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Hydrogels: Introduction, Preparation, Characterization 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. Furthermore, hydrogels can be formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. As a result, hydrogels are commonly used in clinical practice and medicine for a wide range of applications, including Tissue engineering and Regenerative medicine, Diagnostics, Cellular immobilization, separation of biomolecules or cells, and barrier materials to regulate biological adhesions. Hydrogels are also relatively deformable and can conform to the shape of the surface to which they are applied. In the latter context, the mucoadhesive or bioadhesive properties of some hydrogels can be advantageous in immobilizing them at the site of application or in applying them on surfaces that are not horizontal. They have started to create a niche in several fields of medicine like in specific site drug delivery, tissue reconstruction and tissue engineering and even as biosensors. In this review article an attempt has been made to explain the properties of hydrogels, their methods of preparation and its applications.

INTRODUCTION

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of absorbing large amounts ofwater 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].

They are prepared from materials such as gelatin, polysaccharides, cross-linked polyacrylamide polymers, polyelectrolyte complexes, and polymers or copolymers derived from methacrylate esters. They are insoluble in water and are available in dry or hydrated sheets or as a hydrated gel in drug delivery systems designed for single use [11].

Furthermore, hydrogels can be formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. As a result, hydrogels are commonly used in clinical practice and medicine with a wide range of applications, including Tissue Engineering and Regenerative Medicine, Diagnostics, Cellular immobilization, Separation of biomolecules or cells, and barrier materials to regulate biological adhesions [3].

These unique physical properties of hydrogels have stimulated particular interest in their use in drug delivery applications. Their highly porous structure can easily be tuned by controlling the density of cross-links in the gel matrix and the affinity of the hydrogels for the aqueous environment in which they are swollen [3].

Their porosity also permits loading of drugs into the gel matrix and subsequent drug release at a rate dependent on the diffusion coefficient of a small molecule or a macromolecule through the gel network [3].

Since the polymer cannot dissolve due to the covalent crosslinks, water uptakes far in excess of those achievable with hydrophilic linear polymers can be obtained [14].

Indeed, the benefits of hydrogels for drug delivery may be largely pharmacokinetic – specifically that a depot formulation is created from which drugs elute slowly, maintaining a high local concentration of drug in the surrounding tissues over an extended period of time, although they can also be used for systemic delivery [3].

Hydrogels are also generally highly biocompatible, which may be attributed to the high water content of hydrogels. Biodegradability or dissolution in case of hydrogels may be brought about by enzymatic, hydrolytic, or environmental (e.g. pH, temperature, or electric field) pathways; however, degradation is not always desirable depending on the time frame and location of the drug delivery device [3].

Hydrogels are relatively deformable and can conform to the shape of the surface onto which they are applied. In the latter context, the mucoadhesive or bioadhesive properties of some hydrogels can be advantageous by keeping them immobilized at the site of application or in applying them on surfaces that are not horizontal. However the amount and homogeneity of drug loading into hydrogels may be limited, particularly in the case of hydrophobic drugs.The high water content and large pore sizes of most hydrogels often result in relatively rapid drug release, over a period of few hours to a few days. Ease of application can also be problematic; although some hydrogels are sufficiently deformable to be injectable, many are not, necessitating surgical implantation [3].

Above problems restrict the practical use of hydrogel-based drug delivery systems in the clinical practice [3].

Classification of hydrogel products

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

1) Classification based on source

Hydrogels can be classified into two groups based on their natural or synthetic origins [5].

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:

(a) **Homopolymeric hydrogels** 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 [5].

(b) **Copolymeric hydrogels** 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 [5].

(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 [5].

3) Classification based on configuration

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

(a) Amorphous (non-crystalline)
(b) Semicrystalline: A complex mixture of amorphous and crystalline phases
(c) Crystalline [5]

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.

(a) Chemically cross-linked networks have permanent junctions.

(b) 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 [5].

5) Classification based on physical appearance

Hydrogels appearance as matrix, film, or microsphere depends on the technique of polymerization involved in the preparation process [5].

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:

(a) Nonionic (neutral).
(b) Ionic (including anionic or cationic).
(c) Amphoteric electrolyte (ampholytic) containing both acidic and basic groups.
(d) Zwitterionic (polybetaines) containing both anionic and cationic groups in each structural repeating unit [5].

7) Classification according to mechanism controlling the drug release they are classified into:

a. Diffusion controlled release systems
b. Swelling controlled release systems
c. Chemically controlled release systems
d. Environment responsive systems [5]

IMPORTANT PROPERTIES OF HYDROGEL

1) Swelling properties

All polymer chains in hydrogels are cross linked to each other either physically or chemically and thus, considered as one molecule regardless of its size. For this reason, there is no concept of

molecular weight of hydrogels and therefore, sometimes called infinitely large molecules or super macromolecules [2].

