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A hydrogels: Methods of preparation and applications

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Abstract

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of absorbing large amounts of water or biological fluids. Due to their high water content, porosity and soft consistency, they closely simulate natural living tissue, more so than any other class of synthetic biomaterials. Skin is the largest organ of human body and drug delivery through this route is called transdermal drug delivery system. This route of drug administration is used for local as well assystemic delivery of drug. In this review article an attempt has been made to explain the advantages, disadvantages, classification of hydrogels, methods of preparation and applications and future challenges in hydrogel based drug delivery system.
Keywords: Hydrogel, Skin, Gels.

1. Introduction

The hydrogel technologies may be applied to food additives, pharmaceuticals, biomedical implants tissue engineering and regenerative medicines, diagnostics, cellular immobility, separation of biomolecules or cells and barrier materials to regulate biological adhesions, Biosensor and BioMEMs devices and drug carriers. Additionally the ever growing spectrum of functional monomers and macromeres widen its applicability.

Hydrophilic gels called hydrogels are cross-linked materials absorbing large quantities of water without dissolving. Softness, smartness, and the capacity to store water make hydrogels unique materials. The ability of hydrogels to absorb water arises from hydrophilic functional groups attached to the polymer backbone while their resistance to dissolution arises from cross-links between network chains. Water inside the hydrogel allows free diffusion of some solute molecules, while the polymer serves as a matrix to hold water together. Another aspect of hydrogels is that the gel is a single polymer molecule, that is, the network chains in the gel are connected to each other to form one big molecule on macroscopic scale. It is natural to expect that the conformational transitions of the elastically active network chains become visible on the macroscopic scale of hydrogel samples. The gel is a state that is neither completely liquid nor completely solid. These half liquid-like and half solid-like properties cause many interesting relaxation behaviors that are not found in either a pure solid or a pure liquid. From the point of view of their mechanical properties, the hydrogels are characterized by an elastic modulus which exhibits a pronounced plateau extending to times at least of the order of seconds, and by a viscous modulus which is considerably smaller than the elastic modulus in the plateau region.

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of absorbing large amounts of water or biological fluids. Due to their high water content, porosity and soft consistency, they closely simulate natural living tissue, more than any other class of synthetic biomaterials. Hydrogels may be chemically stable or they may degrade and eventually disintegrate and dissolve [1-4].

Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous

manifestations of a general disease (e.g. psoriasis) with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin. Topical gels are transparent or translucent semisolid formulations containing a high ratio of solvent/gelling agent.

Thus, hydrogels can imbibe water nearly 10-20 times its molecular weight and hence become swollen. Some examples of Hydrogels include contact lenses, wound dressing super absorbents. 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. Hydrogels can be prepared from either natural or synthetic polymers. Natural polymers include dextran, alginate, and pectin and chondroitin sulphate While synthetic polymers include, poly(vinyl alcohol), poly(hydroxyl ethyl methacrylate) , poly(ethylene oxide) and poly (N-isopropylacrylamide)Either natural or synthetic polymers indivually have some advantages and disadvantages, but by combining natural and synthetic polymers the physical and biocompatibility properties like in IPN and semi IPN increase.

The properties of a hydrogel depend strongly on the interaction of water and the polymer. The former prevents the polymer aggregating to form a compact mass while the polymer prevents water flowing out.

Semi-interpenetrating polymer networks (semi-IPN) is a way of blending two polymers where only one is cross-linked in the presence of another to produce an additional non-covalent interaction between the two polymers. Semi-IPNs have been developed as a convenient technique for preparing multi-polymeric material and provided an alternative option to modify the properties of natural polymer-based hydrogels [5-7].

1.1. Advantages of Hydrogels[5-7].

1) Posse's high degree of flexibility similar to natural tissues.
2) Bio compatible, bio degradable and that is why they can be injected.
3) Applied locally so by passing first pass metabolism
4) Sustained and prolonged action in comparison to conventional drug delivery systems
5) Decreased dose of administration.
6) Decreased side-effects.
7) Improved drug utilization.
8) Improved patient compliance.
9) Drug targeting to specific site like colon.
10) Protection of mucosa from irritating drugs.
11) Drug loss is prevented by extensive first pass metabolism.
12) Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
13) Drug adapts to suit circadian rhythms of body functions or diseases.
14) Easy to modify
15) Timed release of growth factors and other nutrients to ensure proper tissue growth
16) Entrapment of microbial cells within polyurethanehydrogel beads with the advantage of low toxicity
17) Environmentally sensitive hydrogels have the ability to sense changes of pH, temperature or the concentration of metabolite and release their load as result of such a change.
18) Natural hydrogel materials are being investigated fortissue engineering, which include agarose, methylcellulose, hylaronan, and other naturally derived polymers.
19) Hydrogels also possess good transport properties and easy to modify.
20) Hydrogel is more elastic and stronger than available hydrogels of similar softness. Poly (methyl acrylate-cohydroxyethylacrylate) hydrogel implant material of strength and softness.

