IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
February 2024 Vol.:30, Issue:2

A Review on Hydrogel Based Controlled Drug Delivery System

IJPPR
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ISSN 2349-7203
HUMAN

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Submitted: 19 January 2024
Accepted: 24 January 2024
Published: 29 February 2024

HUMAN JOURNALS
ijppr.humanjournals.com

Keywords: Hydrogels, Controlled release, drug delivery system, Macroscopic design, microgels and nano gels, release mechanism, Drug diffusion coefficient, Applications.

ABSTRACT

This review provides a comprehensive overview of the use of hydrogels in drug delivery systems. It traces the historical development of hydrogels from their first appearance in literature in 1891 to their current applications in regenerative medicine, tissue engineering, and agriculture. The paper discusses the various classifications of hydrogels based on source, composition, structure, cross-linking, and ionic charges, as well as the different techniques for their preparation. Furthermore, it highlights the role of hydrogels in diffusion-controlled, swelling-controlled, and chemically controlled drug delivery systems, and their diverse macroscopic forms for different delivery routes. Additionally, the paper presents a list of research articles covering topics such as self-assembled hydrogels, in situ forming hydrogels, nanogels, and microgels, and their applications in cancer therapy, protein delivery and controlled drug delivery. It also explores the use of hydrogels in various drug delivery routes, including subcutaneous, oral, rectal, and topical/transdermal administration and provides examples of marketed hydrogel products for drug delivery. Overall, this paper serves as a valuable resource for researchers and practitioners interested in the properties, applications, and synthesis of hydrogels in drug delivery.

INTRODUCTION [1-6]

Novel drug delivery systems (NDDS) are one type of pharmaceutical device that has been the subject of much research and development in recent years. A range of physical shapes, such as slabs, microparticles, nanoparticles, coatings, and films, can be created using hydrogel formulations [1]. Because hydrophilic moieties are present in hydrogels, which are hydrophilic polymers, the materials possess a three-dimensional network structure that enables them to absorb substantial amounts of water. Van n Bemmelen was the first to create the word "hydrogel" in 1884. A type of hydrophobic gel known as cross-linked hydroxyethyl methacrylate (HEMA) hydrogels was first presented by Wichterle and Lim in 1960 and was created for biological purposes. Hydrogels are the subject of several studies in the fields of regenerative medicine, drug delivery, tissue engineering, and agriculture [2]. Stimulus-responsive hydrogels based on biopolymers are frequently used as drug carriers that enhance drug release properties. Because natural biopolymers are less expensive, more readily available, non-cytotoxic, and biodegradable than synthetic polymers, their use in controlled drug release applications has grown significantly. However, natural biopolymers do have certain drawbacks, such as microbiological contamination, an uncontrollably high rate of hydration, a decrease in viscosity during storage, etc. The unique properties of hydrogels, such as their controlled drug release behavior and reduction of burst release effects, make them intriguing [3]. Physically cross-linked or reversible hydrogels break down and dissolve during water absorption, whereas chemically cross-linked or permanent hydrogels are robust to deterioration during swelling. Polymers are joined together by hydrogen bonds, ionic bonds, or hydrophobic bonds in physically cross-linked hydrogels, as opposed to covalent bonds in chemically cross-linked hydrogels [4]. Chemical residues like hydroxylic (-OH), carboxylic (-COOH), amidic (-CONH-), primary amidic (-CONH2), sulphonic (-SO3H), and others that are present in the polymer backbone or as lateral chains give it its hydrophilicity network [5]. Fully swollen hydrogels have low interfacial tension with water or biological fluids and a soft, rubbery consistency, which are characteristics of living tissues. After implantation, it has been discovered that the elastic properties of fully hydrated or swollen hydrogels reduce tissue irritation [6].