One of the variables that effects capacity of water absorption is the degree of cross linking and the type of cross linking agent used [2].

A small change in environmental condition may trigger fast and reversible changes in hydrogel. The alteration in environmental parameters like pH, temperature, electric signal, presence of enzyme or other ionic species may lead to a change in physical texture of the hydrogel [2].

These changes may occur at macroscopic level as precipitate formation, changes in size and water content of hydrogels [2].

The amount of the aqueous medium incorporated in a hydrogel is determined gravimetrically and can be expressed by its swelling ratio

$$\text{Swelling} = \frac{Ws - Wd}{Wd}$$

Where, Ws is the weight of hydrogel in swollen state and Wd is the weight of hydrogel in dry state [8].

The difference in concentration of mobile ions in the hydrogel interior relative to external solution (osmotic pressure), changes in solvent pH, drives the volume change. Hydrogels with acidic or basic functional groups respond to the fluctuations in the external environmental pH. Degree of ionization of the functional groups dictates its swelling profile and hence the volume changes [2].

2) Mechanical properties

Mechanical properties of hydrogels are very important from the pharmaceutical and biomedical point of view. The evaluation of mechanical property is essential in various biomedical applications viz. ligament and tendon repair, wound dressing material, matrix for drug delivery, tissue engineering and as cartilage replacement material. The mechanical properties of hydrogels

should be such that it can maintain its physical texture during the delivery of therapeutic moieties for the predetermined period of time [2].

By changing the degree of crosslinking the desired mechanical property of the hydrogel can be achieved. Increase in the degree of crosslinking, a stronger hydrogel can be obtained through the higher degree of crosslinking decreases the % elongation of the hydrogels creates a more brittle structure [2].

3) Biocompatible properties

It is important for the hydrogels to be biocompatible and nontoxic in order to make it applicable in biomedical field. Most polymers used for this purpose must pass cytotoxicity and *in-vivo* toxicity tests [2].

Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application. Biocompatibility studies consists of two parameters namely biosafety and biofunctionality:

(a) Biosafety i.e. appropriate host response not only systemic but also local (i.e. surrounding tissue), the absence of cytotoxicity, mutagenesis, and/or carcinogenesis and

(b) Biofunctionality i.e. the ability of material to perform the specific task for which it is intended.

This definition is particularly relevant in tissue engineering since the nature of tissue construct is to continuously interact with the body through the healing and cellular regeneration process as well as during scaffold degradation [2].

Furthermore, initiators, organic solvents, stabilizers, emulsifiers, unreacted monomers and crosslinkers used in polymerization and hydrogel synthesis may be toxic to host cells if they seep out to tissues or encapsulated cells [2].

To remove hazardous chemicals from preformed gels, various purification processes should be followed such as solvent washing or dialysis [2].

Evaluation of biocompatibility

1) *In vitro* cell culture tests are often used to screen the tissue compatibility of implantable devices. The cell culture methods are also known as cytotoxicity tests. Three primary cell culture assays are used to evaluate biocompatibility of the hydrogels:[2]

a) Elution (extract dilution)

b) Direct contact

c) Agar diffusion

These assays are described in the US Pharmacopeia and in standards published by the International Standards Organization [2].

The *in vivo* assessment of tissue compatibility of a hydrogel is the knowledge of chemical composition of the biomaterial and the conditions of tissue exposure (including nature, degree, frequency and duration of exposure). Principles generally applied to the biological evaluation of hydrogels are described as follows:

The material(s) of manufacture; Intended additives, process contaminants, and residues; Leachable substances; Degradation products; other components and their interactions in the final product determine the properties and characteristics of the final product [2].

Most of the problems associated with hydrogel regarding toxicity, are the unreacted monomers, oligomers and initiators that leach out during application [2].

Modifying the kinetics of polymerization and extensive washing of the resulting hydrogel can reduce the toxicity. The formation of hydrogels without any initiators and using alternate path like radiation may eliminate the problem of the residual initiator [2].

Technologies adopted in the preparation of hydrogels

In general, hydrogels can be prepared from either synthetic polymers or natural polymers. The synthetic polymers are hydrophobic in nature and chemically stronger compared to natural polymers. Their mechanical strength results in slow degradation rate, but on the other hand,

mechanical strength provides the durability as well. These two opposite properties should be balanced through optimal design [5].

Water-soluble linear polymers of both natural and synthetic origin are cross-linked to form hydrogels in a number of ways:[5]

1. Linking polymer chains via chemical reaction.
2. Using ionizing radiation
3. Physical interactions such as entanglements, electrostatics, and crystallite formation.

In general, the three integral parts of the hydrogels preparation are monomer, initiator, and cross-linker.

To control the heat of polymerization and the final hydrogels properties, diluents can be used, such as water or other aqueous solutions [5].

