



## Review Article

# An overview on current trends and future outlook of hydrogels in drug delivery

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## ABSTRACT

Hydrogels are widely used in biomedical fields including drug delivery due to their unique properties such as biocompatibility, biodegradability, flexibility, and non-toxicity. Because of their advanced properties, the interest in hydrogels is increasing day by day. Although researchers have been working on developing new hydrogels and enhancing the properties of the existing ones, there are still many remaining unsolved challenges for the improvement. This review paper handles the topic of hydrogels as drug delivery systems (DDS). Herein, we summarize the properties, advantages, classification, and preparation methods of hydrogels. We highlighted some recent progress of hydrogels as unique drug delivery vehicles. The future perspective of the use of them were eventually enlightened.

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## INTRODUCTION

The terminology “Drug Delivery System” (DDS) refers to a method of introducing a drug into the body and increasing its efficiency by regulating the rate and time at which the medication is released into the targeted organ. To get over the disadvantages of traditional drug formulations, controlled drug delivery systems that provide drugs at predetermined rates have been developed [1]. There are many types of the DDSs that are in use nowadays. In this study, the hydrogels were investigated as drug carriers for a controlled drug release.

Hydrogels are three-dimensional hydrophilic polymeric matrices that may absorb large amounts of water or biological fluids. Due to their high water content, porosity, and soft

consistency, hydrogels are more similar to living tissues than other artificial biomaterials. [2]. As a result of their swelling capability, hydrogels, which have become extremely desirable materials nowadays, are commonly used in medicine and healthcare. Hydrogels can provide optimum conditions and environments for biological interactions to take place.

One of the most significant materials of option is hydrogel, which is employed in bio generators, drug delivery systems, contact lenses, wound dressings, and biomedical applications.

Hydrogels are appropriate for medical applications because they can contain high water content, and have rubbery qualities comparable to real tissues, also they have little or no resistance to physiological fluids. They may be employed as controlled medication release systems in

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the biomedical industry [3]. Controlled drug release is an important element of the disease's therapy.

## SYSTEMS OF DRUG DELIVERY

The term “Drug Delivery System” (DDS) refers to the mediator that relates the human body to the pharmaceutical remedy. It's a way to introduce a drug to the body and increase its effectiveness by monitoring the rate, and time depending on the targeted organ that will absorb the drug in. This operation is accomplished through the administration of the medicinal substance, the release of the effective component from the medical substance, the transfer of the effective component through the internal tissues to the targeted organ [4].

The ideal drug delivery system should perform three tasks:

1. Transferring the optimum quantity of the drug needed to the targeted site in order to obtain the intended curative response,
2. Transferring the drug with useful kinetics to increase its curative response and to decrease unwanted side effects,
3. Confirm that the drug is obtainable at the targeted site at the determined times within particular periods.

The rate of release, the frequency of dosage, and the route of administration all affect the previously mentioned roles [5–7].

### Classifications of Drug Delivery Systems

In the following figure, the main classifications of DDSs are illustrated:

#### Classical drug delivery systems

Classical DDSs are ordinary techniques to deliver a medical substance into specific cells. When a quick drug release is required, such systems are usually preferred. Conventional DDSs include models of normal oral, inhaled, topical, or injection models [8,9].

#### New drug delivery systems

A new drug delivery system (NDDS) which is characterized to be a controllable drug delivery system, is a

mixture of new dosage forms and developed methodologies aimed at improving drug influence, drug release controlling, safety, and drug delivery to the targeted tissue [10].

The following are the several types of NDDSs:

1. DDS with pre-programmed rates
2. DDS with activation modulation
3. DDS with a feedback loop
4. Site-specific DDS [11,12].

#### Drug delivery systems based on the route of administration

DDSs are divided into classes according to the route of administration, which refers to the way taken by the medication entering the human body. The following are the primary categories:

1. Oral delivery,
2. Buccal/Sublingual Delivery,
3. Rectal Delivery,
4. Parenteral Administration: Intravenous, Subcutaneous, and Intramuscular [13].

#### Drug delivery systems relying upon dosage form physical properties

DDSs are categorized according to the physical properties of different dose forms. Generally, it is possible to categorize dose forms mainly into four types which are given as:

1. Gaseous forms (ex. anesthetics),
2. Liquid forms (ex. solutions),
3. Semisolid forms (ex. gels),
4. Solid forms (ex. Tablets) [7].

#### Drug-loading mechanism-based classification of DDSS

Loading a drug is described as encapsulating a certain drug which means putting a small amount of the drug in the carrier [14].

The need to encapsulate the drugs has resulted from many reasons, such as:

- Reducing the effect of toxicity,
- Enhancing the solubility,
- Protecting the drug from exterior conditions (enzymes, oxidation, and pH),
- Improving availability and circulation time.

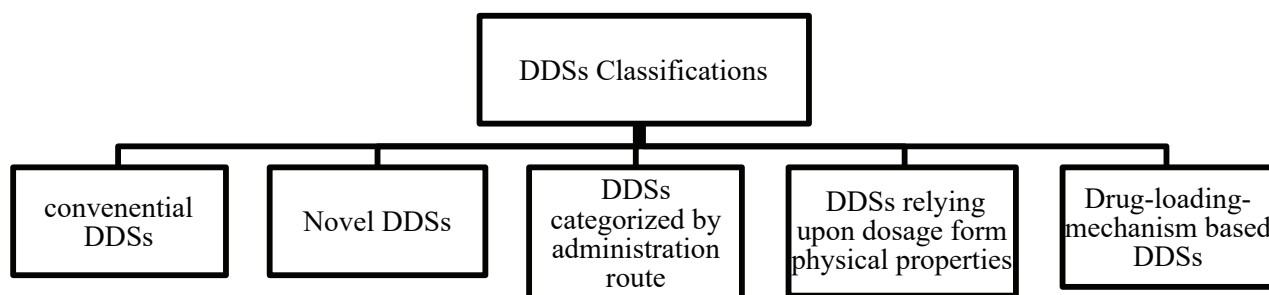


Figure 1. Classifications of DDSs.

