016 Sep 4;2:163-70.
24. Holback H, Yeo Y, Park K. 1-Hydrogel swelling behavior and its biomedical applications. Rimmer S, editor. Woodhead Publishing Series in Biomaterials Biomedical Hydrogels; 2011. p. 3-24.
25. Sornkamnerd S, Okajima MK, Kaneko T, Kaneko T. Tough and porous hydrogels prepared by simple lyophilization of LC gels. ACS Omega. 2017 Aug 31;2(8):5304-14. doi: 10.1021/acsomega.7b00602, PMID 31457799.
26. Luo R, WU J, Dinh ND, Chen CH. Gradient porous elastic hydrogels with shape-memory property and anisotropic responses for programmable locomotion. Adv Funct Materials. 2015;25(47):7272-9. doi: 10.1002/adfm.201503434.
27. DE France KJ, XU F, Hoare T. Structured macroporous hydrogels: progress challenges and opportunities. Adv Healthc Mater. 2018;7(1):1700927. doi: 10.1002/adhm.201700927, PMID 29195022.
28. Am R, Prabhu SS, JD JR, Sundaram SK, RM, TK V. Hydrogel formulation from calotropis gigantea plant extract against foot ulcer causing bacteria in diabetes. Asian J Pharm Clin Res. 2021 Nov 7;14(11):96-9.
29. Gemeinhart RA, Park H, Park K. Pore structure of superporous hydrogels. Polym Adv Technol. 2000;11(8-12):617-25. doi: 10.1002/1099-1581(200008/12)11:8/12<617::AID-PAT12>3.0.CO;2-L.
30. Thakur S, Thakur VK, Arotiba OA. History classification properties and application of hydrogels: an overview. In: Hydrogels recent advances. Thakur VK, Thakur MK, editors. Gels Horizons: From Science to Smart Materials: 2018. p. 29-50. doi: 10.1007/978-981-10-6077-9_2.
31. Zhan Y, FU W, Xing Y, MA X, Chen C. Advances in versatile anti-swelling polymer hydrogels. Mater Sci Eng C Mater Biol Appl. 2021 Aug 1;127:112208. doi: 10.1016/j.msec.2021.112208, PMID 34225860.
32. Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm. 2000 Jul 3;50(1):27-46. doi: 10.1016/s0939-6411(00)00090-4, PMID 10840191.
33. Lin CC, Metters AT. Hydrogels in controlled release formulations: network design and mathematical modeling. Adv Drug Deliv Rev. 2006 Nov 30;58(12-13):1379-408. doi: 10.1016/j.addr.2006.09.004, PMID 17081649.
34. Kim D, Park K. Swelling and mechanical properties of superporous hydrogels of poly (acrylamide-co-acrylic acid)/polyethylenimine interpenetrating polymer networks. Polymer. 2004 Jan 1;45(1):189-96. doi: 10.1016/j.polymer.2003.10.047.
35. Gemeinhart RA, Chen J, Park H, Park K. pH-sensitivity of fast responsive superporous hydrogels. J Biomater Sci Polym Ed. 2000 Jan 1;11(12):1371-80. doi: 10.1163/156856200744390, PMID 11261878.
36. Huglin MB, Liu Y, Velada J. Thermoreversible swelling behaviour of hydrogels based on N-isopropylacrylamide with acidic comonomers. Polymer. 1997 Nov 1;38(23):5785-91. doi: 10.1016/S0032-3861(97)00135-3.
37. Brannon Peppas L, Peppas NA. Equilibrium swelling behavior of pH-sensitive hydrogels. Chem Eng Sci. 1991 Jan 1;46(3):715-22. doi: 10.1016/0009-2509(91)80177-Z.
38. Kasai RD, Radhika D, Archana S, Shanavaz H, Koutavarapu R, Lee DY. A review on hydrogels classification and recent developments in biomedical applications. Int J Polym Mater Polym Biomater. 2023;72(13):1059-69. doi: 10.1080/00914037.2022.2075872.
39. Younis MK, Tareq AZ, Kamal IM. Optimization of swelling drug loading and release from natural polymer hydrogels. IOP Conf Ser Mater Sci Eng. 2018 Dec;454(1):012017. doi: 10.1088/1757-899X/454/1/012017.
40. Ovadia M, Silverstein MS. High porosity responsive hydrogel copolymers from emulsion templating. Polym Int. 2016;65(3):280-9. doi: 10.1002/pi.5052.
41. Huang T, XU HG, Jiao K, Zhu LP, Brown H, Wang H. A novel hydrogel with high mechanical strength: a macromolecular microsphere composite hydrogel. Adv Mater. 2007 May 15;19(12):1622-6. doi: 10.1002/adma.200602533.