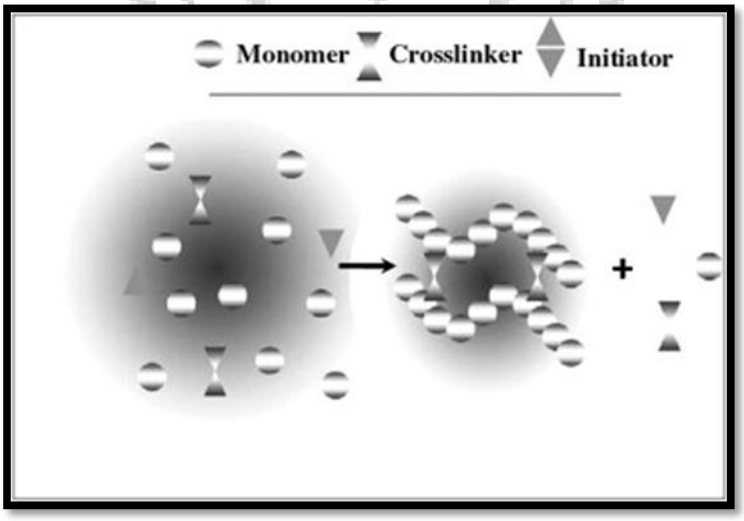


Fig. 1. Schematic diagram of hydrogel preparation

Hydrogels are usually prepared from polar monomers. According to their starting materials, they can be divided into natural polymer, synthetic polymer, and combinations of the two [5].

1) Bulk polymerization

Many vinyl monomers can potentially be used for the productions of hydrogels. Bulk hydrogels can be formed with one or more types of monomers. Usually, a small amount of cross-linking agent is added to hydrogel formulation. The polymerization reaction is normally initiated with radiation, ultraviolet, or chemical catalysts [5].

The choice of a suitable initiator depends upon the type of monomers and solvents being used. The polymerized hydrogel may be produced in a wide variety of forms including films and membranes, rods, particles, and emulsions [5].

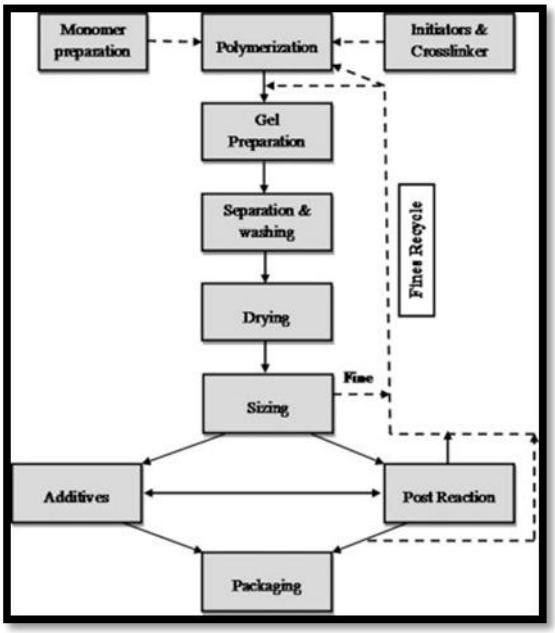
Bulk polymerization is the simplest technique, which involves only monomer and monomer-soluble initiators. The viscosity of reaction increases markedly with the conversion which generates the heat during polymerization. These problems can be avoided by controlling the reaction. The bulk polymerization of monomers to make a homogeneous hydrogel produces a glassy, transparent polymer matrix which is very hard. When placed in water, the glassy matrix swells to become soft and flexible [5].

2) Solution polymerization/cross-linking

In solution copolymerization/cross-linking reactions, the ionic or neutral monomers are mixed with the multifunctional cross-linking agent. The polymerization is initiated thermally by UV-irradiation or by a redox initiator system [5].

The prepared hydrogels need to be washed with distilled water to remove the monomers, oligomers, cross-linking agent, the initiator, the soluble and extractable polymer, and other impurities. Phase separation occurs and the heterogeneous hydrogel is formed when the amount of water during polymerization is more than the water content corresponding to the equilibrium swelling [5].

Typical solvents used for solution polymerization of hydrogels include water, ethanol, water–ethanol mixtures, and benzyl alcohol [5].