1.2. Disadvantages of Hydrogels [5-7].

1) They cause a sensation due to the movement of maggots.
2) In case of contact lenses cause lens deposition, hypoxia, dehydration, and eye reactions.
3) These are the high cost and the sensation felt by movement of the maggots.
4) Its disadvantage includes thrombosis at anastomosis sites and then surgical risk associated with the device implantation and retrieval.
5) Disadvantages of hydrogel in contact lenses are lens deposition, hypoxia, dehydration and red eye reactions.
6) The main disadvantage of hydrogel is that they are non-adherent and may need to be secured by a secondary dressing and also causes sensation felt by movement of the maggots. Hydrogels have low mechanical strength and difficult to handle and are expensive.

2. Desired features of hydrogel material [2,3]

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

1) Must have highest absorption capacity (maximum equilibrium swelling) in saline.
2) Must show desired rate of absorption (preferred particle size and porosity) depending on the application requirement.
3) Must exhibit the highest absorbency under load (AUL).
4) Should show lowest soluble content and residual monomer.

5) Have lowest price.
6) Must have highest durability and stability in the swelling environment and during the storage.
7) Must have highest biodegradability without formation of toxic species following the degradation.
8) PH-neutrality after swelling in water.
9) Colorless, odorless, and absolutely non-toxic.
10) Must have good photo stability.
11) Re-wetting capability (if required) the hydrogel has to be able to give back the imbibedsolution or to maintain it; depending on the application requirement (e.g., in agricultural orhygienic applications)
12) Drug should have a molecular weight of less than 500 Daltons.
13) Drug must have adequate hydrophilicity.
14) A saturated aqueous solution of the drug should have a pH value between 5 and 9.
15) Drug highly acidic or alkaline in solution is not suitable for topical delivery.

3. Preparation methods of hydrogel [2,10]

Based on the methods of preparation, hydrogels may be classified as

A) Homo polymer

B) Copolymer

C) Semi interpenetrating network

D) Interpenetrating network

A) **Homopolymer:**

These are referred to polymer network derived from a single species of a monomer, which is a basic structural unit comprising of any polymer network. Homopolymers may have cross-linked skeletal structure depending on the nature of the monomer and polymerization technique.

B) **Copolymer :**

These are comprised of two or more different monomer species with at least one hydrophilic component, arranged in a random, block or alternating configuration along the chain of the polymer network.

C) **Multipolymer Interpenetrating Polymeric Hydrogel (IPN)**:

An important class of hydrogels, is made of two independent cross-linked synthetic and/or natural polymer components, contained in a network form. In semi-IPN hydrogel, one component is a cross linked polymer and other component is a non-cross-linked polymer.

D) **Interpenetrating Network**

They are the combination of two polymers. From which at least one is synthesized or cross linked in the presence of other. In this type of reaction method a polymerization initiator and suitable monomers are placed in a solution and then immersing a pre polymerized hydrogel completes the reaction method. This method produced hydrogels which are stiffer, tougher mechanical properties and more efficient drug loading than conventional methods of hydrogel preparation.

4. Classification of hydrogel products [8,12]

The hydrogels can be broadly classified on different bases as detailed below and Table 1:

4.1. Classification based on source

Hydrogels can be classified into two groups based on their natural or synthetic origins.

4.2. Classification according to polymeric composition

The method of preparation leads to formations of some important classes of hydrogels. These can be exemplified by the following:

4.2.1 Homopolymer hydrogels

4.2.2 Copolymer hydrogels

4.2.3 Multipolymer interpenetrating polymeric hydrogel (IPN),

4.3. Classification based on configuration

The classification of hydrogels depends on their physical structure and chemical composition can be classified as follows:

4.3.1 Amorphous (non-crystalline)

4.3.2 Semicrystalline: A complex mixture of amorphous and crystalline phases

4.3.3 Crystalline

4.4. Classification based on type of cross-linking

Hydrogels can be divided into two categories based on the chemical or physical nature of the cross-link junctions.