42. Gong JP. Why are double network hydrogels so tough? Soft Matter. 2010 Jun 8;6(12):2583-90. doi: 10.1039/b924290b.
43. Haque MA, Kurokawa T, Kamita G, Gong JP. Lamellar bilayers as reversible sacrificial bonds to toughen hydrogel: hysteresis self-recovery fatigue resistance and crack blunting. Macromolecules. 2011 Nov 22;44(22):8916-24. doi: 10.1021/ma201653t.
44. HU J, Hiwatashi K, Kurokawa T, Liang SM, WU ZL, Gong JP. Microgel reinforced hydrogel films with high mechanical strength and their visible mesoscale fracture structure. Macromolecules. 2011 Oct 11;44(19):7775-81. doi: 10.1021/ma2016248.
45. Suekama TC, HU J, Kurokawa T, Gong JP, Gehrke SH. Double network strategy improves fracture properties of chondroitin sulfate networks. ACS Macro Lett. 2013 Feb 19;2(2):137-40. doi: 10.1021/mz3006318, PMID 35581775.
46. Chen Q, Chen H, Zhu L, Zheng J. Fundamentals of double network hydrogels. J Mater Chem B. 2015 Mar 31;3(18):3654-76. doi: 10.1039/c5tb00123d, PMID 32262840.
47. Chen Y, Dong K, Liu Z, XU F. Double network hydrogel with high mechanical strength: performance progress and future perspective. Sci China Technol Sci. 2012 Aug 1;55(8):2241-54. doi: 10.1007/s11431-012-4857-y.

48. Argenta DF, Dos Santos TC, Campos AM, Caon T. Chapter 3-hydrogel nanocomposite systems: physic chemical characterization and application for drug delivery systems. Mohapatra SS, Ranjan S, Dasgupta N, Mishra RK, Thomas S, editors. Elsevier: Nanocarriers for drug delivery; 2019. p. 81-131. doi:10.1016/B978-0-12-814033-8.00003-5.
49. Haraguchi K, Takehisa T. Nanocomposite hydrogels: a unique organic–inorganic network structure with extraordinary mechanical optical and swelling/de-swelling properties. Adv Mater. 2002 Aug 16;14(16). doi: 10.1002/1521-4095(20020816)14:16<1120::AID-ADMA1120>3.0.CO;2-9.
50. XU K, Wang J, Xiang S, Chen Q, Yue Y, SU X. Polyampholytes superabsorbent nanocomposites with excellent gel strength. Compos Sci Technol. 2007 Dec 1;67(15-16):3480-6. doi: 10.1016/j.compscitech.2007.02.009.
51. Das D, Kar T, Das PK. Gel nanocomposites: materials with promising applications. Soft Matter. 2012 Feb 2;8(8):2348-65. doi: 10.1039/C1SM06639K.
52. Kabiri K, Omidian H, Hashemi SA, Zohuriaan Mehr MJ. Synthesis of fast-swelling superabsorbent hydrogels: effect of crosslinker type and concentration on porosity and absorption rate. Eur Polym J. 2003 Jul 1;39(7):1341-8. doi: 10.1016/S0014-3057(02)00391-9.
53. Chavda H, Patel C. Effect of crosslinker concentration on characteristics of superporous hydrogel. Int J Pharm Investig. 2011;1(1):17-21. doi: 10.4103/2230-973X.76724, PMID 23071915.
54. Kabiri K, Zohuriaan Mehr MJ. Porous superabsorbent hydrogel composites: synthesis morphology and swelling rate. Macro Materials & Eng. 2004;289(7):653-61. doi: 10.1002/mame.200400010.
55. Annabi N, Mithieux SM, Boughton EA, Ruys AJ, Weiss AS, Dehghani F. Synthesis of highly porous crosslinked elastin hydrogels and their interaction with fibroblasts *in vitro*. Biomaterials. 2009 Sep 1;30(27):4550-7. doi: 10.1016/j.biomaterials.2009.05.014, PMID 19500832.
56. Pandey M, Mohd Amin MC, Ahmad N, Abeer MM. Rapid synthesis of superabsorbent smart swelling bacterial cellulose/acrylamide based hydrogels for drug delivery. Int J Polym Sci. 2013 Aug 28;2013:1-10. doi: 10.1155/2013/905471.
57. Gupta NV, Shivakumar HG. Preparation and characterization of superporous hydrogels as pH-sensitive drug delivery system for pantoprazole sodium. Curr Drug Deliv. 2009 Oct 1;6(5):505-10. doi: 10.2174/156720109789941722, PMID 19863492.