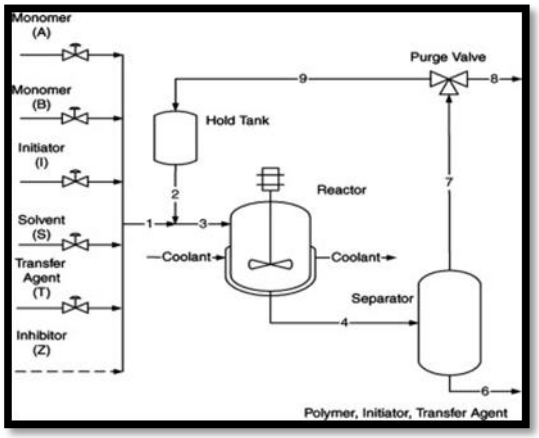
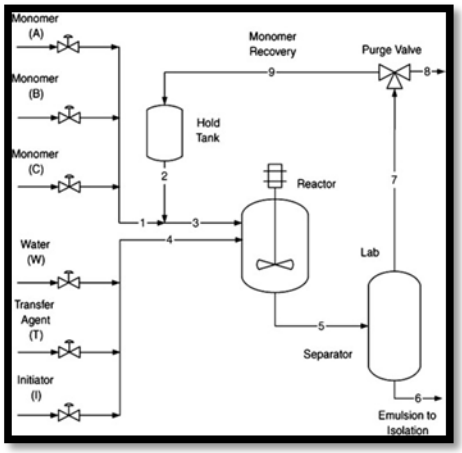


Fig. 2. Hydrogel preparation block diagram Fig. 3. Solution polymerization with (solution polymerization/cross-linking procedure) recycle loop

3) Suspension polymerization or inverse-suspension polymerization

Dispersion polymerization is an advantageous method since the products are obtained as powder or microspheres (beads), and thus, grinding is not required. Since water-in-oil (W/O) process is chosen instead of the more common oil-in-water (O/W), the polymerization is referred to as "inverse-suspension" technique [5].

In this technique, the monomers and initiators are dispersed in the hydrocarbon phase as a homogenous mixture. The viscosity of the monomer solution, agitation speed, rotor design, and dispersant type mainly governs the resin particle size and shape. The dispersion is thermodynamically unstable and requires both continuous agitation and addition of a low hydrophilic–lipophilic-balance (HLB) agent [5].



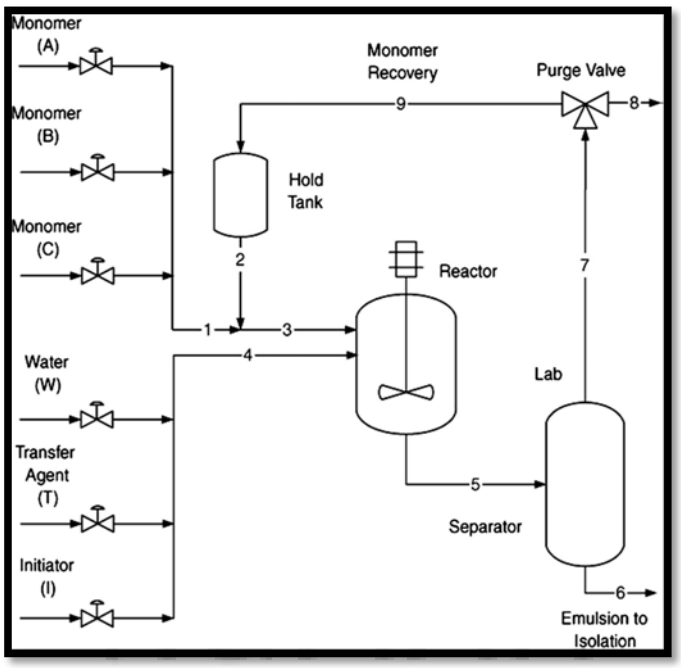


Fig. 4. Suspension terpolymerization process with recycle loop

4) Polymerization by Irradiation

Ionizing high energy radiations like gamma rays and electron beams have been used as an initiator to prepare the hydrogels of unsaturated compounds. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains. Also, radiolysis of water molecules results in the formation of hydroxyl radicals, which also attack the polymer chains, resulting in the formation of macro-radicals [5].

The major advantage of the radiation initiation over the chemical initiation is the production of relatively pure and initiator-free hydrogels [5].

5) Grafting to a support

Generally, hydrogels prepared by bulk polymerization have inherent weak structure. To improve the mechanical properties of a hydrogel, it can be grafted on surface coated onto a stronger support. This technique involves the generation of free radicals onto a stronger support surface and then polymerizing monomers directly onto it as a result a chain of monomers are covalently bonded to the support [5].

Desired features of hydrogel material

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

- ✓ Must have highest absorption capacity (maximum equilibrium swelling) in saline.
- ✓ Must show desired rate of absorption (preferred particle size and porosity) depending on the application requirement.
- ✓ Must exhibit the highest absorbency under load (AUL).
- ✓ Should show lowest soluble content and residual monomer.
- ✓ Have lowest price.
- ✓ Must have highest durability and stability in the swelling environment and during the storage.
- ✓ Must have highest biodegradability without formation of toxic species following the degradation.
- ✓ pH-neutrality after swelling in water.
- ✓ Colorless, odorless, and absolutely non-toxic.
- ✓ Must have good photo stability.
- ✓ 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) [7].