4.4.1 Chemically cross-linked networks have permanent junctions.

4.4.2 While physical networks have transient junctions that arise from either polymer chain entanglements or physical interactions such as ionic interactions, hydrogen bonds, or hydrophobic interactions.

4.5. Classification based on physical appearance

Hydrogels appearance as matrix, film, or microsphere depends on the technique of polymerization involved in the preparation process.

4.6. Classification according to network electrical charge

Hydrogels may be categorized into four groups on the basis of presence or absence of electrical charge located on the cross-linked chains:

4.6.1 Nonionic (neutral).

4.6.2 Ionic (including anionic or cationic).

4.6.3 Amphoteric electrolyte (ampholytic) containing both acidic and basic groups.

4.6.4 Zwitterionic (polybetaines) containing both anionic and cationic groups in each structural repeating unit.

4.7. Classification according to mechanism controlling the drug release they are classified into:

4.7.1 Diffusion controlled release systems
4.7.2 Swelling controlled release systems
4.7.3 Chemically controlled release systems
4.7.4 Environment responsive systems

5. Hydrogels in drug delivery

Hydrogels were studied as antibiotics and anticancer drug delivery depots soon after their discovery. Initial studies concentrated on polyHEMA, withlater studies focused on hydrogels based on HEMA copolymers, polyacrylamide, N-vinylpyrrolidonecopolymers, and polyvinyl alcohol. HEMA hydrogels were studied as matrices for proteindelivery. Different chemical structures have beentailor-made to match the physiological need. For example, HPMA copolymer based hydrogels were synthesized with entrapped anticancer drugs or containing degradable oligopeptide crosslinks and the drug (DOX) bound via a degradable oligopeptide spacer. Various natural polysaccharides were used for drug delivery, poly-alginate hydrogels were designed to permit combination delivery of anticancer drugs with different release profiles [1,4,5, 8]

Hydrogels now a day are more attracted because of their controlled as well as sustained release of drugs. They are able to release the drugs at suitable and targeted sites. Hydrogels are utilized in a number of ways as described below and Table 2.

5.1 Wound healing

Hydrogels are cross linked materials they have the ability to hold water and drug inthem. Due to their water holding ability they can hold and retain wound exudates. Gelatin and sodium alginate based hydrogels when applied have the ability to cover and protect the wound from bacterial infection.

5.2 Hydrogels for eye

According to estimation 75 % of ophthalmic solution is lost due to then also acrimal drainage and the desired bioavailability of the drug decreases. Some other factors like the blinking tear drainage also effects drug bioavailability. These hydrogelsare 100 % safe and are implanted under conjunctiva. Xyloglucan based gel is used for sustained delivery of pilocarpine and timolol in eye.

5.3 Hydrogels for transdermal drug delivery

Hydrogels when utilized by topical transdermal have many advantages like they bypass the hepatic metabolism, thusincreases drug efficacy and bioavailability. For achieving a constant drug release transdermal drug delivery system is used. Hydrogels as they are swollen and resemble living tissues can be easily removed rather than the other dosage forms like patches, ointments. Transdermal drug delivery is usedto administer drugs systemically as well as for topical disorders like for delivery ofgluocorticoid budesonide transdermal hydrogels are prepared. Poloxamer 407based novel hydrogels contain in ggentamycin are more effective in treating skin infections, rather than the gentamycin parentral administration causing serious disorders.

5.4 Vaginal route

Drugs to be administered through vagina must be in the form of like creams, suppositories, gels, foams or tablet formulations. Vaginal route of drug administration have many advantages of bypassing the hepatic metabolism. Due to thelarge surface area of vagina there is an increase in the systemic drug absorption. Drugs with high molecular weights are permeable due to vaginal epithelium. Natural progesterone's bioavailability decreases due to the hepatic metabolism so vaginal route isthe preferable one. Flat faced disk containing bleomycin anticancer drug cross-linked with carbopol 934 and hydroxyl propyl cellulose releases the drug for over 23 hours.

5.5 Oral route

Oral route have many advantages like it is easily accessible. Oral route is used for local viral and fungal infections. This route also reduces the first pass metabolism. A mucosal adhesive tablet of lidocaine was formulated by combining carbopol 934, hydroxypropyl cellulose, and magnesium sterate. Tablet having a diameter of 1 cm and thickness of 2 mm.

