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HYDROGEL AS A PROMISING DRUG DELIVERY SYSTEM: AN OVERVIEW

A. Sarvaiya and *P. Bhargava
Shrinathji Institute of Pharmacy, Nathdwara (Raj.)

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ABSTRACT:

Hydrogels are three dimensional hydrophilic polymer networks capable of swelling in water or biological fluids. Their ability to absorb water is due to the presence of hydrophilic groups. Hydrogels play a critical role in many tissue engineering scaffolds, biosensor and bioMEMS devices and drug carries. Hydrogels have attracted considerable attention as excellent candidates for controlled release devices. Hydrogels can also be engineered to exhibit bio-adhesiveness to facilitate drug targeting, especially through mucus membranes, for non-invasive drug administration. Hydrogel based drug delivery devices have become a major area of research interest with several commercial products already developed. With ongoing research in advanced drug delivery formulations to provide stable and economical drug delivery systems, the focus is on hydrogel which are known to reduce the problems of not only conventional dosage forms but also of novel drug delivery systems which require a biocompatible, convenient and stable drug delivery system for molecules as small as NSAIDs (Non-steroidal anti-inflammatory drugs) or as large as proteins and peptides. In present review article, our aim is to highlight the promising benefits offered by hydrogel delivery system in delivery of many drug moieties.

Keywords: Hydrogel, Hydrophilic, Swelling, Drug delivery.

***Corresponding Author:**
Mrs. Paridhi Bhargava
Shrinathji institute of pharmacy,
Nathdwara (Raj.)
E-mail: paridhimph@gmail.com

INTRODUCTION

Since the establishment of the first synthetic hydrogels by Wichterle and Limin 1954, the growth of hydrogel technologies has advanced many fields ranging from food additives to pharmaceuticals to biomedical implants. In addition, the development of an ever-increasing spectrum of functional monomers and macromers continue to broaden the versatility of hydrogel applications. Hydrogels are three dimensional hydrophilic polymer networks capable of swelling in water or biological fluids, and retaining a large amount of fluids in the swollen state. Their ability to absorb water is due to the presence of hydrophilic groups such as $-OH$, $-CONH-$, $-CONH_2$, $-COOH$, and $-SO_3H$. The water content in the hydrogel affects different properties like permeability, mechanical properties, surface properties, and biocompatibility. Hydrogels have similar physical properties as that of living tissue, and this similarity is due to the high water content, soft and rubbery consistency, and low interfacial tension with water or biological fluids. The ability of molecules of different size to diffuse into (drug loading), and out (release drug) of hydrogels, permit the use of hydrogel as delivery systems. Since hydrogels have high permeability for water soluble drug, water content, cross linking density, and crystallinity, can be used to control the release rate and release mechanism from hydrogels[1].

Hydrogels can be prepared from natural or synthetic polymers. Although hydrogels made from natural polymers may not provide sufficient mechanical properties and may contain pathogens or evoke immune/inflammatory responses, they do offer several advantageous properties such as inherent biocompatibility, biodegradability, and biologically recognizable moieties that support cellular activities.

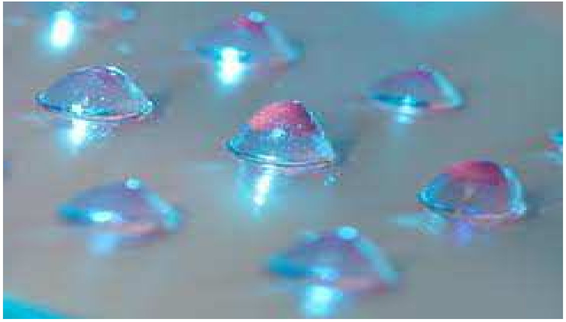

Fig.1 Hydrogel

Synthetic hydrogels do not possess these inherent bioactive properties. Fortunately, synthetic polymers usually have well defined structures that can be modified to yield tailorable degradability and functionality. Natural polymers as well as synthetic monomers are commonly used in hydrogel fabrication[2].