58. Haque MD A, Kurokawa T, Gong JP. Super tough double network hydrogels and their application as biomaterials. Polymer. 2012 Apr 17;53(9):1805-22. doi: 10.1016/j.polymer.2012.03.013.
59. LI X, Wang H, LI D, Long S, Zhang G, WU Z. Dual ionically cross linked double-network hydrogels with high strength toughness swelling resistance and improved 3D printing process ability. ACS Appl Mater Interfaces. 2018 Sep 19;10(37):31198-207. doi: 10.1021/acsami.8b13038, PMID 30148345.
60. Mishra RK, Datt M, Banthia AK. Synthesis and characterization of pectin/PVP hydrogel membranes for drug delivery system. AAPS Pharm Sci Tech. 2008 Jun 1;9(2):395-403. doi: 10.1208/s12249-008-9048-6, PMID 18431673.
61. Sharma S, Jain P, Tiwari S. Dynamic imine bond based chitosan smart hydrogel with magnified mechanical strength for controlled drug delivery. Int J Biol Macromol. 2020 Oct 1;160:489-95. doi: 10.1016/j.ijbiomac.2020.05.221, PMID 32479933.
62. Pourjavadi A, Kurdtabar M, Mahdavinia GR, Hosseinzadeh H. Synthesis and super swelling behavior of a novel protein based superabsorbent hydrogel. Polym Bull. 2006 Oct 1;57(6):813-24. doi: 10.1007/s00289-006-0649-5.
63. Zahra Q, Minhas MU, Khan S, WU PC, Suhail M, Iqbal R. Fabrication of polyethylene glycol hydrogels with enhanced swelling; loading capacity and release kinetics. Polym Bull. 2022 Jul 1;79(7):5389-415. doi: 10.1007/s00289-021-03740-8.
64. Lazaridou M, Nanaki S, Zamboulis A, Papoulia C, Chrissafis K, Klonos PA. Super absorbent chitosan based hydrogel sponges as carriers for caspofungin antifungal drug. Int J Pharm. 2021 Sep 5;606:120925. doi: 10.1016/j.ijpharm.2021.120925, PMID 34303816.
65. Cai B, Luo Y, Guo Q, Zhang X, WU Z. A glucose sensitive block glycopolymer hydrogel based on dynamic boronic ester bonds for insulin delivery. Carbohydr Res. 2017 Jun 5;445:32-9. doi: 10.1016/j.carres.2017.04.006, PMID 28395252.
66. Zhang J, Zhao D, LU K. Mechanisms and influencing factors of peptide hydrogel formation and biomedicine applications of hydrogels. Soft Matter. 2023 Oct 11;19(39):7479-93. doi: 10.1039/d3sm01057k, PMID 37756117.
67. Parhi R. Cross linked hydrogel for pharmaceutical applications: a review. Adv Pharm Bull. 2017 Dec;7(4):515-30. doi: 10.15171/apb.2017.064, PMID 29399542.
68. Pragya A, Mutalik S, Younas MW, Pang SK, SO PK, Wang F. Dynamic cross-linking of an alginate acrylamide tough hydrogel system: time resolved in situ mapping of gel self assembly. RSC Adv. 2021 Mar 10;11(18):10710-26. doi: 10.1039/d0ra09210j, PMID 35423570.
69. Bashir S, Hina M, Iqbal J, Rajpar AH, Mujtaba MA, Alghamdi NA. Fundamental concepts of hydrogels: synthesis properties and their applications. Polymers. 2020 Nov 16;12(11):2702. doi: 10.3390/polym12112702, PMID 33207715.
70. Berger J, Reist M, Mayer JM, Felt O, Gurny R. Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. Eur J Pharm Biopharm. 2004 Jan;57(1):35-52. doi: 10.1016/s0939-6411(03)00160-7, PMID 14729079.
71. Xue X, HU Y, Wang S, Chen X, Jiang Y, SU J. Fabrication of physical and chemical crosslinked hydrogels for bone tissue engineering. Bioact Mater. 2022;12:327-39. doi: 10.1016/j.bioactmat.2021.10.029, PMID 35128180.
72. Naranjo Alcazar R, Bendix S, Groth T, Gallego Ferrer G. Research progress in enzymatically cross linked hydrogels as injectable systems for bioprinting and tissue engineering. Gels. 2023 Mar 15;9(3):230. doi: 10.3390/gels9030230, PMID 36975679.