5.6 Gastro Intestinal Tract

G.I tract is most common and popular route of drug administration. G.I tract is also usedto deliver drugs locally. Famotidine anti-ulcerdrug used for local effects. Sustained release gastro retentive hydrogels are made to increase the effects and bioavailability of poorly absorbed oral drugs.

5.7 Hydrogels for Brain

Like other barriers in human body, bloodbrain barrier is also a challenge for drug delivery. About 98 % of the newlysynthesized drugs fail to cross this barrier. Due to that reason a low number of drugs are present for drug delivery for CNS. Long term sustained effect of camptothecin loaded with PLGA microspheres was observed in rats. These microspheres increase the survival period in rats against malignant gliomas.

5.8 Soft Contact Lenses

The first commercially available silicon hydrogels adopted two different approaches. First approach by Bausch and Lomb was a logical extension of its development of silicon monomers with enhanced compatibility in hydrogel forming monomers. The second by Ciba vision was the development of siloxy monomers containing hydrophilic polyethylene oxide segments and oxygen permeable polysiloxane units.

5.9 Industrial Applicability

Hydrogels are used as absorbents for industrial effluents like methylene blue dye. Another example is adsorption of dioxins by hydrogel beads.

5.10 Tissue Engineering

Micronized hydrogels are used to deliver macromolecules (phagosomes) into cytoplasm of antigen-presenting cells. This property is also utilized in cartilage repairing. Natural hydrogel materials used for tissue engineering include agarose, methylcellulose and other naturally derived products.

5.11 Rectal Delivery

Hydrogels showing bioadhesive properties are used for rectal drug delivery. Miyazaki et al explored the xyloglucan gel with a thermal gelling property as matrices for drug delivery.

5.12 Subcutaneous Delivery

Hydrogel formulations for subcutaneous delivery of anticancer drugs are being prepared viz. crosslinked PHEMA was applied to cytarabine (Ara-c). Implantable hydrogels are now leading towards the development of biodegradable systems which don't require surgical removal once the drug has been administered.

5.13 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**.**

5.14 Hydrogel 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 conditions.

5.15 Cosmetology

Hydrogels when implanted into breast accentuate them for aesthetic reasons. These implants have silicon elastomer shell and are filled with hydroxyl propyl cellulose polysaccharide gel.

5.16 Topical Drug Delivery

Instead of conventional creams, hydrogel formulations are employed to deliver active components like Desonide, a synthetic corticosteroid used as an anti – inflammatory for better patient compliance Table 3.

5.17 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.

Table 1: Classification of gels

Sr. No	Colloidal phase	Nature of solvent	Rheological properties	Physical nature
1	Inorganic	Hydrogel	Plastic gel	Elastic gel
2	Organic	Organic gel	Pseudo plastic gel	Rigid gel
3	-	Xerogel	Thixotropic gel	-

Table 2: Hydrogel structure

Sr. No.	Structure	Range	Release mechanism
1	Macro porous	0.1-10um	Depend on drug diffusion coefficient
2	Micro porous	100-1000um	Molecular Diffusion and convection
3	Non-porous	10-100	Diffusion

Table 3: Topical Formulations

Liquid preparation	Semisolid preparation	Solid preparation	Miscellaneous preparation
Liniment	Ointments	Topical	Transdermal drug delivery
Lotions	Cream	Powder	Tapes and Gauzes
Paint	Pastes	Poultices	Rubbing alcohol
Topical solution	Gels	-	Liquid cleanser
Topical tincture	Poultices	-	Topical aerosol

6. Design criteria for hydrogels in drug delivery formulations

Nature of material and network fabrication governs the rate and mode of drug release from hydrogel matrices. There are various design criteria for drug that must be evaluated before hydrogel fabrication and drug loading. These criteria play a vital role in Mathematical modeling of drug release. Design criteria for hydrogels in drug delivery formulations are shown in the table 4.

Table 4: Design criteria for hydrogels

Sr. No.	Design criteria	Design variables
1	**Polymer transport properties** Molecule diffusion	Molecular weight of polymer Molecular weight and size of protein Cross linking density Hydrogel degradation rate
2	**Physical properties** Gelling mechanism/conditions Structural properties Biodegradability	Polymer/cross-linker/initiator concentration Temperature, Ph, ionic strength Molecular properties of polymer Mechanical strength
3	**Biological properties** Biocompatibility	Cytotoxicity of the hydrogel Capsule formation

Hydrogel formulation even designed with proper physical and transport properties, may still fail to show therapeutic effect when implanted in vivo due to localized inflammatory response. Fibrous capsule formed around the delivery device gives rise to additional diffusion barriers that may limit drug release rates while increased photolytic activity may increase rates of matrix and drug degradation. Thus, proper material selection, fabrication process and surface texture are important parameters in designing biocompatible hydrogel formulations for controlled release. Drug incorporation into hydrogel device can be achieved by one of the following methods.