Extending the effectiveness of hydrogels for drug delivery

The high water content of most hydrogels typically results in relatively rapid release of drugs from the gel matrix over the period of hours or days, particularly in the case of hydrophilic drugs for which hydrogel delivery is typically applied. The release profile is much shorter than those which can be achieved using microspheres or macroscopic devices based on more hydrophobic polymers (for example, PLGA). In response, a range of strategies have been explored to reduce the release rate of drug from hydrogels. These strategies can be categorized by whether they enhance the interactions between the drug and the hydrogel matrix and/or increase the diffusive barrier to drug release from the hydrogel [3].

I) Drug–hydrogel interactions

Both physical and chemical strategies can be employed to enhance the binding between a loaded drug and the hydrogel matrix to extend the duration of drug release, as illustrated schematically in the Fig. 5 [3].

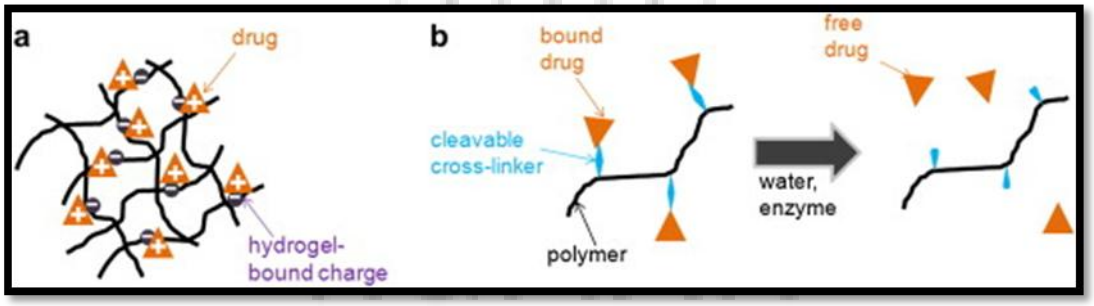


Fig. 5. Physical (a) and chemical (b) strategies for enhancing the interaction between a loaded drug and a polymeric gel to slow drug release.

a) Physical interactions

Charge interactions between ionic polymers and charged drugs have frequently been employed to increase the strength of the interactions between the gel and a target drug to delay drug release [3].

Both anionic and cationic functional groups typically found in carbohydrate-based polymers can have significant effects on prolonging the release of a drug of opposite charge [3].

b) Covalent bonding

Drugs can also be covalently conjugated to the hydrogel matrix such that their release is primarily controlled by the rate of chemical or enzymatic cleavage of the polymer–drug bond [3].

Drug release may be regulated via the hydrolysis of the polymer backbone, possibly inducing the release of a partially modified drug analogue. For example, methacrylic-functionalized non-steroidal anti-inflammatory drugs have been conjugated to methacrylic-functionalized dextrans via UV irradiation. The cross-linker can be engineered to give specific durations of release [3].

II) Gel network engineering

A simple method of performing such modifications is to increase the percentage of cross-linking monomer incorporated into the gel. However, highly cross-linked gels exhibit very slow responses to environmental stimuli and may possess undesirable mechanical properties. As a result, more sophisticated strategies may be required [3].

a) Interpenetrating polymer networks (IPNs)

An interpenetrating polymer network is formed when a second hydrogel network is polymerized within a pre-polymerized hydrogel.

This is typically done by immersing a pre-polymerized hydrogel into a solution of monomers and a polymerization initiator. IPNs can be formed either in the presence of a cross-linker to produce a fully interpenetrating polymer network (full IPN) or in the absence of a cross-linking mechanism to generate a network of embedded linear polymers entrapped within the original hydrogel (semi-IPN). Dense hydrogel matrices can be produced with stiffer and tougher mechanical properties, more widely controllable physical properties, and (frequently) more efficient drug loading compared to conventional hydrogels [3].

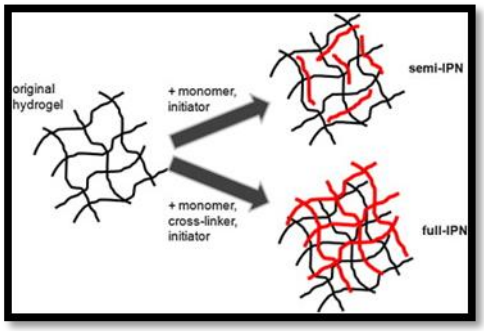


Fig. 6. Formation and structure of semi- and full interpenetrating polymer networks (IPN)

IPNs can also moderate the effect of environmental changes on hydrogel responses and burst drug release effect because of their ability to restrict the equilibrium swelling of either or both of the interpenetrating phases according to the elasticity (i.e. cross-linking density) of either or both gel phases [3].

b) Surface diffusion control

As an alternative to changing the bulk structure of a hydrogel, surface-specific modifications can be performed to generate a reduced-permeability "film" layer at the hydrogel surface, often in conjunction with a thermosensitive switch for on–off drug release [3].