Also, the encapsulating carrier can help in delivering the drug to specified target in the body [15].

Two categories of loading approaches can be used to obtain a certain drug dose in the delivery device, these are:

1. In situ drug loading which means direct processing; refers to combining the drug with the carrier during the carrier production.
2. Ex situ drug loading which means indirect processing; is a process consisting of two steps. In the first one the carrier is made, in the second step the drug is added to the carrier [16].

There have been tremendous attempts in the last 20 years to examine medication delivery, since it is difficult to release and deliver the medicine with the precise rates sought by researchers. Recent research has concentrated on the utilization of cross-linked hydrogels that swell with water as the foundation for pharmaceutical drug delivery development [17].

Hydrogels are well-known substances that are used in various fields, such as: biomedicine, pharmaceuticals, and agriculture. The first polymer capable of absorbing water was created in 1938 [18].

## HYDROGELS

In 1894, the term “hydrogel” was introduced; previously, hydrogels were known as colloidal gels of inorganic salts. Then, substantial advancements in this discipline resulted in numerous innovations. In 1958, gamma irradiation was used to create a cross-linked Polyvinyl Alcohol (PVA) hydrogel. In 1960, Wichterle and Lim invented poly 2-Hydroxyethyl methacrylate (HEMA) hydrogels for contact lens application, and so on [8,19].

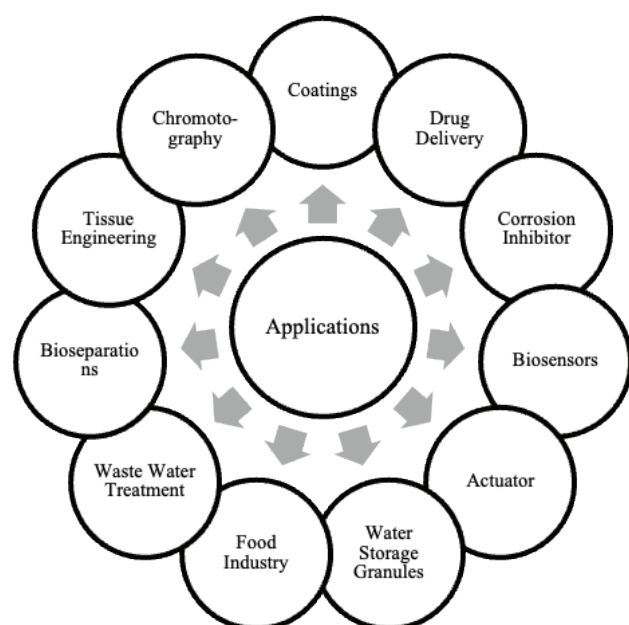


Figure 2. Applications of hydrogels.

Because of the existence of polar compounds such as amide, hydroxyl, sulphonic, and carboxyl groups, Hydrogels are water-absorbent cross-linked three-dimensional network structures. Hydrogels are joined together via chemical crosslinks or physical interactions. Hydrogels have different crosslinks or physical interactions. Hydrogels have different amounts of swelling behavior depending on the polymer composition and the water environment. Hydrogels are sometimes known as “smart gels” because they are sensitive to the temperature and pH of the environment. Also, they can be sensitive to other external conditions such as ionic strength. Which allows them to be used in many applications [20,21].

Hydrogels are utilized in many applications as a result of their distinct qualities like non-toxicity, biocompatibility, and water absorption properties. These properties enabled hydrogels to be useful in chromatography, proteomics, electrophoresis, food, bio-separation, and water remediation applications [22]. The main applications of hydrogels are presented in Figure 2.

## Properties of Hydrogels

The most important properties of hydrogels are defined below:

1. Swelling: Swelling is the main characteristic of hydrogels. These structures allow free diffusion of solute molecules in an aqueous media with the polymer network of the hydrogel working as a container to keep the solvent. They have the ability to absorb thousands of times of their dry weight in liquid media [23].
2. Permeation: The permeation process occurs through pores. Pores are formed in hydrogels as a result of phase separation within the synthesis. The fundamental factors of a unique hydrogel are the average size of the pore, the size distribution, and interconnections among them [24,25].

After defining these properties, the swelling property will be further discussed since it is the most remarkable feature of hydrogels. The hydrogels have a three-dimensional insoluble crosslinked structure which allows them to immobilize biomolecules like proteins, peptides and active agents in an effective manner. Also, it allows them to release these compounds under specific biological conditions. The human body contains many diverse biological fluids which create a distinct environment for each organ and this fact makes hydrogel’s capability to swell and release different drugs very useful in localized drug delivery applications. There are some factors that affect the swelling property of hydrogels [26,27]. These factors are:

1. The crosslinking ratio: known to be the proportion of mole quantity of crosslinker to mole quantity of monomer molecules. The further the crosslinker agent is included in the hydrogel matrix, the greater the crosslinking ratio will be. Hydrogels that have low crosslinking ratios can swell more than

hydrogels that are highly crosslinked. The mobility of the polymer chain is hampered by crosslinking which decreases the swelling ratio [26].