Table 1: Natural polymers and synthetic monomers used in hydrogel fabrication

ADVANTAGES

Natural polymers	Synthetic monomer
Chitosan	Hydroxyethyl methacrylate (HEMA)
Alginate	N-(2-hydroxypropyl) methacrylate (HPMA)
Fibrin	N-vinyl-2-pyrroolidone (NVP)
Collagen	N-isopropyl acrylamide
Gelatin	Acrylic acid
Hyaluronic acid	Methacrylic acid
Dextran	Polyethylene glycol acrylate/methacrylate

- ❖ A history of safety: The base polymer materials used to make the most common hydrogels are known to be inert (non-reactive and non-toxic) and have been around for many years. They were first tested in simple forms as a safe medium for drug and cell delivery and scaffolds for tissue engineering.
- ❖ Clophosome™ Liposomes for Efficient Macrophage Depletion Best Activity, Stability and Price.
- ❖ Uniform PLGA Microspheres with 75:25 &50:50 ratios available in 3 size ranges; 75, 100 & 120μm.
- ❖ Rabbit Monoclonal Abs Full-length protein based antigens High Specificity & High Sensitivity.
- ❖ The protection factor: The hydrophilic nature of hydrogels permits drug delivery of therapeutic materials that would otherwise denature due to hydrophobic interactions, and the protective structure also prevents destruction of cells or proteins by host immune responses, since matrix pore size can be made small enough to prevent the entry of large immune cells and antibodies. An example of this is enhanced survival of encapsulated pancreatic islet cells for treatment of type I diabetes.
- ❖ Control over the polymer properties: The properties of materials like poly (ethylene glycol) (PEG), one of the simplest polymer materials used to make hydrogels, can be controlled to optimize features like pore size, which is used to control rates of diffusion of the deliverable drugs or cells.
- ❖ Introduction of smart polymers: The design/synthesis of a basic hydrogel matrix can be modified to make them "smart" polymers. Changes to the polymer structure or added ligands that allow control over the release of deliverables using various biological triggers like changes in pH or temperature, or the presence/absence of bio-molecules like glucose.
- ❖ In situ and ex situ control: More complex modifications like polymer cross-links or photodegradable linkages add to our ability to control the release of deliverables. Polymer cross-links targeted by specific enzymes are used to open up the gel matrix in situ. Photolysis of hydrogels with a photodegradable cross-linker enables external control through irradiation.
- ❖ Enhanced survival of encapsulated cells: In cases of cell delivery therapy or tissue engineering, polymer modifications can also be made to enhance the survival and performance of the encapsulated cells. For example, the immobilization of a molecule called GLP-1 (glucagon-like peptide 1) in hydrogels containing islet cell, helps to increase insulin secretion and reduce cell death[3].

PROPERTIES OF HYDROGEL

- Physical
- Chemical
- Toxicological

Factors affecting swelling of hydrogels: The crosslinking ratio is one of the most important factors that affect the swelling of hydrogels. Highly crosslinked hydrogels have a tighter structure, and will swell less compared to the same hydrogels with lower crosslinking ratios. Crosslinking hinders the mobility of the polymer chain, hence lowering the swelling ratio. The chemical structure of the polymer may also affect the swelling ratio of the hydrogels. Hydrogels containing hydrophilic groups swell to a higher degree compared to those containing hydrophobic groups. Hydrophobic groups collapse in the presence of water, thus minimizing their exposure to the water molecule. Swelling of environmentally-sensitive hydrogels can be affected by specific stimuli. Swelling of temperature-sensitive hydrogels can be affected by changes in the temperature of the swelling media. Ionic strength and pH affect the swelling of ionic strength- and pH-sensitive hydrogels, respectively There are many other specific stimuli that can affect the swelling of other environmentally-responsive hydrogels.

- Dynamics of swelling: The swelling kinetics of hydrogels can be classified as diffusion-controlled (Fickian) and relaxation-controlled (non-Fickian) swelling. When water diffusion into the hydrogel occurs much faster than the relaxation of the polymer chains, the swelling kinetics is diffusion-controlled[3].
- Mechanical properties: Mechanical properties of hydrogels are very important for pharmaceutical applications. For example, the integrity of the drug delivery device during the lifetime of the application is very important to obtain FDA approval, unless the device is designed as a biodegradable system. A drug delivery system designed to protect a sensitive therapeutic agent, such as protein, must maintain its integrity to be able to protect the protein until it is released out of the system. Changing the degree of crosslinking has been utilized to achieve the desired mechanical property of the hydrogel.
- Cytotoxicity and in-vivo toxicity: Cell culture methods, also known as cytotoxicity tests can be used to evaluate the toxicity of hydrogels. Three common assays to evaluate the toxicity of hydrogels include extract dilution, direct contact and agar diffusion. Most of the problems with toxicity associated with hydrogel carriers are the unreacted monomers, oligomers and initiators that leach out during application. Therefore, an understanding the toxicity of the various monomers used as the building blocks of the hydrogels is very important[4]. Several measures have been taken to solve this problem, including modifying the kinetics of polymerization in order to achieve a higher conversion, and extensive washing of the resulting hydrogel. The formation of hydrogels without any initiators has been explored to eliminate the problem of the residual initiator. The most commonly used technique has been gamma irradiation[5-9].