By using this mechanism, thermosensitive PNIPAM polymers can be grafted onto the surface of hydrogels to provide temperature-dependent surface permeability. Drug release is rapid at low temperatures but is significantly slowed down at higher temperatures as the thermosensitive polymer undergoes a phase transition and collapses onto the hydrogel surface. Alternately, a drug-loaded hydrogel can be coated with a dense polyelectrolyte multilayer film, limiting drug diffusion out of the bulk hydrogel [3].

The rate of diffusion can be designed to be dependent on the pH of the medium, the degradation rate of the film, or the environmentally controlled swelling state of the coated hydrogel, which can exert mechanical pressure on the coating to cause film rupture and thus burst drug release at site of target organ [3].

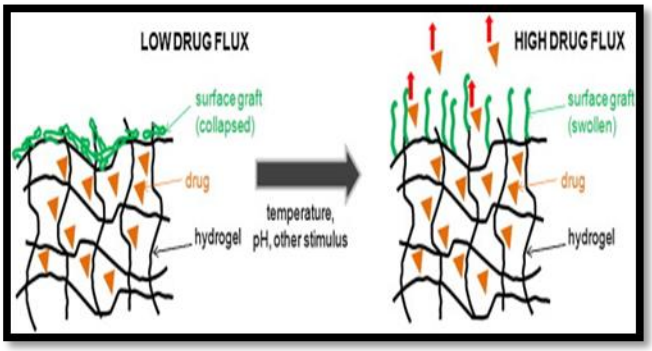


Fig. 7. Surface diffusion control

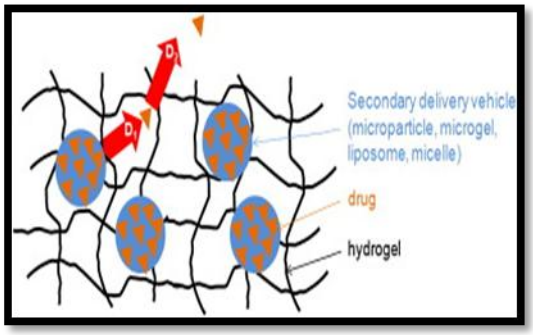


Fig. 8. Composite hydrogel

D_1 = release from entrapping secondary release vehicle

D_2 = diffusion through hydrogel

c) Composite hydrogels

Microspheres, liposomes, and other types of particulate drug delivery vehicles have proven capacity for long-term release. As a result, growing interest has focused on overcoming the inherent pharmacological limitations of hydrogels by co-formulating particulate systems into the hydrogel matrix to form composite or "plum pudding" hydrogel networks, as illustrated in the Fig. 8 [3].

The formation of composite hydrogel drug release vehicles may increase the biocompatibility of the particulate vehicle by "hiding" the microparticles within the hydrogel and also preventing microparticle migration away from their targeted site *in vivo* [3].

The hydrogel phase may also improve the kinetic release profile of microspheres by providing an additional diffusion barrier to drug release, moderating or eliminating the burst release typically observed with microspheres and extending release of drugs [3].

Surfactant-stabilized microemulsion droplets, surfactant micelles, and polymeric micelles can similarly be entrapped in hydrogel networks to provide prolonged drug release. Polymeric micelles based on block copolymers have particular promise due to their lower toxicity given the absence of small-molecule surfactants or organic solvents [3].

Expanding the range of drugs amenable to hydrogel-based delivery

Classically, hydrogels have been used to deliver hydrophilic, small-molecule drugs which have high solubility in both the hydrophilic hydrogel matrix and the aqueous solvent swelling the hydrogel [3].

In this case, it is relatively simple to load a high quantity of drug into a swollen hydrogel by simple partitioning from a concentrated aqueous drug solution and subsequently release the hydrophilic drug into an aqueous environment [3].

However, this process is relatively inefficient in the case of large macromolecular drugs (e.g. proteins, nucleic acids, etc.) which have diffusive limitations to their partitioning into a hydrogel phase or hydrophobic drugs which are sparingly soluble in both the aqueous and the hydrogel phases [3].

Both of these classes of drugs, however, are becoming increasingly important clinically as a result of improved understanding of the molecular basis of disease and the more frequent application of molecular design approaches for small-molecule drug design. Macromolecular drug uptake is typically restricted by the diffusion of the macromolecular drug payload through the hydrogel network and thus can be addressed at least partially by engineering the pore size of hydrogels [3].

Hydrogel-based hydrophobic drug delivery is in many respects a more difficult problem given the inherent incompatibility of the hydrophilic hydrogel network and the hydrophobic drug. Thus, the problem of hydrophobic drug delivery is two-fold: how to load the hydrophobic drug into the gel matrix and, once present, how to effectively release the drug into the aqueous gel environment [3].