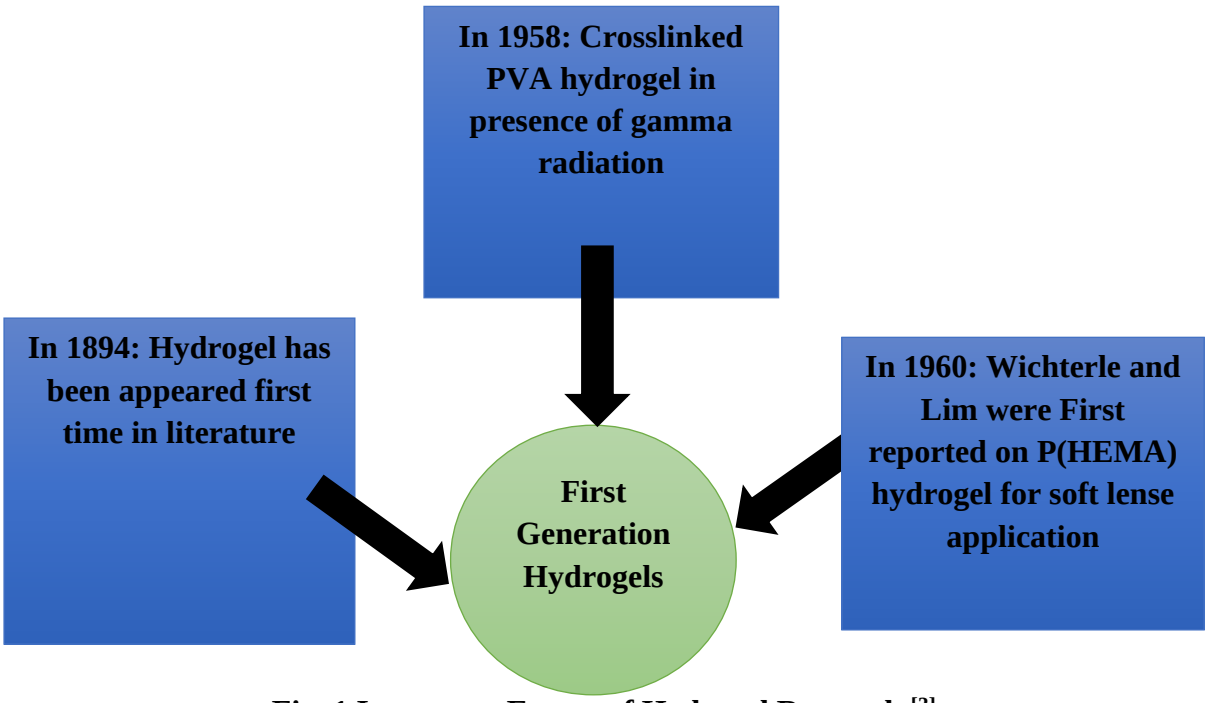

Fig. 1 Important Events of Hydrogel Research [3]

1. CLASSIFICATION OF HYDROGEL[713]

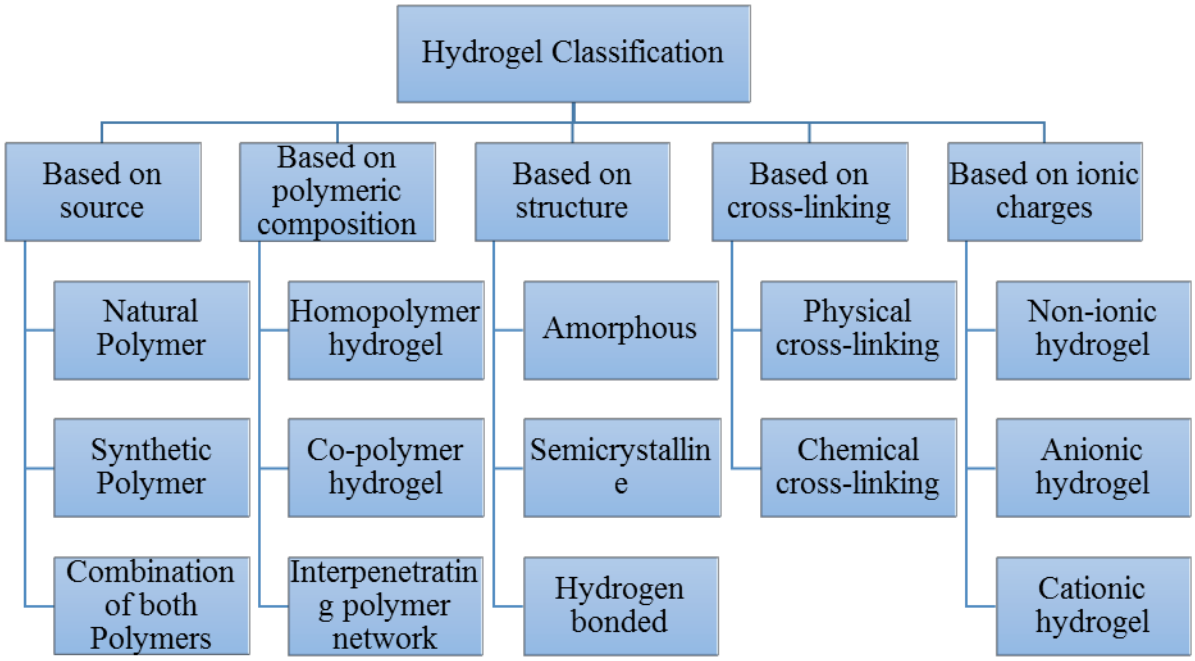

Fig: 2 Classification of Hydrogels

2.1. Based on source

It is possible to produce Hydrogel by using either natural or synthetic and a combination of both polymers.