TYPES OF HYDROGEL

1. **Temperature-sensitive hydrogels:** Temperature sensitive hydrogels are probably the most commonly studied class of environmentally sensitive polymer systems in drug delivery research. Many polymers exhibit a temperature-responsive phase transition property.
2. **pH-sensitive hydrogels:** All the pH-sensitive polymers contain pendant acidic (e.g. carboxylic and sulfonic acids) or basic (e.g. ammonium salts) groups that either accept or release protons in response to changes in environmental pH.
3. **Glucose-sensitive hydrogels:** Delivery of insulin is different from delivery of other drugs, since insulin has to be delivered in an exact amount at the exact time of need. Thus, self-regulated insulin delivery systems require the glucose sensing ability and an automatic shut-off mechanism. Many hydrogel systems have been developed for modulating insulin delivery, and all of them have a glucose sensor built into the system.
4. **Electric signal-sensitive hydrogels:** Electric current can also be used as an environmental signal to induce responses of hydrogels. Hydrogels sensitive to electric current are usually made of polyelectrolytes, as are pH-sensitive hydrogels. Electro-sensitive hydrogels undergo shrinking or swelling in the presence of an applied electric field.
5. **Light-sensitive hydrogels:** Light-sensitive hydrogels have potential applications in developing optical switches, display units and ophthalmic drug delivery devices. Since the light stimulus can be imposed instantly and delivered in specific amounts with high accuracy, light-sensitive hydrogels may possess special advantages over others. Light-sensitive hydrogels can be separated into UV-sensitive and visible light-sensitive hydrogels[10].

PREPARATION OF HYDROGEL

Several techniques have been reported for the synthesis of hydrogels[11]. The monomers and the crosslinking agents used in the preparation of hydrogels are given

- **Solution polymerization/crosslinking:** In solution, co-polymerization/crosslinking reactions, and ionic or neutral monomers are mixed with the multifunctional crosslinking agent. The polymerization is initiated thermally, by UV-light, or by redox initiator system. The prepared hydrogels need to be washed with distilled water to remove the unreacted monomers, crosslinking agent, and the initiator. The best example is preparation of poly (2-hydroxyethyl methacrylate)[12] hydrogels from hydroxyethyl methacrylate, using ethylene glycol dimethacrylate as crosslinking agent. Using the above method, a great variety of hydrogels has been synthesized[13]. The hydrogels can be made pH-sensitive or temperature-sensitive, by incorporating methacrylicacid[14] or N-isopropylacrylamide[15], as monomers.
- **Suspension polymerization:** This method is employed to prepare spherical hydrogel micro-

particles with size range of 1 µm to 1mm. In suspension polymerization, the monomer solution is dispersed in the non-solvent forming fine droplets, which are stabilized by the addition of stabilizer. The polymerization is initiated by thermal decomposition of free radicals. The prepared micro-particles then washed to remove unreacted monomers, crosslinking agent, and initiator.

- **Polymerization by irradiation:** High energy radiation like gamma and electron beam, have been used 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 hydroxyl radicals, which also attack the polymer chains, resulting in the formation of macro-radicals. Recombination of the macro=radicals on different chains results in the formation of covalent bonds, and finally a crosslinked structure is formed[16].
- **Chemically crosslinked hydrogels:** Polymers containing functional groups like -OH, -COOH, -NH_2, are soluble in water. The presence of these functional groups on the polymer chain, can be used to prepare hydrogels by forming covalent linkages between the polymer chains and complementary reactivity such as amine-carboxylic acid, isocyanate-OH/NH_2 or by Schiff base formation[17].
- **Physically crosslinked hydrogels:** Most of the covalent crosslinking agents are known to be toxic, even in small traces. A method to overcome this problem and to avoid a purification step is to prepare hydrogels by reversible ionic crosslinking. Chitosan, a polycationic polymer can react with positively charged components, either ions or molecules, forming a network through ionic bridges between the polymeric chains. Among anionic molecules, phosphate bearing groups, particularly sodium tripolyphosphate is widely studied[18,19].

CHARACTERIZATION OF HYDROGEL

An easy way to quantify the presence of hydrogel in a system is to disperse the polymer in water using a cylindrical vial and visually observe the formation of insoluble material. Visual monitoring of the solution viscosity by turning the universal up-side down can also provide quick measure of the bulk viscosity reported in literature.

