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Review Article

A COMPREHENSIVE REVIEW ON HYDROGELS

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ABSTRACT

Polymers play a vital role in pharmaceutical development. Efforts have been continuously made to search a polymer that act in a controlled& desired way. Hydrogel development has solved many such issues. Hydrogels are hydrophilic, three-dimensional networks. Which are able to imbibe large amounts of water or biological fluids & thus resembles to a large extent, a biological tissue. They are insoluble due to the presence of physical or chemical crosslinks such as entanglements& crystallites. These materials can be synthesized to respond to a number of physiological stimuli present in the body, such as PH, ionic strength, temperature. The main aim of this article is to give a concise review on introduction, preparation methods, types, & various applications of hydrogels in the pharmaceutical field.

Keywords: Hydrogels, Types of hydrogels, Preparation methods, Applications.

INTRODUCTION

The existence of hydrogels dates back to 1960 when Wichterle and Lim first proposed the use of hydrophilic networks of poly (2-hydroxyethyl methacrylate) (PHEMA) in contact lenses. Since Then, the use of hydrogels has extended to various biomedical and pharmaceutical applications. In comparison to other synthetic biomaterials, hydrogels resemble living tissues closely in their Physical properties because of their relatively high water content and soft and rubbery Consistency. Several terms have been coined for hydrogels, such as intelligent gels (or) smart gels. Hydrogels are 'smart' or 'intelligent' in the sense that they can perceive the prevailing stimuli and respond by exhibiting changes in their physical or chemical behaviour, resulting in the release of entrapped drug in a controlled manner. By definition, hydrogels are polymeric networks with a three-dimensional configuration capable of imbibing high amounts of water or biological fluids.

Their affinity to absorb water is attributed to the presence of hydrophilic groups such as–OH,–CONH–,–CONH2–, and–SO3H in polymers forming hydrogel structures. Due to the contribution of these groups and domains in the network, the polymer is thus hydrated to different degrees (sometimes, more than 90%wt.), depending on the nature of the aqueous environment and polymer composition. Hydrogels show a swelling behaviour instead of being dissolved in the aqueous surrounding environment as a consequence of the critical crosslink's present in the hydrogel structure. These crosslink's are of two main categories including I) physical (entanglements or crystallites), and ii) chemical (tie-points and junctions). The crosslink's in the polymer network are due to covalent bonds, hydrogen binding, Vander Waals interactions, or physical entanglements [1, 2].

General benefits of hydrogels [3, 4]

- Biocompatible
- Can be injected *in vivo* (in a whole, living organism) as a liquid that then gels at body temperature
- Protect cells
- Good transport properties (such as nutrients to cells or cell products from cells)
- Timed release of medicines or nutrients
- Easy to modify
- Can be biodegradable or bioabsorbable.

General limitations of hydrogels [5-8]

- High cost
- Low mechanical strength
- Can be hard to handle
- Difficult to load with drugs/nutrients
- May be difficult to sterilize
- Non-adherent.

Hydrogel technical features [9]

The functional features of an ideal hydrogel material can be listed as follows:

- The highest absorption capacity (maximum equilibrium swelling) in saline.
- The desired rate of absorption (preferred particle size and porosity) depending on the application requirement.
- The highest absorbency under load (AUL).
- The lowest soluble content and residual monomer.
- The lowest price.
- The highest durability and stability in the swelling environment and during the storage.
- The highest biodegradability without formation of toxic species following the degradation.
- PH-neutrality after swelling in water.
- Colourlessness, odorlessness, and absolutely non-toxic.
- Photostability.
- Re-wetting capability (if required) the hydrogel has to be able to give back the imbibed solution or to maintain it;
- Depending on the application requirement (e. g., in agricultural or hygienic applications).

Preparation methods of hydrogels

1. Use of crosslinkers

- Copolymerization of monomers using multifunctional co-monomer, which acts as cross Linking agent, chemical initiator

initiates the polymerization reaction which can be carried out in bulk, solution or suspension.

❖ Cross-linking of linear polymers by irradiation or by chemical compounds. Monomers used here contain an ionisable group that can be ionized or can undergo a substitution reaction after the polymerization is completed.

❖ Thus, the hydrogels synthesized may contain weakly acidic groups like carboxylic acids or weakly basic groups like substituted amines or a strong acidic and basic group like sulfonic acid and quaternary ammonium compounds.

❖ Cross linkers incorporated are glutaraldehyde, calcium chloride and oxidized konjac glucomannan DAK). They impart sufficient mechanical strength to the polymers and thus prevent burst release of the medicaments.