Natural Polymer	Synthetic Polymer	Combination of both Polymers
Anionic polymers **Alginic acid, pectin**	PEG-PLGA-PEG	Collagen-PEG
Cationic polymers **Chitosan, Polylysine**	PEG-PLA-PEG	Collagen-hydroxyethyl methacrylate
Amphipathic polymers **Collagen, Fibrin**	PEG-PCL-PEG	Alginate-Poly (sodium acrylate-co-acrylamide)
Neutral polymers **Dextran, Agarose**	PLA-PEG-PLA	Collagen-g-poly (acrylic acid)

2.2. Based on the method of polymeric composition

There are three types of compositions:

(I) Homopolymer hydrogel:

They consist of one form of hydrophilic monomer. They frequently have a backbone made of crosslinks. There are several ways to prepare homopolymer hydrogel. For instance, researchers used a novel technique of radiation cross-linking between the polymers Polyvinyl Pyrrolidone (PVP) and Poly (Acrylic Acid) (PAA), containing glucose oxidase as a glucose indicator in a deoxygenated aqueous medium with hydrogen peroxide as a source of free radicals, to create a hydrogel with glucose sensing properties. This method is one of the effective ways to form cross-linked homopolymer hydrogels. The Homo-polymeric cross-linked gel containing glucose oxidase is Frequently used as a glucose detector or in glucose-sensitive equipment [7].

(II) Co-polymer hydrogel:

It is made up of at least two co-monomer species, and at least one of the monomers must be hydrophilic for it to swell. loaded with a quality felt by stimulus Hydrogels are in high

demand and are widely employed as smart materials [8] for optical biosensors, transducers [9], actuators [10].

(III) Interpenetrating polymer network:

Two polymers that are crosslinked between similar molecules but do not create a covalent connection together make up an interpenetrating polymer network. Applications for continuously providing medication over an extended period enhance the interpenetrating polymer network. The amount of cross-linking imparts the ability to administer the medicine in a regulated manner. An interpenetrating polymer network mix microsphere of chitosan and hydroxyethyl cellulose containing isoniazid, an anti-tuberculosis medication, was synthesised and cross-linked with glutaraldehyde to observe the drug release in a controlled way [11]. Angadi et al, Isoniazid microspheres that were created demonstrated extended cumulative release lasting up to 16 hours, delivering up to 75% of the medication with an encapsulation effectiveness of between 50 and 66% [12].

2.3. Based on structure [11]

(I) Amorphous: Macromolecular chains have a random arrangement.

(II) Semicrystalline: Their organized, dense sections of macromolecular chains serve as a distinguishing feature.

(III) Hydrogen bonded: They have a well-known three-dimensional (3D) structure.

2.4. Based on cross-linking:

Hydrogels are classified into two groups based on the forms of cross-linking: chemical and physical cross-linking.