A variety of strategies for introducing hydrophobic domains directly into otherwise hydrophilic hydrogel networks have permitted significant improvements in the loading of hydrophobic drugs. These basic strategies are illustrated schematically below [3].

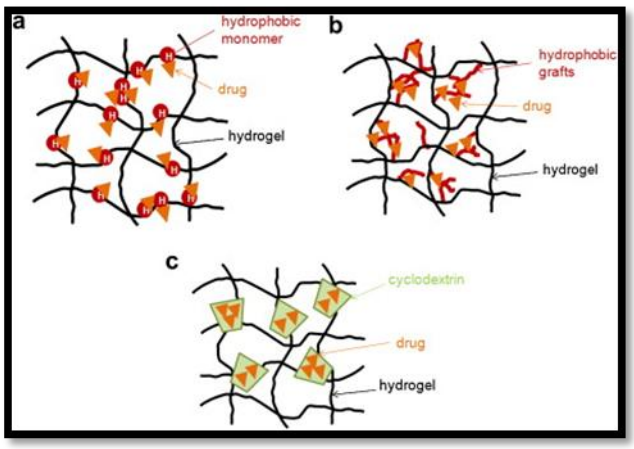


Fig. 9.Strategies for hydrophobic drug delivery via hydrogels (a) random copolymerization of a hydrophobic monomer; (b) grafting of hydrophobic side-chains; (c) incorporation of cyclodextrin

a) Incorporation of hydrophobic sites

The most common approach for generating hydrophobic domains within hydrogels is the copolymerization with hydrophobic comonomers, introducing statistically distributed hydrophobic sites within the networks. This strategy introduces binding sites for hydrophobic drugs and condenses the bulk dimensions of the gel, reducing the average pore size and slowing diffusion-limited release [3].

Applications

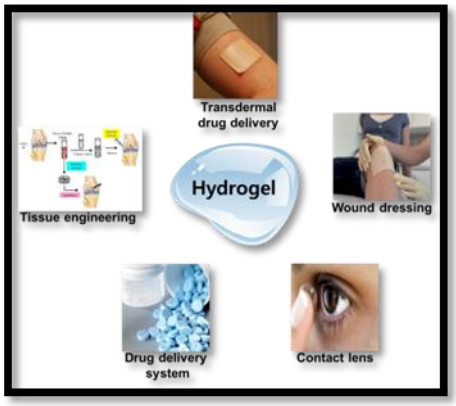


Fig. 10. Several applications of hydrogels

Biomedical applications of hydrogels

1) Contact lenses and ocular implants

Soft contact lenses are one of the most widely used applications of hydrogels. One of the main characteristics is the comfort since the hydrogel perfectly adapts to the global ocular curvature. Also they allow atmospheric oxygen to reach the cornea by dissolving in the water of lens [6].

The PHEMA-based hydrogels are extensively used as soft contact lenses due to their excellent biocompatibility and mechanical properties. Several companies subsequently developed a range of hydrogel contact lens materials containing various monomers such as N-VP, MAA, MMA and glyceryl methacrylate among others which are incorporated to increase the water content of hydrogel contact lens, in the attempt to obtain materials with suitable mechanical properties, which allow them to resist the force of the eyelid along with an elevated permeability to oxygen [6].

Medicated contact lenses are attracting keen interest for ophthalmic drug delivery, as they significantly increase residence time of the drug in the precorneal area because of the geometric barrier provided by the contact lenses to the drug when it diffuses out from the gel matrix into the tear film [6].

2) Tissue regeneration and tissue engineering

Hydrogels have a micro-architecture similar to that of natural extracellular matrix (ECM hence these have been utilized to support and assist restoration of range of tissues such as bones, cartilage, nerves, vessels and skin [6].

Scaffolds act as three-dimensional artificial templates in which the tissue targeted for reconstruction is cultured to grow onto. The high porosity of hydrogel allows for the diffusion of cells during migration, as well as the transfer of nutrients and waste products away from cellular membranes [6].

The micronized hydrogels (microgels) have been used to deliver macromolecules like phagosomes into cytoplasm of antigen-presenting cells. The release is because of acidic

conditions. Such hydrogels mold themselves to the pattern of membranes of the tissues and have sufficient mechanical strength. This property of hydrogels is also used in cartilage repairing [10].

Examples of various tissue engineering employing various hydrogels have been provided below: Collagen-coated tissue culture inserts are used for growing three- dimensional corneal implant, tracheal gland cells etc. [12].

Poly (lactic-co-glycolic acid) (PLGA) polymer foams are seeded with preadipocytes for the epithelial cell culture of the breast. [12]

Porous scaffolding (e.g. filter, swatch of nylon, transwell, biodegradable microcarrier) coated with fibrillar collagen, ideally type III collagen mixed with fibronectin or with Matrigel are used for the culture of the normal mature liver cells (polyploidy liver cells) [12].