2. Hydrogel's chemical structure: Hydrogels that contain hydrophilic groups within their structure are able to swell more than hydrogels that contain hydrophobic groups. When exposed to water, hydrophobic groups shrink to reduce their accessibility to the water. Thus, compared to hydrogels with hydrophilic groups, the hydrogels with hydrophobic groups will swell far less [26].
3. Specific responses to different stimuli: In smart hydrogels swelling behavior can be affected by specific stimuli. For example, by changing the temperature of the medium the swelling ability of temperature-sensitive hydrogels can be changed. Also, changing the pH value will definitely affect the swelling behavior of pH-sensitive hydrogels. There are a variety of different stimuli that can cause changes in other environmentally sensitive hydrogel's swelling behavior [26].

In the following section the swelling ratio which is an important quantity in measuring the swelling behavior of hydrogels will be discussed.

Swelling ratio:

The swelling ratio ( $R_s$ ) of hydrogels can be defined with the following equation.

$$R_s = \frac{W_s - W_d}{W_d}$$

In this equation:

$W_s$ : is the weight of the swollen hydrogel,

$W_d$ : is the hydrogel's weight before swelling water [28].

The ability to monitor the de-swelling behavior of hydrogels is important. Hydrogels are permitted to swell in water at room temperature for this purpose, and differences in hydrogel weight are recorded at different time intervals. The water retention ( $W_r$ ) may then be calculated using the equation below.

$$W_r = \frac{W_t - W_d}{W_s} \times 100$$

In this equation:

$W_t$ : The mass of the hydrogels measured at a specific time interval,

$W_s$  and  $W_d$ : are the weight of hydrogels in the before and after swelling, respectively [28].

The swelling degree of a hydrogel is impacted by several parameters, including the composition of the solvent, network density, and the polymer-solvent interaction [29,30].

swelling equilibrium, ( $\alpha$ ) can be calculated through the equation given below.

$$\alpha = \frac{m_{sw}}{m_{dr}}$$

In this equation:

$m_{sw}$ : mass of hydrogel before drying.

$m_{dr}$ : mass of hydrogel after drying.

### Advantages of Hydrogels

Important advantages of hydrogels which make them useful in many applications are listed below [22].

- They show high absorption capacity,
- They are available at low cost,
- They maintain the pH value neutral after swelling into water,
- They have the least soluble content and the least residual monomer,
- They achieve the desired rate of absorption related to the needs of the application,
- They have high durability and stability during storage,
- They have high biodegradability,
- They are colorless, odorless, and non-toxic,
- They have high photostability.

### Preparation Methods of Hydrogels

Polymer networks made from natural or manmade polymers make up hydrogels. Chemical cross-linking, physical cross-linking, grafting polymerization, and radiation cross-linking are some of the preparation methods employed [31].

The next sections explain how to prepare hydrogels in general.

### Methods of Physical Crosslinking

Intermolecular forces like hydrogen bonding and ionic interactions can be changed to achieve physically cross-linking. External stimuli which can be pH, light, temperature, heat, and electrical fields can cause these changes. Also, physical cross-linking can be achieved through maturation (heat induced aggregation) [32].

The advantages of these types of gels are [33]:

- The ease of production,
- Avoiding toxic crosslinkers and catalysts,
- Ability to design hydrogels with different mechanical strengths, gelation times and rates of degradation.

### Ionic Interaction

The inclusion of di- or trivalent counterions can be used to cross-link ionic polymers. This method explains how to get a polyelectrolyte solution (for example,  $\text{Na}^+$  alginate) with a multivalent ion with opposing charges (for example,  $\text{Ca}^{2+} + 2\text{Cl}^-$ ). Chitosan-polylysine, chitosan-glycerol phosphate salt, and chitosan-dextran hydrogels are some further examples.

### H-Bonding

By decreasing the pH of a polymeric aqueous solution containing carboxyl groups, H-bonded hydrogels can be made. Hydrogen-bound carboxymethyl cellulose (CMC) networks and carboxymethylated chitosan (CM-chitosan) hydrogels are examples of this type of hydrogel. Hydrogels made of polyacrylic acid and polyethylene oxide (PEO-PAAc) are another example [34].

### Maturation (Heat Induced Aggregation)

Heat treatment causes proteinaceous components to aggregate, increasing their molecular mass and resulting in a hydrogel that has improved mechanical characteristics and water linking capabilities [35].

The molecular modifications that occur during the maturation phase show that a hydrogel with finely organized molecular dimensions can be made. For denture care, the procedure is applied on gums such as gum ghatti and *Acacia kerensis* [33].

### Cross-Linking by Chemical Means

This method includes grafting the monomers onto polymer chains or binding two polymer chains together with a cross-linking agent. The reaction between functional groups like  $\text{NH}_2$ ,  $\text{COOH}$ , and  $\text{OH}$  with cross-linking agents that can be aldehyde causes cross-linking of synthetic and natural polymers. Hydrogels which are cross-linked chemically can be produced in a variety of ways. Crosslinking via complimentary groups chemical reactions, crosslinking with free radical polymerization, and crosslinking with enzymes are the three most common chemical processes [36].

### Complimentary Group Cross-Linking Reaction

Polymers which contain hydrophilic groups like  $\text{NH}_2$ ,  $\text{COOH}$ , and  $\text{OH}$  can be utilized in preparing hydrogels. Isocyanate- $\text{OH}/\text{NH}_2$  reactions, amine-carboxylic acid reactions, and Schiff base production are all examples of reactions that can be utilized to understand covalent connections among the chains of polymers [36].