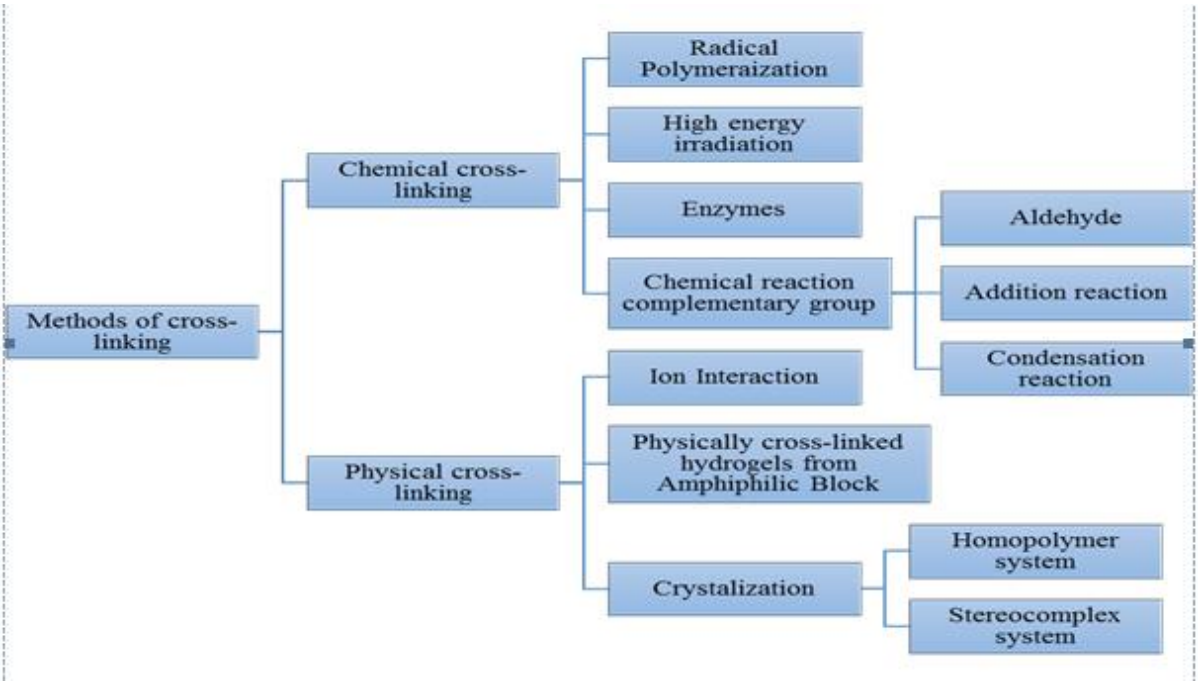

Figure 3: Hydrogels cross-linking [11]

2.5. Based on ionic charges

Hydrogels based on ionic charges are of three types:[13]

a. Non-ionic hydrogel

b. Anionic hydrogel

c. Cationic hydrogel

3. PREPARATION OF HYDROGEL [11,14]

Hydrogel is produced using both chemical and physical cross-linking techniques. Either non-covalent or covalent interactions result in the formation of the cross-linking. Hydrogel Physical gels are the result of processing non-covalent contact, whereas chemical gels are the result of processing covalent interaction [14].

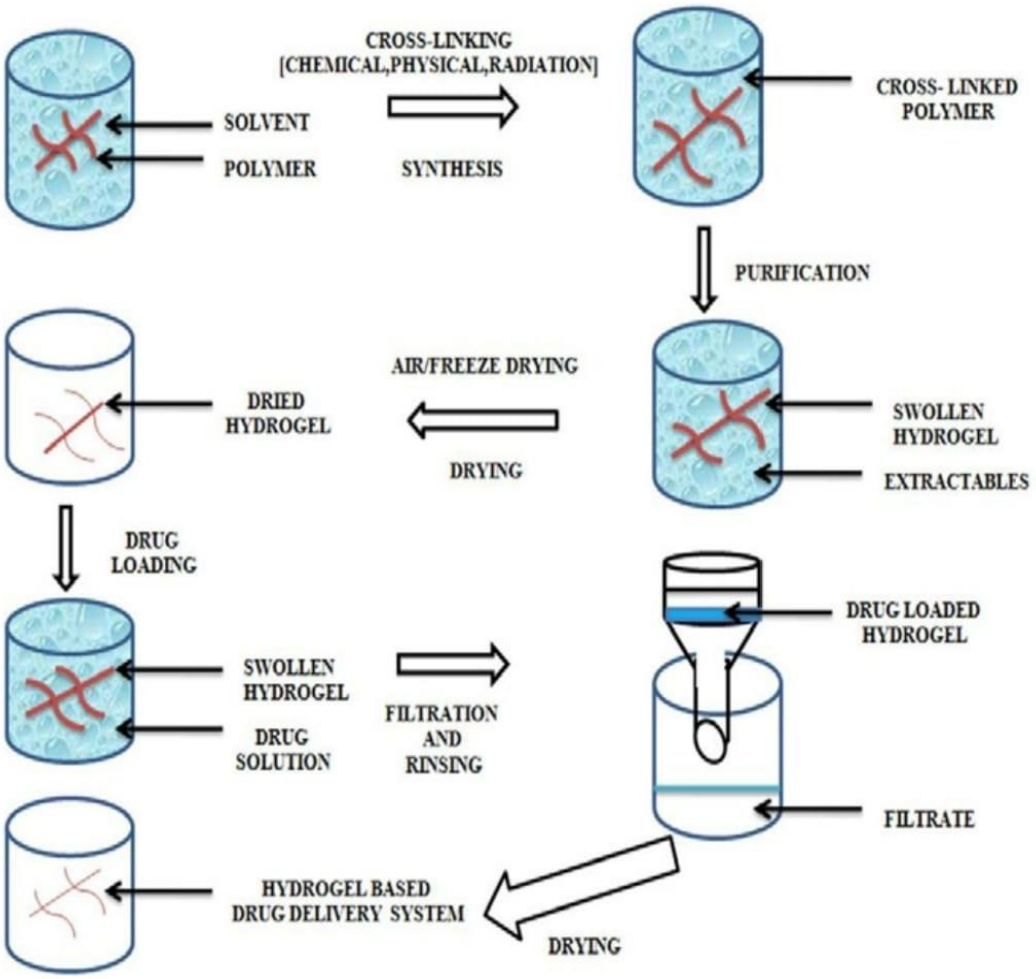

Figure: 4 Method of Preparation of Hydrogel [11]