There is a growing interest in using hydrogels in the regeneration of the central nervous system. Chemically cross-linked PHEMA tube shave been created by synthesizing centrifugal force; the outer diameter of these tubes is 2.4 mm and wall thickness is 40-400 um, which could be used for guided regeneration in the nervous system [6].

3) Biosensors

Hydrogels are used in the preparation of biosensors, acting as supports for immobilization of enzymes. The microenvironment that surround the immobilized enzyme can act as a barrier for the free diffusion of molecules but it also may attract or repel the substrate or product to its surface thus concentrating or depleting the immediate vicinity of the enzyme. The Verones group has prepared diverse biosensors for enzyme immobilization, one of them being an amperometric sensor constructed by using PEG modified glucose oxidase immobilized in a PVA cryogel membrane, obtained by a freezing-thawing cyclic process. This sensor allows for determination of glucose electrochemically by measuring the hydrogen peroxide production as a result of the enzymatic reaction, which can be used in the determination of serum glucose. In view of the importance of sugar in foods and beverage industries, it is rather important to have e a detection method that is simple, sensitive and fast. Thus a biosensoric method of fructose determination has been developed based on polymer matrix of Polyethyleneimine (PEI) and

Polycarbamoylsulphonate hydrogel used for immobilization of the enzyme D-fructose dehydrogenase [6].

4) Wound dressings

Hydrogel dressings are available in several forms including amorphous hydrogels (that can take up the shape of the wound), saturated gauzes or hydrogel sheets. Hydrogels that are shapeless or amorphous are composed of insoluble non-crosslinked hydrophilic polymers such as polyvinyl pyrrolidine or polyacrylamide in the form of a gel containing 70-95% water. Amorphous hydrogels may be packaged in tubes, spray bottles or foil packs. The gel is applied directly to the wound and is usually covered with a secondary dressing (for example foam or gauze). Exudate is absorbed into the gel whilst moisture evaporates through the secondary dressing [9].

Saturated gauzes, obtained when gauze is impregnated with amorphous hydrogel, are sometimes used to fill the dead space in deeper wounds [9].

Hydrogel sheets do not need a secondary dressing as a semi-permeable polymer film backing which may or may not have adhesive borders, controls the amount of water vapour transmitted through the dressing [9].

They are nonadherent dressings that through semipermeable film allow a high rate of evaporation (and cooling) without compromising wound hydration. This makes them useful in burn treatment. Hydrogels are also very useful in hairy are where entrapment of hair into the dressing would not be traumatic [16].

Poultice is a drug-in-adhesive type of TDS and is very popular in eastern countries. The hydrogel PSA is a base adhesive for poultice, as well as for skin care cosmetic sheets [15].

5) Oral

The oral administration of drugs through hydrogels is one of the routes that have aroused the highest interest among researchers, which have tackled this form of administration, mainly through two strategies [6].

One of these strategies is the development of mucoadhesive hydrogels that interact with mucous as a result of physical entanglement and secondary bonding, mainly through hydrogen bonding and Van der Waals forces, due to the presence of hydroxyl, carboxyl, amine, and amide groups on the surface of polymeric matrix, thus prolonging the residence time of the dosage form on the absorption site [6].

The use of buccal cavity for placing devices of controlled drug release allows it to avoid the first-pass metabolism and prevents degradation of the drug in the GIT [6].

Another area of the GI tract being considered for hydrogel drug delivery is the colon. One advantage that the colon has is that there is less proteolytic activity there compared to the small intestine. Various hydrogels, particularly enzyme-sensitive hydrogels, are currently being considered and developed for use in colon-specific drug delivery [7].

Rectal Delivery has been used to deliver many types of drugs for treatment of diseases associated with the rectum, such as hemorrhoids. This route is an ideal way to administer drugs suffering heavy first-pass metabolism [5].

6) Super porous hydrogel systems

These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro miter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material [13].

7) Sealant

Research into the use of self-healing hydrogels has revealed an effective method for mitigating acid spills through the ability to selectively crosslink under acidic conditions. Research carried out by the University of California San Diego, various surfaces were coated with self-healing hydrogels and then mechanically damaged with 300 micrometer wide cracks with the coatings

healing the crack within seconds upon exposure to low pH buffers. The hydrogels also can adhere to various plastics due to hydrophobic interactions. Both findings suggest the use of these hydrogels as a sealant for vessels containing corrosive acids [4].

CONCLUSION

Hydrogels are hydrophilic polymeric networks which are capable of absorbing large amounts of water or biological liquids, due to which they are widely being used in the medical industry as dressings and even in tissue regeneration and tissue engineering.

Vast improvements have been made in the properties of hydrogels used in drug delivery. However further improvements needs to be made to improve the applicability of hydrogels. Further progress needs to be achieved in the delivery of hydrophobic molecules. Progress and success in such aspects would significantly improve the delivery of drugs through hydrogels to certain desired locations in the body.

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