73. Badali E, Hosseini M, Mohajer M, Hassanzadeh S, Saghati S, Hilborn J. Enzymatic crosslinked hydrogels for biomedical application. Polym Sci A. 2022 Feb;63:S1-S22.
74. MA H, Peng Y, Zhang S, Zhang Y, Min P. Effects and progress of photo-crosslinking hydrogels in wound healing improvement. Gels. 2022 Sep 23;8(10):609. doi: 10.3390/gels8100609, PMID 36286110.
75. Czarnecki S, Rossow T, Seiffert S. Hybrid polymer network hydrogels with tunable mechanical response. Polymers. 2016;8(3):82. doi: 10.3390/polym8030082, PMID 30979176.
76. XU J, Zhu X, Zhao J, Ling G, Zhang P. Biomedical applications of supramolecular hydrogels with enhanced mechanical properties. Adv Colloid Interface Sci. 2023 Nov;321:103000. doi: 10.1016/j.cis.2023.103000, PMID 37839280.
77. Palmese LL, Thapa RK, Sullivan MO, Kiick KL. Hybrid hydrogels for biomedical applications. Curr Opin Chem Eng. 2019 Jun;24:143-57. doi: 10.1016/j.coche.2019.02.010, PMID 31844607.
78. Villalba Rodriguez AM, Martinez Gonzalez S, Sosa Hernandez JE, Parra-Saldivar R, Bilal M, Iqbal HM. Nanoclay/polymer based hydrogels and enzyme-loaded nanostructures for wound healing applications. Gels. 2021 May 14;7(2):59. doi: 10.3390/gels7020059, PMID 34068868.
79. Zhang Y, Huang Y. Rational design of smart hydrogels for biomedical applications. Front Chem. 2020;8:615665. doi: 10.3389/fchem.2020.615665, PMID 33614595.
80. Golmohamadi M, Davis TA, Wilkinson KJ. Diffusion and partitioning of cations in an agarose hydrogel. J Phys Chem A. 2012 Jun 28;116(25):6505-10. doi: 10.1021/jp212343g, PMID 22394244.
81. Lacroce E, Rossi F. Polymer based thermoresponsive hydrogels for controlled drug delivery. Expert Opin Drug Deliv. 2022 Oct;19(10):1203-15. doi: 10.1080/17425247.2022.2078806, PMID 35575265.
82. Moriya G, Mazumder R, Padhi S, Mishra R. Gastrorententive hydrogels responsive to external stimuli for novel drug delivery. Int J App Pharm. 2024 Jul 7;16(4):1-14. doi: 10.22159/ijap.2024v16i4.51051.
83. Kakkar V, Narula P. Role of molecularly imprinted hydrogels in drug delivery a current perspective. Int J Pharm. 2022 Sep 25;625:121883. doi: 10.1016/j.ijpharm.2022.121883, PMID 35870667.

84. Ghanem AM. A review on recent advances in transdermal drug delivery systems of tamsulosin. Int J App Pharm. 2024 Mar;16(2):28-33. doi: 10.22159/ijap.2024v16i2.49950.
85. Khan F, Atif M, Haseen M, Kamal S, Khan MS, Shahid S. Synthesis classification and properties of hydrogels: their applications in drug delivery and agriculture. J Mater Chem B. 2022 Jan 5;10(2):170-203. doi: 10.1039/d1tb01345a, PMID 34889937.
86. Dimatteo R, Darling NJ, Segura T. In situ forming injectable hydrogels for drug delivery and wound repair. Adv Drug Deliv Rev. 2018 Mar 1;127:167-84. doi: 10.1016/j.addr.2018.03.007, PMID 29567395.
87. MO F, Jiang K, Zhao D, Wang Y, Song J, Tan W. DNA hydrogel based gene editing and drug delivery systems. Adv Drug Deliv Rev. 2021 Jan;168:79-98. doi: 10.1016/j.addr.2020.07.018, PMID 32712197.
88. Andriano K. Controlled release of highly water soluble drugs from the SQZ gel oral drug delivery system. Drug Deliv Technol. 2010 Jan;10(1):42.
89. https://www.rxlist.htm#description.Com/metrogel-vaginal-drug. [Last accessed on 20 Feb 2024].
90. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125277s000PharR_P1.pdf. [Last accessed on 20 Aug 2024].
91. https://www.drugs.com/pro/maxidex.html. [Last accessed on 23 Apr 2023].
92. https://www.medicines.org.uk/emc/product/135/smpc#gref. [Last accessed on 15 Mar 2024].
93. https://www.supprelinla.com. [Last accessed on 15 Mar 2024].