4. RELEASE MECHANISM

4.1. Diffusion-controlled drug delivery system

Calculations for controlled-release drug diffusivities are based on ideas related to volume, hydrodynamics, or blockage. Diffusion types are separated into two categories: polymer hydrogel membrane and reservoir system [15]. While the drug is completely distributed throughout the polymeric network in a matrix system, the drug core is covered by the polymeric membrane in a reservoir. The crosslinked network's mesh size, which is influenced by several variables including composition, gel structure, crosslinking density, and external stimuli, is primarily responsible for drug diffusion. The mesh size of the polymeric network can range from 50 to 100 nm when the hydrogel is inflated, which is significantly larger than the drug molecules. Diffusion therefore proceeds in the enlarged state [16]. Diffusion-controlled release models typically employ Fick's law of diffusion with constant or variable

diffusion coefficients [17]. It is possible to describe the release of drugs over the membrane using Fick's first rule of diffusion:

$$J_i = -D_{ip}\frac{dC_i}{dX}$$

where, J_i = the molar flux of the drug (mol/cm^2)

C_i = the concentration of drug

D_{ip} = Diffusion coefficient

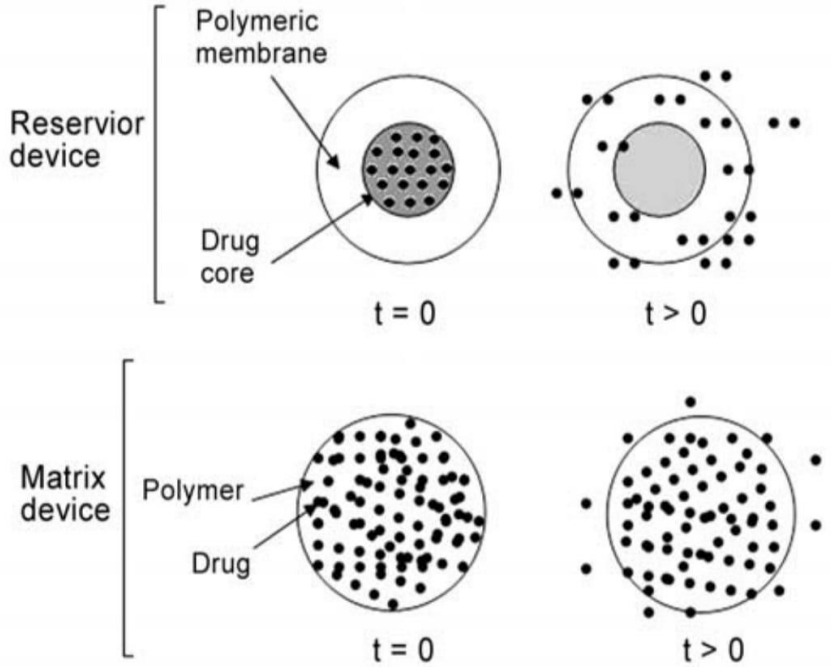

Fig 5: Schematic representation of diffusion-controlled reservoir and matrix devices [1].

4.2. Swelling Controlled delivery system

The rate of swelling in the swelling-controlled hydrogel is substantially slower than that of drug diffusion. This method produces a solvent flux because of the polymer matrix swelling. Glassy polymers are used to dissolve or spread the medication. The swelling occurs in two stages: an inner glassy phase and an outward rubbery phase, which are caused by the polymeric network's interaction with biological fluids. Diffusion of drugs begins in the rubbery phase of the polymer. Swelling-controlled DDS are created by utilizing methyl cellulose and HPMC matrices [16]. The rate-limiting step in diffusion-controlled delivery systems is the drug diffusion time-scale, t (where $t = \delta_{(t)}^2/D$ and $\delta_{(t)}$ is the time-dependent thickness of the swollen phase); in swelling-controlled delivery systems, the rate-limiting step

is the polymer relaxation time-scale, λ. The Deborah number (De) is used to compare these two time scales [1,17].