### Cross-Linking With Aldehydes

Glutaraldehyde can be used to cross-link hydrophilic polymers with  $-\text{OH}$  groups, such as polyvinyl alcohol [37]. In order to achieve cross-linking, a specific environment is used which provides low acidic pH with high temperature, and addition of a quencher like methanol. Another method is to cross-link amine-group polymers with the same cross-linker under moderate conditions where generation of Schiff base occurs. This approach was created specifically for the production of cross-linked proteins like albumin [38], and gelatin [39] as well as amine-containing polysaccharides [40].

### Via Use of Addition Reactions

Hydrophilic polymer functional groups can interact with Bis or higher functional cross-linkers via addition reactions. Polysaccharides can be cross-linked with divinyl-sulfone [41], 1,6-hexamethylenediisocyanate, or 1,6-hexanedibromide [42].

### Via The Use of Condensation Reactions

This reaction which involves  $-\text{OH}$  groups or  $-\text{NH}_2$  with  $-\text{COOH}$  or derivatives can be utilized to make polyesters and polyamides, respectively. These reactions are utilized in hydrogel preparation. *N,N*-(3-dimethylaminopropyl)-*N*-ethyl carbodiimide is a particularly effective agent to cross-link amide groups with hydrophilic polymers [43].

### Cross-Linking Via Free Radical Polymerization

Free radical polymerization of hydrophilic polymers, and vinyl monomers mixtures can be used in making chemical cross-linked hydrogels. In this method, natural, artificial, and semi-artificial hydrophilic polymers were utilized to make gels. Methacrylic groups have been incorporated into mono and disaccharides, which can be utilized to make hydrogels, with the help of enzymes that act as catalysts [44–46].

### Cross-Linking Via Enzymes

Sperinde et al. devised a technique for synthesizing PEG-based gels by employing an enzyme. Tetrahydroxy PEG was used to functionalize glutamyl groups (PEG-Qa). PEG networks were created when transglutaminase was added to aqueous solutions of poly (lysine-co-phenylalanine) and PEG-Qa. The creation of an amide bond among the -amine group of lysine and the -carboxamide group of PEG-Qa was mediated by transglutaminase [47].

### Cross-Linking Via Radiation

The fact that in this method there is no requirement to use chemical additives, preserving hydrogel's biocompatibility, has made it a popular approach. Furthermore, the alteration and sterilizing may be completed in one step, making it an economical technique for modifying hydrogels with specific uses in medical applications [48]. The process is based on the production of free radicals in the polymer upon exposure to a high-energy source such as an x-ray, gamma ray, or electron beam. The polymer environment, such as dilute solution, concentrated solution, or solid state, will largely determine the action of radiation, which might be direct or indirect.

### Classifications of Hydrogels

Hydrogels are divided into different groups according to several factors such as physical structure, origin, ionic charge, composition, and cross-linking. These classifications will be presented in Figure 3.

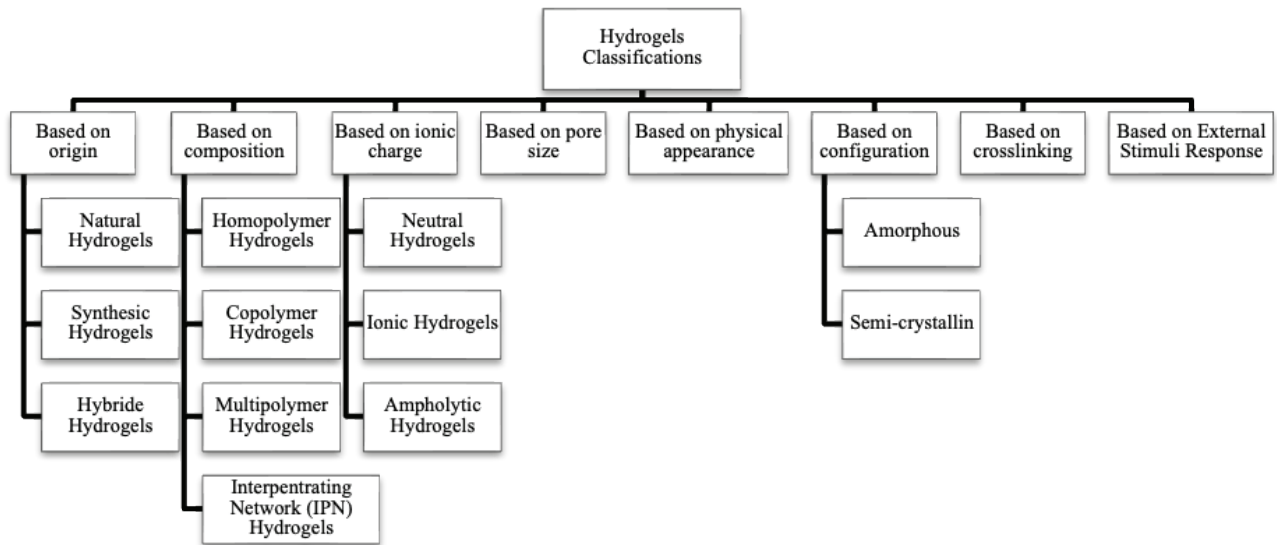


Figure 3. Classifications of hydrogels.

### Origin-Based Classification

#### Hydrogels with natural origin

This type of hydrogels is made from natural materials. Animals and living plants can provide them. Microorganisms are also capable of producing biodegradable polymers. Some examples of polymers that are used to make these hydrogels can be proteins and polysaccharides such as dextran, chitosan, and alginate [49].

#### Synthetic hydrogels

These hydrogels are created in the laboratory. Chemical polymerization with synthetic monomers is used to make them. These hydrogels are classified as homopolymeric, copolymeric, or multipolymeric [50].