2. Isostatic ultra high pressure (IUHP)

Suspension of natural biopolymers (eg.-starch) are subjected to an ultra high pressure of 300-700 MPa for5 or 20 min in a chamber which brings about changes in the morphology of the polymer (i.e. gelatinization of starch molecules occur). Temperature in the chamber varies from 40 to 52 °C

3. Use of nucleophilic substitution reaction

A pH and temperature sensitive hydrogel viz. hydrogel of N-2-dimethylamino ethyl meth acrylamide (DMAEMA) has been prepared using nucleophilic substitution reaction between meth acryloyl chloride and 2-dimethylamino ethylamine.

4. Use of gelling agent

Gelling agents like glycophosphate1-2propanediol, glycerol, trehalose, mannitol, etc have been used in the preparation of hydrogels. However, the presence of negatively charged moieties and turbidity are the problems associated with the method.

5. Use of irradiation and freeze-thawing

Irradiation method is suitable as well as convenient, but the processing is costly along with the poor mechanical strength of the product. Freeze-thawing method imparts sufficient mechanical strength and stability to the hydrogels except that they are opaque in appearance with little swelling capacity. However, hydrogels prepared from microwave irradiation are more porous than conventional methods.

6. Synthesis of hydrogel in industry

Formulation of monomer along with initiators and additives lead to polymerization which forms the gel. The gel is dried, sieved and mixed with other additives and post treatment is done if needed. The final formulation is packed and dispatched.

Other methods are mentioned below [10, 11].

The general methods to produce physical& chemical gels are mentioned below:

Physical cross-linking

1. Heating (or) cooling a polymer solution.
2. Ionic interaction.
3. Complex coacervation.
4. Hydrogen bonding.
5. Heat-induced aggregation.
6. Freeze-thawing.

Chemical cross-linking

1. Chemical cross-linkers.
2. Grafting.
3. Chemical grafting.
4. Radiation grafting.

➢ The polymers commonly used in the preparation of hydrogels with pharmaceutical and biological applications are from natural or synthetic origins. Typical examples of natural, synthetic and combinational, i.e., semi-synthetic polymers used in hydrogel preparations are summarized below.

Natural polymers and their derivatives

- Anionic polymers: hyaluronic acid, alginic acid, pectin, carrageenan, chondroitin sulphate, dextrin sulphate.
- Cationic polymers: chitosan, polylysine
- Amphipathic polymers: collagen (and gelatine), carboxy methyl chitin, fibrin
- Neutral polymers: dextrin, agarose, pullulan.

Synthetic polymers

Polyesters: PEG-PLA-PEG, PEG-PLGA-PEG, PEG-PCL-PEG, PLA-PEG-PLA, PHB, P (PFCo-EG) 6 acrylate end groups, P (PEG/PBO terephthalate).

Combinations of natural and synthetic polymers: P (PEG-co-peptides), alginate-g-(PEO-PPO-PEO), P (PLGA-co-serine), collagen-n-acryl ate, alginate-acryl ate, P-(HPMA-g-peptide), HA-g-NIPAAm.

Types of hydrogels

Hydrogels can be classified into two groups depending on the nature of the cross-linking reaction. If the cross-linking reaction involves the formation of covalent bonds, then the hydrogels are termed as *permanent hydrogel*. If the hydrogels are formed due to the physical interactions, viz. molecular entanglement, ionic interaction and hydrogen bonding, among the polymeric chains then the hydrogels are termed as ***physical hydrogels***. Hydrogels can also be categorized as conventional and stimuli-responsive hydrogels. Conventional hydrogels are the cross-linked polymer chains which absorb water when put in an aqueous media and there is no change in the equilibrium swelling with the change in the pH, temperature or electric field of the surrounding environment while the stimuli-responsive hydrogels are the polymeric networks which change their equilibrium swelling with the change of the surrounding environment.

Table 1: Depending up on nature of cross-linking reaction

Type of hydrogel	Example
Permanent hydrogels	PMMA and PHEMA
Physical hydrogels	Polyvinyl alcohol-glycine hydrogels, gelatin gels& agar-agar gels.
conventional hydrogels	
Stimuli-responsive hydrogels	Ethylene-co-vinyl acetate (EVAC), PHEMA.

Table 2: Depending upon method of preparation

Type of hydrogels
Homopolymer hydrogels
Copolymer hydrogels
Multipolymer hydrogels
Interpenetration polymeric hydrogels

Table 3: Other types of hydrogels

Intelligent (or) smart hydrogels
PH sensitive hydrogels
Temperature-sensitive hydrogels
Complexing hydrogels
Insitu hydrogels