$$D_e = \frac{\lambda}{t} = \frac{\lambda D}{\delta_{(t)^2}}$$

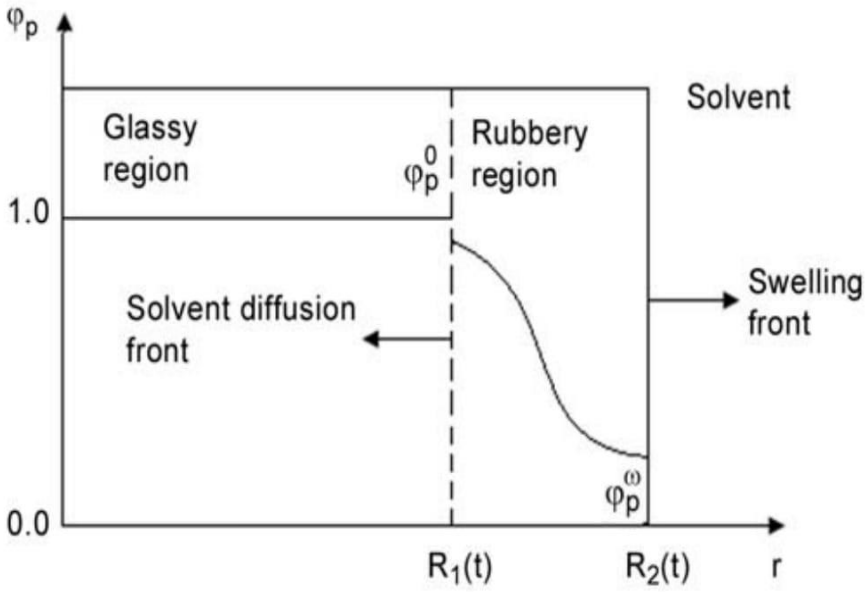

Fig 6: Schematic diagram representing the swelling of the hydrogels with the inward movement of the diffusing front of the solvent [1].

4.3. Chemically Controlled delivery system

The release of molecules that is controlled by reactions that take place inside a delivery matrix is referred to as chemically-controlled release. In hydrogel delivery systems, the most frequent reactions are either reversible or irreversible interactions between the polymer network and releasable drug, or breakage of polymer chains by hydrolytic or enzymatic degradation [18]. This system is either an erodible system or a suspended chain system, depending on the drug release mechanism. Drug release in the erodible system is regulated by the polymer's breakdown and degradation. On the other hand, in a suspended chain system, the drug release is guided by hydrolytic or enzymatic breakdown [17].

5. MACROSCOPIC DESIGN

Almost any size and shape can be achieved by casting or shaping hydrogels to fit the specifications of the delivery pathway into the human body. Based on their size, hydrogel

delivery systems fall into three primary categories: macro-gels, microgels, and nanogels. The size of the hydrogel matters since it can be applied or shaped into nearly any shape or form.

5.1. Macroscopic hydrogels

Macroscopic hydrogel is often surgically inserted into the body [19]. Clinical application has proven successful, as demonstrated by Infuse, a type I collagen gel that secretes recombinant human bone morphogenetic protein and is surgically inserted into the body to treat long bone fractures and spinal fusions [20]. It is also utilized for transepithelial drug administration when it comes into contact with the body [19]. Macroscopic Hydrogel's size is often measured in millimetres or centimeters. There are some categories of delivery routes: (1) Macro-porous gels (2) shear-thinning gels (3) In situ-gelling gels.

5.1.1. Macro-porous gels

Manufacturing sizable hydrogels with interconnected holes that have the ability to physically collapse and recover reversibly is another method for making injectable hydrogels. Here, hydrogel is injected using a syringe and needle. Water is then forced out of the pores, causing the hydrogel to collapse, and allowing the needle to pass through. The hydrogel in the body nearly instantly returns to its original shape after the gel is extruded and the mechanical restriction caused by the needle walls is eliminated. These hydrogels behave similarly to foams and can be reversibly compressed with up to 90% strain without causing the hydrogel network irreversible damage [21]. After gelation, the macropores can facilitate payload integration and cell penetration. The potential of this strategy has been shown by the subcutaneous injection of alginate and gelatin cryogels into mice, which resulted in the regulated delivery of immunomodulatory substances and the regression of pre-existing tumors [22]. These kinds of gel have been made using a variety of techniques that have been documented over time, including microemulsion, gas foaming, and freeze-drying. The volume percentage of polymers and the diffusion length for drug release may be greatly shortened by interconnected pores, which could result in an overly quick release and a limited drug loading capacity [20].

5.1.2. Shear thinning Hydrogels

It is possible to pre-gel some hydrogels outside of the body and then inject them by applying shear force. Under shear tension during injection, these hydrogels behave like low-viscosity fluids, but as soon as the shear stress in the body is removed, they rapidly return to their

original stiffness. This conduct results in physically reversible crosslinks. The dynamic rivalry between pro-assembly forces, which include hydrophobic contacts, hydrogen bonding, π-stacking, and electrostatic interactions, causes physical cross-links to be reversible [23]. To create injectable hydrogels for controlled drug delivery, β¬-hairpin peptides, also known as MAX peptides, were developed. These peptides consist of two blocks of alternative hydrophobic and charged amino acids that form long fibrils up to 200 nm long that can undergo a solution-to-gel transition [24]. Other supramolecular peptide-based hydrogels are being researched for their shear-thinning or self-healing qualities, even though the MAX peptide family is well known for its shear-thinning capabilities. Mechanical stiffness is improved by an increase in hydrophobic contacts between molecules, and shear thinning is also increased by an increase in hydrogen bonding interactions. [25]