- **Solubility:**
- **Method A:** Normally the hydrogel content of a given material is estimated by measuring its insoluble part in dried sample after immersion in deionised water for 16 h[20]or 48 h at room temperature[21]. The sample should be prepared at a dilute concentration (typically ~ 1%) to ensure that hydrogel material is fully dispersed in water. The gel fraction is then measured as follows: $(\ \%)\ d * 100$
- **Method B:** A more accurate measure of the insoluble fraction (also termed as hydrogel can be determined by measuring the weight retained after vacuum filtration. This is essentially the method prescribed by JECFA (Joint Expert Committee on Food Additives) for hydrocolloids which we have modified by changing the solvent from mild alkaline to water. The weight (W1) of a 70 mm glass fibre paper (pore size 1.2 micron) is determined following drying in an oven at 105oC for 1 hour and subsequently cooled in a desiccators containing silica gel. Depending on the test material, 1-2 wt% (S) dispersion can be prepared in distilled water followed by overnight hydration at room temperature. The hydrated dispersion is then centrifuged for 2-5 minutes at 2500 rpm prior to filtration. Drying of the filter paper is carried out in an oven at 105oC followed by cooling to a constant weight (W2) %. Insoluble can then be calculated: $\%Hydrogel\ W2\ W1 * 100$[22].
- **Swelling measurement**
  - **Method A:** The Japanese Industrial Standard K8150 method has been used to measure the swelling of hydrogels. According to this method the dry hydrogel is immersed in deionised water for 48 hours at room temperature on a roller mixer. After swelling, the hydrogel is filtered by a stainless steel net of 30 meshes (681 µm).
  - **Method B:** Alternatively, to measure the swelling of hydrogel, in a volumetric vial (Universal) the dry hydrogel (0.05-0.1g) was dispersed into sufficiently high quantity of water (25-30 ml) for 48 hrs at room temperature. The mixture is then centrifuged to obtain the layers of water bound material and free unabsorbed water. The free water is removed and the swelling can be measured according to Method A above.
- **FTIR:** FTIR (Fourier Transform Infrared Spectroscopy) is a useful technique for identifying chemical structure of a substance. The resulting IR absorption spectrum represents a fingerprint of measured sample. This technique is widely used to investigate the structural arrangement in hydrogel by comparison with the starting materials[23,24].
- **Scanning Electron Microscopy (SEM):** SEM can be used to provide information about the sample's surface topography, composition, and other properties such as electrical conductivity. Magnification in SEM can be controlled over a range

of up to 6 orders of magnitude from about 10 to 500,000 times. This is a powerful technique widely used to capture the characteristic 'network' structure in hydrogel[25-26.]

- **Light scattering:** Gel permeation chromatography coupled on line to a multi angle laser light scattering (GPC-MALLS) is a widely used technique to determine the molecular distribution and parameters of a polymeric system[27]. This technique is widely used in quantifying the hydrogels of several hydrocolloids such as gum arabic, gelatin and pullulan.
- **Other techniques:** The main methods used to characterise and quantify the amount of free and bound water in hydrogels are differential scanning calorimetry (DSC) and nuclear magnetic resonance (NMR). The proton NMR gives information about the interchange of water molecules between the so-called free and boundstate[28]. Thermogravimetricanalysis[29] (X-ray diffraction, sol-gel analysis etc. are also used to confirm the formation of cross-linked network gel structures of hydrogel.

CONCLUSION

Hydrogels are three dimensional hydrophilic polymer networks capable of swelling in water or biological fluids. Their ability to absorb water is due to the presence of hydrophilic groups. Hydrogels have similar physical properties as that of living tissue. Hydrogels have high permeability for water soluble drugs and proteins; the most common mechanism of drug release in the hydrogel system is diffusion. Hydrogels can be prepared from natural or synthetic polymers. Proper material selection, fabrication process, and surface texture of the device are always critical in designing biocompatible hydrogel formulations for controlled release. Several techniques have been reported for the synthesis of hydrogels such as copolymerization/crosslinking of co-monomers using multifunctional co-monomer, or crosslinking of linear polymers by irradiation or by chemical compounds. Hydrogels are characterized for their morphology, swelling property and elasticity which indicates their porous structure, release mechanism of the drug, mechanical strength of the network and determines the stability of these drug carriers. Hydrogels play a critical role in many tissue engineering scaffolds, biosensor and bioMEMS devices and drug carriers. Hydrogels have attracted considerable attention as excellent candidates for controlled release devices. Hydrogels can also be engineered to exhibit bio-adhesiveness to facilitate drug targeting, especially through mucus membranes, for non-invasive drug administration.

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