Intelligent (or) smart hydrogels

Hydrogels may exhibit swelling behaviour dependent on the external environment. Over the past 30 y there has been a significant interest in the development and analysis of environmentally or physiologically responsive hydrogels. Environmentally responsive materials show drastic changes in their swelling ratio due to changes in their external pH, temperature, ionic strength, nature and composition of the swelling agent, enzymatic or chemical reaction, and Electrical or magnetic stimuli. In most responsive networks, a critical point exists at which this transition. An interesting characteristic of numerous responsive gels is that the mechanism causing the network structural changes can be entirely reversible in nature. The ability of pH-or temperature-responsive gels to exhibit rapid changes in their swelling behaviour and pore structure in response to changes in environmental conditions lend these materials favourable characteristics as carriers for bioactive agents, including peptides and proteins. This type of behaviour may allow these materials to serve as self-regulated, pulsatile drug delivery systems.

pH Sensitive hydrogels

One of the most widely studied types of physiologically responsive hydrogels is pH-responsive hydrogels. These hydrogels are swollen ionic networks containing either acidic or basic pendant groups. In aqueous media of appropriate pH and ionic strength, the pendant groups can ionize developing fixed charges on the gel. All ionic materials exhibit a pH and ionic strength sensitivity. The swelling forces developed in these systems are increased over those of non-ionic materials. This increase in swelling force is due to the localization of fixed charges on the pendant groups. As a result, the mesh size of the polymeric networks can change significantly with small pH changes. Examples: poly (acryl amide), poly (acrylic acid), poly (methacrylic acid).

Temperature-sensitive hydrogels (or) thermo gels

Another class of environmentally sensitive gels exhibits temperature-sensitive swelling behaviour due to a change in the polymer/swelling agent compatibility over the temperature range of interest. Temperature-sensitive polymers typically exhibit a lower critical solution temperature (LCST), below which the polymer is soluble. Above this temperature, the polymers are typically hydrophobic and do not swell significantly in water. However, below the LCST, the cross linked gel swells to significantly higher degrees because of the increased compatibility with water. Examples: poly (n-isopropyl acryl amide).

Complexing hydrogels

Some hydrogels may exhibit environmental sensitivity due to the formation of polymer complexes. Polymer complexes are insoluble, macromolecular structures formed by the non-covalent association of polymers with affinity for one another. The complexes form as a result of the association of repeating units on different chains (inter polymer complexes) or separate regions of the same chain (intra polymer complexes). Polymer complexes are classified by the nature of the association's stereo complexes, polyelectrolyte complexes, or hydrogen-bonded complexes. The stability of the associations is dependent on such factors as the nature of the swelling agent, temperature, type of dissolution medium, pH and ionic strength, network composition and structure, and length of the interacting polymer chains. In this type of gel, complex formation results in the formation of physical cross-links in the gel. As the degree of effective cross-linking is increased, the network mesh size and degree of swelling is significantly reduced. As a result, if hydrogels are used as drug carriers, the rate of drug release will decrease

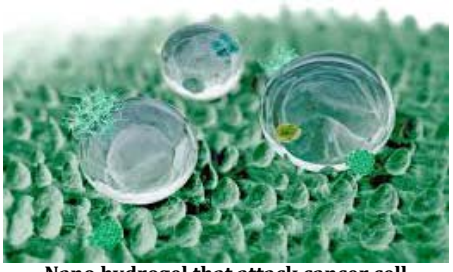
Dramatically up on the formation of inter polymer complexes. Examples: poly (MAA-g-EG).

***Insitu* hydrogels**

Recent advancement in hydrogel engineering has led to the development of *in-situ* hydrogel formation for drug delivery applications. The *in-situ* sol-gel transition enables the surgery or implantation procedure to be performed in a minimally invasive manner. Various physical and/or chemical cross-linking mechanisms have been used for insitu network formation. Physical phenomenon involved in the formation of in-situ hydrogels are as follows:

- Hydrogen bonding
- Hydrophobic–hydrophobic interactions.
- Electrostatic interactions.

For example, sodium alginate hydrogels are formed physically by cross-linking due to addition of calcium ions but are unstable and disintegrate rapidly and Unpredictably. (12-20).



Nano hydrogel that attack cancer cell

Silicon hydrogel contact lens

Self healing hydrogel

Synthetic hydrogels

Applications of hydrogels

Hydrogels have been used for the development of controlled delivery systems for a long time. When the drug bearing hydrogel comes in contact with aqueous medium, water penetrates into the system and dissolves the drug. Diffusion is the main phenomena by which the dissolved drug diffuses out of the delivery systems to the surrounding aqueous medium. The various applications of hydrogels in pharmaceutical & biomedical are given in the following table 4**.**