5.1.3. In Situ-Gelling Hydrogels

These systems can be injected into the body in liquid form, where they go through a Sol-gel transition. The hydrogels that are produced at the injection site conform to the available space, and several techniques can be employed to accomplish the sol–gel transition. Using slow-gelling technologies, which enable gelation to be started outside the body, is the most straightforward tactic. The solution can be administered prior to solidification because this process moves slowly. The ideal kinetics are both fast enough to stop the pre-gel solution from being diluted by body fluids once it enters the body and slow enough to avoid needle clotting. Michael addition, charge interaction, and stereo-complexation are just a few of the gelation mechanisms that have been used using this approach [26]. Hydrogel formation for growth factor delivery may benefit from the non-covalent interactions between heparin and heparin-binding peptides and proteins [27]. The creation of thermosensitive hydrogels is another tactic being looked at. With a low critical solution temperature over which they transition from the sol phase to the gel phase, injectable thermosensitive hydrogels are a promising kind of biomaterial. Because of these properties, it is simple to encapsulate medicinal drugs by injecting them into the solution phase, which is followed by the hydrogel-forming in situ at body temperature [28]. In situ gelation has also been investigated for temperature-responsive devices that gel at body temperature. Since most naturally occurring polymers, like gelatin, gel at low temperatures, they must be introduced to the body at temperatures above physiological thresholds [20]. The in situ antitumor effects of peptide hydrogels loaded with emodin (EM) [29]. Before drug administration, these systems are injectable solutions, and at the site of drug administration, in situ hydrogels that are either

solid or semi-solid are created. Conditions from the outside, such light, temperature, or pH, induce this phase shift. In this instance, the gelator employed was the RADA16–I peptide. An example of an ionic complementary self-assembling peptide is RADA16–I. The growth of the tumour and the harmful side effects of emodin in normal organs were both considerably inhibited by RADA16-I-EM hydrogels that were produced in situ [29].

5.2. Microgels and Nanogels

An alternate technique for least invasive drug administration is the use of tiny hydrogel particles. The dispersion solvent causes the interior gel-like structure of both nanogels and microgels, which are soft, pliable, and permeable materials, to swell. They are attractive as soft model systems in fundamental research as well as for a wide range of applications, especially in the field of biological applications, because of their softness and capacity to respond to external stimuli like temperature, pressure, pH, ionic strength, and different analytes [30]. Comparing microgels and nanogels to their macroscopic counterparts reveals a few advantages. These gels are so much smaller than a needle's diameter that they can be injected with a needle and have a wide surface area for bioconjugation. As a result, they allow easy natural clearance and can improve penetration through tissue barriers.

The way that hydrogels are transported into blood vessels, the gastrointestinal system, and the airways varies depending on their size. Oral delivery is the normal use for microgels smaller than 5 µm, however intravascular delivery is usually not appropriate for them. Because they can enter small blood arteries through fenestrations in the endothelium lining and extravasate into tissues, nanogels with sizes between 10 and 100 nm are appropriate for systemic drug delivery. Kidney filtration can remove hydrogels with a diameter of less than 10 nm [31]. Nanogels are very helpful in directing medication toward tumours; nevertheless, the removal of nanoparticles is restricted by inadequate lymphatic drainage [32]. It was discovered that cationic nanogels made of poly(ethylenimine) and PEO increased the transport of oligonucleotides through the blood–brain barrier as well as the gastrointestinal epithelium [33].

Microgels can be produced by microfluidics and micro molding methods, and nanogels can be produced using emulsion and nanomoulding techniques [34].

6. APPLICATIONS

Devices based on hydrogel offer a superbly regulated release mechanism. Because of its biochemical characteristics, hydrogels are a superior bio-adhesive substance that works well for transdermal, oral, subcutaneous, and ocular drug delivery.

6.1. Subcutaneous delivery

Subcutaneous injections are among the best ways to gauge how well a medication is working and to determine whether a mouse will develop a toxic response in vivo. Since hydrogels are applied in the vascularized subcutaneous area, they have an immune-privileged effect and only slightly irritate the foreign particle. It has been demonstrated that 60 days after injection, polyethylene hydrogels do not show any cytotoxicity in mouse models. Alginate, pectin, chitosan, poly-acrylamide, and gelatin hydrogels all produced outcomes that were comparable. Because chitosan material does not cause inflammation or immunogenicity, it is favored [35].