#### Hybrid hydrogels

Synthetic and natural polymers are combined to create hybrid hydrogels [51].

When one type of substance is insufficient for a given use, these hydrogels are created. When using hybrid hydrogels in tissue engineering, for example, when the natural tissue is complicated, hybrid hydrogels are favored [52].

### Compositional Classification

#### Homopolymeric hydrogels

The structure of these hydrogels consists of identical monomers. Their structure depends on several factors like monomer's nature, polymerization techniques and cross-linking [53]. Homopolymer hydrogels include poly(N-vinyl-2-pyrrolidinone) (PNVP), poly(acrylamide) (PAM), poly(ethylene glycol) (PEG), and poly(vinyl alcohol) (PVA) and other several polymers [54].

#### Copolymeric hydrogels

The structure of these hydrogels is a mixture of two monomer units [55]. These units can be arranged in a variety of ways, including block, graft, alternate, and random. Chemically, these hydrogels can be made by polymerizing or cross-linking both monomers with the help of an initiator and a cross-linker. Different forces, including as hydrogen bonding, chain aggregations, ionic contact, and ion-polymer complexations, can also physically cross-link them [56,57].

#### Multipolymeric hydrogels

Polymerization and cross-linking mechanisms can be used to make multipolymer hydrogels from three or more monomers. This type of hydrogel includes poly(acrylic acid-2-hydroxy ethyl methacrylate)/gelatin hydrogels [58].

#### Interpenetrating Network (IPN)

Two interlaced polymer networks with no chemical bond between the polymers make up this type of hydrogel. One of the polymers has a linearly structured network, while the other polymer's network is cross-linked. There is a diffusion of the linear network into the cross-linked network [59]. Figure 3.11 shows an interpenetrating network (IPN) hydrogel which has a molecular structure that includes the arrangement of monomers and crosslinking.

### Ionic Charge Categorization

Hydrogels can be divided into main three categories using the type of electrical charge of their cross-linked chains [55,60].

#### Neutral Hydrogels

These hydrogels don't have an electrical charge on their side groups [55,60]. Several polymerization procedures or

the conversion of existing polymers can be used to make neutral hydrogels. Whereas generalizations regarding hydrogels can be made, the wide diversity of chemical compositions of the monomers utilized gives them unique qualities in terms of biocompatibility, physical, and chemical properties of the polymer [54].

### Ionic Hydrogels

Cationic and anionic hydrogels are two types of ionic hydrogels.

- Positively charged side groups such as amines and sulphonic acid are found in cationic hydrogels. At low pH, they show an increase in swelling.
- Negatively charged side groups, like carboxylic acid and sulphonic acid, are present in anionic hydrogels. When the pH is too high, they swell more [55,60].

### Ampholytic Hydrogels

These hydrogels can hold both negative and positive electrical charges at one polymer chain. This can lead to a balance at the isoelectric point [55,60]. Based on the existence of electric charge, a schematic representation of several hydrogels is depicted in Figure 3.12.

### Pore Size Categorization

Based on porosity, hydrogels can be divided into main three categories. Non-porous, Micro-porous, and Super-porous are the three types of porous materials [61].

### Physical-Appearance Based Classification

Hydrogels are classified into various types according to their physical appearance. Matrix, film, and microsphere are the three classes that are associated with the polymerization technique [61].

### Configuration Based Classification

Hydrogels can be categorized into the following categories according to their physical structure and chemical content [61].

### Amorphous Hydrogels

Amorphous, or non-crystalline refers to the optically transparent isotropic polymeric networks with randomly distributed macromolecular chains. Localized ordered structures or non-homogeneous structures are frequently found in amorphous hydrogel networks [54].

These hydrogels have a polymeric network with macromolecular chains that are randomly organized [61].

### Semi-Crystalline

The mechanical resistance in some of the standard cross-linked hydrogel networks has resulted in the creation of anisotropic semicrystalline polymer networks characterized by strong covalent links across the polymer chain [54].

Semi-crystalline hydrogels are made up of a complicated blend of non-crystalline and crystalline states. High density regions of organized macromolecular chains are used to describe them [61].

### Cross-Linking Based Classifications

Hydrogels are grouped into main two categories according to the sort of cross-linking used. The two types are chemical hydrogels and physical hydrogels. Covalent cross-linking is utilized to make chemical hydrogels, while physical hydrogels are cross-linked through a variety of physical actions like hydrogen bonding, hydrophobic interactions, and crystallization [62].

### Classification Based on External Stimuli Response

These hydrogels go through rapid and reversible changes as a response to changes that occur in their environment. Smart hydrogels are categorized according to their responses to changes such as changes in pH, temperature, irradiation, pressure, and chemical stimuli. Smart polymers can be used for several applications like medical and engineering applications [63].

### Hydrogels in Drug Delivery Systems

Drug delivery systems are one of the most prominent applications of hydrogels. Because of its unique features such as flexibility, hydrophobicity, and biocompatibility, hydrogels are exploited as drug carriers.

Hydrogels are composed of a hydrophilic network that acts as a water absorber and instantly identifies the desired location. To inject the gel into the targeted tissue, a hole that corresponds to the gel dimension is necessary. Patients may be exposed to danger and discomfort as a result of this application. As a result, to distribute the medicine, three-dimensional matrices must be created. Hydrogels can create three-dimensional matrices with biocompatibility, elasticity, and the ability to absorb water thanks to their cross-linking network. Hydrogels can also administer medicine at a specific moment and with a controlled release [64].

Hydrogels have the ability to undergo structure alterations which enables them to be used as carriers for drugs. Drugs can be released from hydrogels according to their target organ and administration route. In this method, the drug can be delivered to the body in a specific method to meet the precise curative demands [65,66].