Application	Polymers used and purpose
	polyurethane, poly(ethylene glycol), poly(propylene glycol), poly(vinyl pyrrolidone), polyethylene glycol and agar
Wound care	Xanthan, methyl cellulose carboxymethyl cellulose, alginate, hyaluronan and other hydrocolloids.
Drug delivery, pharmaceutic	poly(vinylpyrrolidone) starch, poly(vinylpyrrolidone),poly(acrylic acid)carboxymethyl cellulose, hydroxyl propyl methyl cellulose Polyvinyl alcohol, acrylic acid, methacrylic acid glycerophosphate carrageenan, acrylic acid, 2-acrylamido-2methylpropanesulfonic acid Acrylic acid, carboxymethylcellulose.
Dental	Hydrocolloids (Ghatti, Karaya, Kerensis gum).
Tissue engineering	Poly (vinylalcohol), poly (acrylic acid) hyaluronan collagen. Naturalhydrogelmaterials used for tissue engineering include agarose, methylcellulose and other naturally derived products.
Injectable polymeric system	Polyesters, poly phosphazenes, polypeptides, chitosan, heparin peptide.
Technical products (cosmetic, pharmaceutical)	Starch, gum Arabica, xanthem, pectin, carrageenan, gellan, welan, guar gum, locust bean gum, alginate, starch, heparin, chitin and chitosan.
Others (agriculture, waste treatment, Separation, etc.)	Starch, xantham, polyvinyl alcohol poly (vinyl methyl ether), poly (N-isopropyl acrylamide.
Soft contact lens	Silicon hydrogels and polyacrylamide.
Industrial applicability	Hydrogels are used as absorbents for industrial effluents like methylene blue dye. Another example is adsorption of dioxins by hydrogel beads.
Drug delivery in GI track	Hydrogel deliver drugs to specific sites in the GIT. Drugs loaded with colon specific hydrogels show tissue specificity and change in the pH or enzymatic actions cause liberation of drugs. They are designed to be highly swollen or degraded in the presence of micro flora.
Rectal delivery	Hydrogels showing bio adhesive properties are used for rectal drug delivery. Explored the xyloglucan gel with a thermal gelling property as matrices for drug delivery.
Ocular delivery	Silicon rubber hydrogel composite ophthalmic inserts. Developed *in-situ* forming gelling system of alginate with high gluconic acid contents for the ophthalmic delivery of pilocarpine.
Transdermal delivery	Swollen hydrogels can be used as controlled release devices in the field of wound dressing.
Subcutaneous delivery	Hydrogel formulations for subcutaneous delivery of anticancer drugs is being prepared viz. Cross-linked PHEMA were applied to cytarabine (Ara-c). Implantablehydrogelsarenowleadingtowardsthedevelopmentofbiodegradablesystemswhichdon'trequiresurgicalremal once the drug has been administered.
Novel hydrogel for controlled drug delivery	HYPAN is the novel hydrogel having properties useful controlled drug delivery. Physical network of crystalline clusters distinguishes HYPAN hydrogels from others.
Hydrogels for gene delivery	Modification of hydrogel composition leads to effective targeting and Delivery of nucleic acids to specific cells for gene therapy. Hydrogel versatility has potential application in the treatment of many genetic and/or acquired diseases and condition.
Cosmetology	Hydrogels, when implanted into breast, accentuate them for aesthetic reasons. These implants have silicon elastomeric shell and are filled with hydroxyl propyl cellulose polysaccharide gel.
Tropical drug delivery	Instead of conventional creams, hydrogel formulation is employed to deliver active components like Desonide, a synthetic corticosteroid used as an anti–inflammatory for better patient compliance.
Protein drug delivery	Interleukins conventionally administered as injection are now given as hydrogels which show better compliance and form *in-situ* polymeric network and release proteins slowly.

CONCLUSION

Hydrogels have played a significant role in biomedical applications. Significant progress has been made in improving the properties of hydrogels used for drug delivery and expanding the range of drugs and kinetics which can be achieved using a hydrogel based delivery vehicle. Reduced release efficiency, burst effects, complex geometries and the unknown correlation between *in vitro* and *in vivo* release complicates our understanding of these devices. There is need for continued improvement in the delivery of not only hydrophobic molecules but also the delivery of more sensitive molecules viz. proteins, antibodies or nucleic acids which gets deactivated by interactions with the hydrogel delivery vehicle. Solution of such problems would greatly expand the potential of hydrogel-based drug delivery to successfully deliver the next generation drugs at the desired rate and location in the body. In the recent times newer methods of preparation of hydrophilic polymers and formulation of hydrogels have shown immense potential in drug delivery applications. Recently, many hydrogel based networks have been designed and tailored to meet the needs of different applications.

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ABBREVIATION

PEG-poly (ethylene glycol), PLA-poly (lactic acid), PLGA-poly(lactic-co-glycolic acid), PLC-poly (caprolactone), PHB-poly (hydoxybutyrate), PF-propylene fumarate, EG-ethylene glycol, PBO-poly(butyleneoxide), PHPMA-poly(hydroxypropyl methacrylamide), PMMA-poly(methyl methacrylate), HA-hyaluronic acid.

CONFLICT OF INTERESTS

Declare none

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