6.2. Oral drug delivery

Using a regulated drug delivery system, the body applies therapeutic drugs orally to the oral cavity, stomach, small intestine, or colon. For gastrointestinal tract medicine delivery, clinicians explicitly target this distinct tissue system. When parameters are changeable and patient compliance is guaranteed, this delivery method is the most practical option. Hydrogels that are taken orally need to offer bioavailability based on the specifics of the medium, such as changes in pH throughout the digestive tract [36]. The pH sensitivity and mucoadhesive qualities of chitosan and chitosan-based hydrogels improve the Controlled drug delivery system. Significant pH variation occurs throughout the GI system, with values ranging from 1 to 7.5 [37]. The gels are beneficial for oral administration due to their mucoadhesive qualities. Mucoadhesive and in-situ gelling capabilities have been observed to be the main benefits of using thiolated polysaccharides in gel compositions. [38]

There are some limitations in hydrogel therapy such as:

1. Low permeability through the epithelial membrane into the bloodstream.
2. Superior and inferior digestive systems can represent potential therapeutic targets. [39]

6.3. Rectal Delivery

Rectal administration has several benefits, including regulated release of the substance, minimal adverse responses, quick absorption of the compound, and avoidance of the gastrointestinal tract. Rectal administration of hydrogels with mucoadhesive qualities based on catechol-chitosan has been evaluated in mouse models, and after 10 days, there are no adverse effects observed, based on an earlier work that demonstrated great biocompatibility on the digestive tract [40].

6.4. Topical and Transdermal Delivery

Hydrogel therapy can be either topically or transdermally. Transdermal drug delivery systems can be used to provide medications with low molecular weight and unsuitability for the stomach environment. Because of their high water content, hydrogels have aesthetically pleasing structures that feel good on the skin of the patient and improve compliance during the course of the therapy [41]. Comparing several alternative hydrogel formulations to existing gel-based formulations frequently used in medical settings, graft donors are frequently tested on them and no appreciable adverse effects are observed. Based merely on the diameter, charge, and structure of the nanoparticles, recent research has shown that this delivery strategy is dependable for delivering nanoparticles with different roles [35]. Berberine alkaloid delivery was also accomplished by chitosan hydrogels [42].

7. APPLICATION OF HYDROGEL IN DRUG DELIVERY

Polymer used for manufacturing hydrogel	**Drugs carried within system**	**Application**
Mixture of chitosan and alginate	Bevacizumab	Ocular drug delivery
Polyacrylic acid and gelatin	Vancomycin hydrochloride Gentamycin sulphate	Local drug delivery for antibiotic
Poly (ethylene glycol)-grafted-chitosan	Cyclosporine A	Subcutaneous drug delivery
Quaternized chitosan and poly (ethylene glycol)	Insulin	Nasal drug delivery
P(MAA-g-EG) and P(MAA-co-NVP)	Anti-TNF- α	Transmucosal drug delivery
Copolymer of polyethylene glycol (PEG) onto phthaloyl chitosan	Ciprofloxacin	Pulmonary drug delivery

8. MARKETED PRODUCTS OF HYDROGEL

Product	Product Manufactured by/ marketed by	Hydrogel Composition	Indication	Remarks
SQZ Gel oral release system	Macromed (Sandy, UT, USA)	Chitosan and polyethylene glycol	Hypertension	pH-Sensitive, once-a-day tablet of diltiazem hydrochloride
Hycore-V™ and Hycore-R™	™ CeNeS (Irvine, UK) Drug Delivery	-	Vaginal and rectal infection, respectively	Localized delivery of metronidazole
Cervidil ® Vaginal (PGE2)	Controlled Therapeutics, UK; marketed by insert forest Pharmaceuticals St Louis, MO, USA	Poly (ethylene oxide) and urethane	Initiation and/ or continuation of cervical ripening (at or near term)	The product contains 10mg dinoprostone and exhibits in vivo release rate of 0.3 mg h^{-1}
Smart c Hydrogel	MedLogi Global™ (Plymouth, UK)	Liquid Poly (acrylic acid) (oxypropylene) glycol	Used for development of ophthalmic, buccal, nasal, vaginal and transdermal.	Mucoadhesive composition that undergoes sol-gel transformation at body temperature
Aquamere™	Hydromer (Somerville, NJ, USA)	Interpolymers of PVP and PVP grafted copolymers with urethane	Skincare, topical, and oral drug delivery	-

CONCLUSION

Hydrogels have emerged as versatile materials with a wide range of applications in drug delivery systems. Their ability to absorb water and transition from a liquid to a gel state makes them ideal for the controlled release of drugs. The diverse classifications of hydrogels based on source, composition, and structure, as well as the various techniques for their preparation, offer flexibility in designing drug delivery systems tailored to specific needs. The use of hydrogels in different drug delivery routes, such as subcutaneous, oral, rectal, and topical/transdermal administration, demonstrates their adaptability and potential for commercialization. Additionally, the development of microgels and nanogels for least invasive drug administration further expands the scope of hydrogel applications in drug delivery.

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