There are various routes of administration of hydrogels as drug carriers. Pharmaceutical hydrogels are categorized as follows:

- Oral hydrogel systems,
- Hydrogel systems that are both transdermal and implantable,
- Topical and transdermal hydrogel systems,
- Drug delivery via hydrogel devices in the gastrointestinal (GI) tract,
- Ocular delivery techniques based on hydrogels [67].

The industrial applications of hydrogels as drug delivery systems will be given briefly in Table 1.

### Hydrogels Past and Current

In this section the recent research articles that have been made about hydrogels as drug delivery systems will be presented in Table 2.

**Table 1.** Commercial hydrogel drug examples

Product	Manufacturer	Application	Information	Ref.
Biotene	GlaxoSmithKline	Oral moisturizing agent in dry mouth	Carbomer and hydroxyethyl cellulose	[68]
Simpurity™ Hydrogel	Safe n'Simple	Skin burns, dry wounds, and dry scabs	PEO, PVA, acrylate, polyurethane, and pure water are used to make absorbent sheets.	[69]
Soflens daily disposable	Bausch & Lomb	Short and Long sightedness	By providing moisture around the lens, it can keep the eyes comfortable.	[70]
Nicorette®	GlaxoSmithKline	Smoking cessation	Hydroxypropyl Methylcellulose	[68]
Neutrogena® Hydro Boost®	Johnson and Johnson	Face	Hyaluronic acid is used in the face mask. Provide skin with immediate and long-lasting moisture.	[71]
Sericin	Sigma Aldrich	For malignant melanoma, an optically trackable drug delivery system	Sericin is a protein generated from the cocoon of silkworms that provides a number of advantages for cultivating human cells. It has cryoprotective characteristics, allowing it to be used in cryopreservation media instead of FBS.	[72]
Suprasorb®G	Lohmann & Rauscher Global	Lower leg ulcers, pressure ulcers, first and second-degree burns, and scalds	Acrylic polymers, PE, and phenoxyethanol hydrogel film which contains 70% water.	[73]

**Table 2.** Summary of research articles about hydrogels as DDSs

Ref.	Hydrogel	Method	Results
[74]	PDA/TOCNFs	The process of (TEMPO)-mediated oxidation was used to make cellulose nanofibrils (TOCNFs).	Long-acting antibacterial and wound-healing characteristics, as well as an anticancer agent with high potency, were discovered.
[75]	Chitosan-alginate	Schiff-base reaction occurred to crosslink carboxyethyl chitosan (CEC) with oxidized alginate (OA).	Under physiological conditions, excellent self-healing capabilities.
[76]	pH responsive semi-IPN	Gelatin combined with cellulose nanocrystals was used to make hydrogels with a high sensitivity to pH changes	The addition of CNC to hydrogels enhanced crystallinity and storage moduli. At pH 7, %15 wt percent swelling was achieved.
[77]	Nanocomposite DNA-based hydrogel	oxidized alginate (OA) crosslinking via the production of reversible imine bonds	DNA could be employed as a natural biopolymer in the development of self-healing injectable hydrogels with long-term release qualities for minimally invasive therapeutics.
[78]	Carboxymethyl $\beta$ -cyclodextrin grafted carboxymethyl chitosan hydrogels (CMCD-g-CMCs)	In the presence of N-hydroxysuccinimide, CMCD-g-CMCs were made from carboxymethyl-cyclodextrin (CMCD) and carboxymethyl chitosan (CMC) utilizing a water-soluble carbodiimide as a crosslinker.	In the stomach environment, 90% of insulin was maintained within the hydrogel. Oral insulin with hydrogel form had a long-acting, persistent hypoglycemic impact.
[79]	Cellulose-based hydrogels	A Schiff base reaction was used to combine CMC-NH <sub>2</sub> and CMCCHO polymer solutions containing PEO-b-PDPA copolymer micelles to create an injectable hydrogel composite system.	The pH-triggered, extended, and slow-release characteristics of the synthesized hydrogel were demonstrated. In addition, the hydrogel system showed good storage moduli and controllable degrading properties.