7. Application of hydroge [2,5,8,13]

1. Superior biocompatibility
2. Good oxygen permeability
3. Low protein adsorption and cell adhesion
4. Aqueous surface environment to protect cells and therapeutic drugs (peptides, proteins,oligonucleotides, DNA)
5. Minimal frictional irritation within the surrounding tissues upon implantation
6. Soft and tissue-like physical properties
7. Micro-porous structure for additional transport channels
8. Ease of surface modification with specific biomolecules
9. Can be injected in vivo as a solution that gels at body temperature.
10. Soft Contact Lenses
11. Industrial Applicability
12. Tissue Engineering

8. The future challenges for hydrogel

Recent advances in the development of neutral and ionic hydrogels for drug delivery applications have concentrated on several aspects of their synthesis, characterization and behavior. Major questions that have been addressed or are presently researched in our work include:

1) Synthetic methods of preparation of hydrophilic polymers with desirable functional groups.
2) Synthetic methods of preparation of multifunctional or multiarm structures including branched or grafted copolymers and star polymers.
3) Understanding of the criticality and the swelling/syneresis behavior of novel anionic or cationic polymers.
4) Development of ultrapure polymers, such as cross-linked free PVA gels produced by freezing - thawing of aqueous solutions.
5) Synthesis and characterization of biomimetic hydrogels.
6) Understanding of the relaxational behavior during dynamic swelling.
7) Modeling of any associated dissolution or biodegradation.

New promising methods of delivery of chemotherapeutic agents using hydrogels have been recently reported. For example, bio recognition of various sugar-containing copolymers can be used for the release of chemotherapeutic agents. Kopeck and associates have used poly (N-2-hydroxypropyl Meth acrylamide) carriers for the release of a wide range of such agents. For example, we have synthesized self-organized nanostructures based on triblock copolymers that may have applications in controlled drug delivery. Novel biodegradable polymers include polyrotaxanes, which are considered to be particularly exciting molecular assemblies for drug delivery.

In the last few years, there have been new creative methods of preparation of hydrophilic polymers and hydrogels that may be used in the future in drug delivery applications. Dendrimers and starpolymers are exciting new materials because of the large number of functional groups available in a very small volume other hydrogels with great promise as drug delivery vehicles include neutral gels of PEO or PVA, and gels of star molecules and other complex structures. Some examples of hydrogel formulation are show in the table-5.

Table 5: Hydrogel Formulation

Drug	Category	Route of administration	Application	References
Nicotine	Stimulant	Transdermal	Agar	Conaghey et al.(1998)[41]
Loratadine	Antihistamine	Topical	Carbapol980	Capkova et al.(2006)[42]
Diclofenac Sodium	Anti-inflammatory	Oral	Sodium alginate	Qin and Andaiquinwang(2009)[43]
Silymarine	Antioxidant	Oral	Sodium alginate	EL-Sherbiny et al.(2011)[44]
Bovine Serum	Protein	Oral	HPMC	Nochis et al.(2008)[45]
Prazocine Hydrochloride	Antihypertensive	Transdermal	Sodium alginate	Raghvendra et al.(2010)[46]

9. Conclusion

Hydrogel polymers have enabled them to find extensive applications in traditional, modern, and novel pharmaceutical area. Desirable hydrogel properties for a given application can be achieved by selecting a proper hydrogel material, crosslinking method, as well as processing techniques. The synthesis of new polymers and cross linkers with more biocompatibility and better biodegradability would also be essential for successful applications. It is also expected that principles from the expanding research area will be applied to design novel types of hydrogels. Hydrogels have found extensive applications in various fields including drug delivery, tissue engineering, regenerative medicine, barrier materials to regulate biological adhesions, contact lenses, membrane separation and adhesives. The discovery of hydrogels brings new transformations in the field of drug delivery because of their enormous properties likeporosity, resemblance to natural tissues, biocompatibility and high permeability rate for oxygen and essential nutrients, tunable viscoelasticity and high water holding capacity.

Conflict of Interest Statement

We declare that we have no conflict of interest.

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