**Table 2.** Summary of research articles about hydrogels as DDSs (continue)

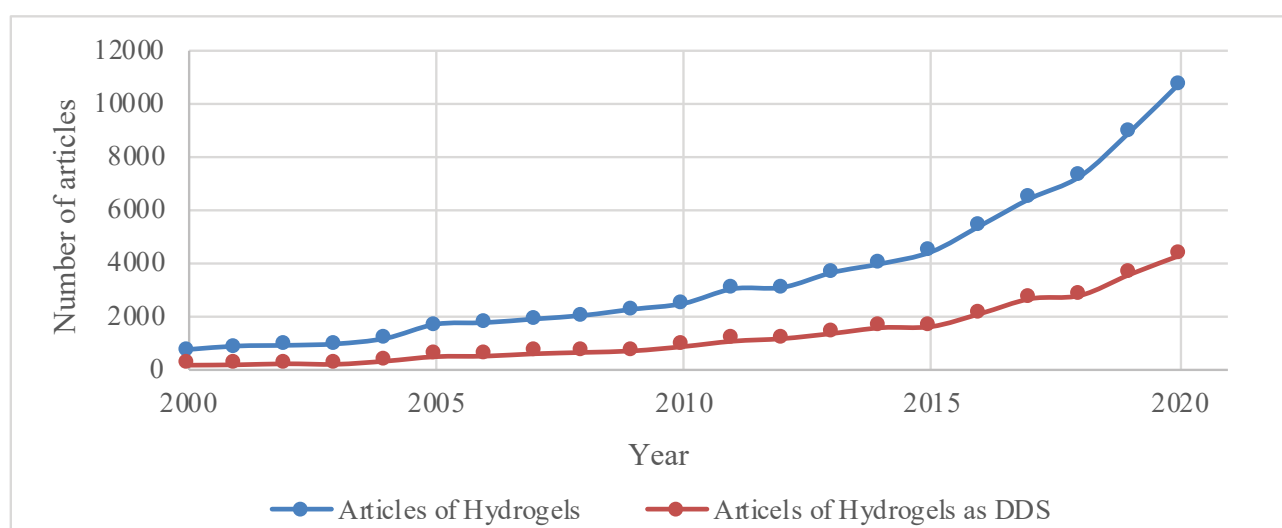
Ref.	Hydrogel	Method	Results
[80]	Hydrogels based on chitosan-grafted-dihydrocaffeic acid (CS-DA) and oxidized pullulan (OP)	Hydrogels were prepared via Schiff base reaction	According to the findings, the injectable pH-responsive adhesive hydrogels appear to be great candidates for developing colon cancer medication delivery carriers or mucoadhesive drug delivery systems.
[81]	Xan-CHO/NOCC hydrogel	Aldehyde-modified xanthan (Xan-CHO) and carboxymethyl-modified chitosan self-crosslink to form a polysaccharide-based hydrogel (NOCC).	The advantage of Xan-CHO/NOCC hydrogel over conventional fibrin gel in terms of preventing drug eruption in liquids, which is beneficial for wet wounds.
[82]	Dopamine-based and polydopamine crosslinked injectable hydrogels	Under physiological conditions, dopamine-based hydrogels are made by oxidizing a combination of quaternized chitosan, gelatin, and dopamine.	As long-term localized drug delivery systems, these hydrogels showed considerable potential. Anti-inflammatory drugs and free dopamine can be encapsulated in these hydrogels in situ.
[83]	2-hydroxyl ethylmethacrylate (HEMA) based hydrogels	Photopolymerization was carried out in the presence of three distinct photo-initiators (Irg184, Irg651, Irg2959) and a (ethylene glycol dimethacrylate) cross-linking agent to produce HEMA-based hydrogels.	The findings indicated that this type of hydrogel could be useful in the controlled release of drugs.
[84]	Polyethylene glycol diacrylate (PEG-DA) based hydrogels	Photopolymerization employing three distinct photo initiators (Irgacure 651, Irgacure184, Irgacure 185, Irgacure 2959). Also, PEG-DA hydrogels were modified using hydroxyapatite (HAp).	PEG-DA-based hydrogels performed well for drug delivery. The mixture of PEG-DA and HAp may slow the rate of hydrogel deterioration in simulated gastrointestinal fluid.
[85]	Ternary sodium alginate-based hydrogels	g-cellulose, clinoptilolite, modified clinoptilolite and 4-acryloyl morpholine (4 AcM) were mixed with sodium alginate (NaAlg).	The release activity of donepezil hydrochloride from the hydrogels was found to be so sensitive with the medium pH. Sodium alginate-based composite hydrogels might be useful for controlled drug release.
[86]	PEG-DA and PEG-DA/HEMA based hydrogels	synthesized PEG-DA/HEMA based hydrogels with modified HAp via photopolymerization.	pH sensitive behavior was seen in synthesized hydrogels. The kind and quantity of photo-initiators had a significant impact on the release behavior of hydrogels. The findings demonstrate that Donepezil HCl is released in a regulated manner.
[87]	Poly(ethylene gly-col) diacrylate (PEG-DA).	PEG-DA based hydrogels were made by using photopolymerization technique using photoinitiators (Irg184, Irg651, Irg2959) and a crosslinking agent (ethylene glycoldimethacrylate).	PEG-DA hydrogels with TiO <sub>2</sub> showed a regulated re-lease behavior with a substantially slower release rate. The findings suggest that combining PEG-DA with TiO <sub>2</sub> in drug-delivery systems might be beneficial.
[88]	HEMA/PEG-DA Based Hydrogels	Photo-initiators (Irg 184, Irg 651, Irg 2959) and a crosslinking agent were used to synthesize PEG-DA and HEMA/PEG-DA based hydrogels (ethylene glycol dimethacrylate)	According to the findings, the medication release of the hydrogel increased as the pH increased. The maximum release was seen with synthesized hydrogels in the presence of Irgacure 2959.
[89]	Chitosan(CS)/polyvinyl alcohol (PVA) hydrogel	Chitosan and PVA were used as the base components for self-healing. At low temperatures, the precursor was in the liquid state, which was later transformed into a hydrogel.	The hydrogel is biocompatible and may be created in situ on tumor cells quickly and readily. The hydrogel can produce localized regulated drug release and boost anti-tumor activity when loaded with 5-FU. This self-healing hydrogel has the potential to improve anti-tumor treatment.

**Table 2.** Summary of research articles about hydrogels as DDSs (continue)

Ref.	Hydrogel	Method	Results
[90]	Thermosensitive chitosan-based hydrogel	A local eye drop solution for the prolonged release of latanoprost to manage ocular hypertension was created using a thermosensitive latanoprost-loaded hydrogel.	TA-induced high IOP in a rabbit model of glaucoma was dramatically reduced within 7 days and sustained within a normal range. In the near term, chitosan-based formulation could offer a non-invasive alternative to standard eye drops for lengthy IOP control.
[91]	Bacterial cellulose and gelatin-based hydrogel composites.	The amine and hydroxyl groups, which were the functional groups of gelatin and bacterial cellulose, respectively, were used to copolymerize bacterial cellulose and gelatin.	The chemical resistance, stability, and tensile qualities of the hydrogel composites were all good. Hydrogel composites are of high-quality candidates for drug-delivery systems. The hydrogel network swells 400–600% in water, according to the researchers.
[92]	Magnetic nanocellulose alginate hydrogel	Using the co-precipitation process, CNCs also were changed with iron oxide nanoparticles. Magnetic cellulose nanocrystals, or m-CNCs, were added to alginate hydrogel beads, which serve as medication carriers.	The addition of magnetic nanocellulose to the alginate hydrogel beads increased their physical and mechanical properties, boosting swelling and slowing drug release.
[93]	Chitosan based hydrogel grafted with cyclodextrin	Graft polymerization of chitosan coated magnetic nanoparticles (CS-MNP) with acrylic acid and grafted with ethylenediamine derivative of cyclodextrin (-CD) for the prolonged and regulated release of curcumin, an anticancer medication (CUR).	The findings revealed that the drug delivery carrier had been successfully developed. The evidence on drug release in two pH mediums indicates that drug release is greatest in the intestinal fluid.
[94]	Polydopamine/nanocellulose hydrogel	Physical Ca <sup>2+</sup> cross-linking of PDA and TOCNFs was used to make hydrogels.	The produced PDA/TOCNFs composite hydrogel has several distinct advantages: 1) simple production; 2) no chemical crosslinking agent is employed; 3) multi-responsive features (such as pH, NIR response, and long-term drug release); 4) high wound healing capacity.
[95]	Hydrogel composed of carboxymethyl chitosan (CMCS) and poloxamer 407(F127)	A crosslinking process using genipin, a naturally occurring harmless crosslinking agent, was used to create the hydrogel (GP)	A new nanostructured lipid carrier (NLC) based on a double hydrogel was developed. The hydrogel is a prospective and promising ocular medication delivery technology since it is temperature and pH responsive.
[96]	Inulin-based hydrogels	Inulin hydrogels were fabricated by crosslinking oxidized inulin with adipic acid dihydrazide (AAD) without the use of a catalyst or initiator.	Blank gels did not show any appreciable cytotoxicity, whereas 5FU-loaded hydrogels demonstrated efficacy against HCT116 colon cancer cells, which further confirms the potential use of these delivery platforms for direct targeting of 5-FU to the colon.
[97]	Trimethyl chitosan and sodium alginate-based hydrogels nanoparticles	Nanoparticles, loaded with different progesterone concentrations, have been obtained by polyelectrolyte complex formation between trimethyl chitosan and sodium alginate, followed by ionotropic gelation with sodium tripolyphosphate as a cross-linking agent.	In vivo results demonstrate that the selected nanoparticles could be an efficient carrier for PG brain delivery useful in the treatment of different neurodegenerative disorders.
[98]	P-Lys-Ala-PLX and Pluronic F-127 mixed hydrogel	The block copolymer P-Lys-Ala-PLX was prepared through a two-step ring-opening polymerization of Ala-NCA and Lys-(Z)-NCA with PLX as the macroinitiator.	The newly designed formulation of mixed hydrogels is a promising delivery system for tacrolimus and, perhaps, other highly hydrophobic compounds.

**Table 2.** Summary of research articles about hydrogels as DDSs (continue)

Ref.	Hydrogel	Method	Results
[99]	Zein/poly 4-mercaptophenyl methacrylate-carbon nano-onions hydrogels	Poly 4-mercaptophenyl methacrylate-carbon nano-onions (PMPMA-CNOs = f-CNOs) reinforced natural protein (zein) composites (zein/f-CNOs) were fabricated using the acoustic cavitation technique.	Results suggest that zein/f-CNOs hydrogel could be a potential pH-responsive drug transporter for a colon-selective delivery system.
[100]	CBZ Oral Gel	The CBZ was first prepared as sustained release microparticles, and then the microparticles were embedded in alginate beads, and finally, the beads were suspended in a gel vehicle	CBZ in a gel sustained release dosage form combines the advantages of the suspension form in terms of dosing flexibility, and the advantages of the tablet form in regard to the sustained release profile.

**Figure 4.** Number of articles published yearly about hydrogels and hydrogels as a drug delivery system.

### Future Prospect of Hydrogels

Nowadays hydrogels are an important research topic for biomedical applications and many other applications. It can be predicted that the research related to these materials will increase in the future since the interest given for hydrogels is growing day after day. To support this prediction the following figure was constructed to illustrate the increasing interest of hydrogels generally and hydrogels as a drug delivery system. Figure 3.3 shows the number of articles about hydrogels which were published in science direct website between 2000 and 2020 [101]. The increasing number of articles about hydrogels emphasizes the importance of hydrogels as a promising topic in the future.

### CONCLUSION

In this review, the topics of hydrogels and drug delivery systems were discussed. Hydrogels are very popular materials that are used in drug delivery systems. Nowadays these materials carry great importance in the medical field. Hydrogels managed to attract scientist's attention due to

their unique properties and multiple advantages. In the future it is expected that hydrogels will continue to be the topic of many research in the future. Also, hydrogel's technology will continue to grow and evolve and will be applicable in further applications.

### AUTHORSHIP CONTRIBUTIONS

Authors equally contributed to this work.

### DATA AVAILABILITY STATEMENT

The authors confirm that the data that supports the findings of this study are available within the article. Raw data that support the finding of this study are available from the corresponding author, upon reasonable request.

### CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## ETHICS

There are no ethical issues with the publication of this manuscript.

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