Sariga Mohan et al /J. Pharm. Sci. & Res. Vol. 11(7), 2019, 2574-2578

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

An Insight into Hydrogel Drug Delivery

Sariga Mohan*, R Deepa Manohar
Department of Pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, Neyyattinkara- 695124, TVM, Kerala, India.

Abstract

Hydrogels have become very popular due to their unique properties such as high water content, softness, flexibility and biocompatibility. Natural and synthetic hydrophilic polymers can be physically or chemically cross-linked in order to produce hydrogels. These materials can be synthesized to respond to a number of physiological stimuli present in body such as pH, ionic strength and temperature. Their resemblance to living tissue opens up many opportunities for applications in biomedical areas. Currently, hydrogels are used for manufacturing contact lenses, hygiene products, tissue engineering scaffolds, drug delivery systems and wound dressings.

Keywords: Hydrogel, Smart hydrogel, Preparation Techniques, Drug delivery, Applications

INTRODUCTION

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 have affinity to absorb water due to the presence of hydrophilic groups such as –OH, –CONH–, –$CONH_2$–, and –SO_3H in polymers forming hydrogel structures. Due to the contribution of these groups and domains in the network, the polymer is hydrated to different degrees depending on the nature of the aqueous environment and polymer composition.

Hydrogels are insoluble due to the presence of chemical and/or physical crosslinks. The crosslinks in the polymer network are due to covalent bonds, hydrogen bonding, Vander Waals interactions, or physical entanglements[1].

Hydrogels are formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, discs, coatings, and films. They 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[2].

The highly porous structure of hydrogel 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. 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].

Benefits Of Hydrogels[4]

- Biocompatible
- Easy to modify
- Timid release of medicines
- Biodegradable or bioabsorbable

Limitations Of Hydrogels[5]

- Difficult to sterilize
- Hard to handle
- Low mechanical strength
- Non- adherent

Technical Features Of Hydrogels[6]

- Highest absorbency under load
- Highest absorption capacity
- Highest durability and stability in the swelling environment and during storage
- Highest biodegradability without formation of toxic species
- pH neutrality after swelling in water

Classification Of Hydrogels[2]

1) **Based on source:**
   - Natural
   - Synthetic
2) **Based on polymeric composition:**
   - **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.
   - **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.
   - **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 crosslinked polymer and other component is a non-cross-linked polymer.
3) **Based on configuration:**
   - Amorphous
   - Semicrystalline
   - Crystalline

4) **Based on type of crosslinking:**
   - Chemically cross-linked networks have permanent junctions.
   - 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) **Based on network electrical charge:**
   - Nonionic (neutral).
   - Ionic (including anionic or cationic).
   - Amphoteric electrolyte (ampholytic) containing both acidic and basic groups.
   - Zwitterionic (polybetaines) containing both anionic and cationic groups in each structural repeating unit.
6) **Based on mechanism controlling the drug release:**
   - Diffusion controlled release systems
   - Swelling controlled release systems
   - Chemically controlled release systems
   - Environment responsive systems

SMART HYDROGELS[7]

Smart hydrogels are the hydrogels that sense and act quickly according to the stimuli or signals perceived. They expand or shrink in their volume with respect to changes in the environment such as the change in temperature, pH, glucose, light, electric current, sound as in fig. (i).

- **pH sensitive hydrogel:**

pH sensitive hydrogel is a gel composition that responds to the pH of the environment. The principle of the gel is a structure that either shrinks or swells in response to the pH of the system. pH sensitive polymers contain acidic or basic side groups attached to their backbone that may accept or release the proton with respect to the change in the surrounding pH. Polymers with a wide range of ionizable group are called as the polyelectrolyte. In the case of anionic/acidic group, volume of hydrogel increases as the pH of the media increases while declines for polymer containing cationic/basic groups. Polymers typically used for fabricating pH responsive hydrogel are poly (hydroxyethyl methacrylate-co-acrylic acid), Polyvinyl Pyrrolidine (PVP), chitosan, Poly (methacrylic acid).

- **Temperature sensitive hydrogel:**

Hydrogels showing response towards the change in temperature are known as thermosensitive or temperature sensitive hydrogel. The sole stimulus of their sensitivity is temperature, which is required for its gelation. Temperature sensitive polymers exhibit a transition such as lower or upper critical solution temperature in the aqueous environment. In the case of polymers with Low Critical Solution Temperature (LCST), they remained water soluble below the LCST, but changes to water insoluble or sparingly water soluble at Upper Critical Solution Temperature (UCST). Some typical examples of thermo responsive polymers are Poly(N-isopropylacrylamide) – LCST, Poly(N-acryloylasparaginamide) (PNAAAM)- UCST.

- **Glucose sensitive hydrogel:**

Glucose sensitive hydrogel are composed of polymers such as N-(2-(dimethylamino) ethyl)-methacrylamide, N,N- (dimethylacrylamide) that can model the function of sensitive organs and tissue such as pancreas whose function is to release insulin. The mechanism behind the controlled release of insulin from the hydrogel system to maintain its level in a diabetic patient involves an enzyme substrate reaction where glucose reacts with glucose oxidase forming gluconic acid, resulting in a decrease in the pH of the environment. With the change in pH, the gel swells or shrink depending on the characteristics of the particular polymer of the system. Insulin is released from the system with the change in the pores size of the polymer.

- **Light sensitive hydrogel:**

The light sensitive hydrogel has been widely used in various biotechnological application such as light controlled enzymatic bioprocessing system, photo triggered targeted drug delivery systems, and photo controlled separation/recovery systems in bioMEMs (Biological microelectro mechanical system) formats. These hydrogels are supposed to deliver the light in a controlled way with accuracy. The light sensitive hydrogel is applicable in the fabrication of optical switches, display unit, and especially in optical drug delivery system.

- **Electric current sensitive hydrogel:**

Electric current induced hydrogel are basically composed of polyelectrolyte and shrinks or swells in response to an applied electric field. Polymers contain a large number of the ionizable group on their backbone chain thus sensitive towards both pH and electricity. Many reports are already existing stating about the use of electric current *in vivo* in the form, for instance, iontophoresis and electroporation in the application of dermal and transdermal drug delivery. Lin et al. reported, synthesis, structure and electric field sensitive conductive IPN hydrogel of polyacrylate/ polyaniline (PAA/PANI) and poly (2-acrylamido-2-methyl propylsulfonic acid-acrylic acid)/polyaniline [P(AMPSAA)/ PANI] for its application in drug delivery, switches, sensors and for actuators. The fabricated conductive IPN hydrogel showed a porous structure of numerous PANI nanofibers. To observe its affinity towards electric field they subjected the hydrogel in an aqueous solution of sodium chloride resulted in its bending towards the anode and as soon as the stimulus was removed the hydrogel returned to its original position.

- **Sound sensitive hydrogel:**

Ultrasound sensitive hydrogel is potential to deliver the drug in an “on-off switch” manner. For these system sound acts as a permeation enhancer and helps the drug to cross the biological barrier. For instance, Kwok et al prepared a self assembled ultrasound sensitive system made up of methylene chain where the drug insulin present within the polymer (co-polymer of 2-hydroxyethyl methacrylate and ethylene glycol dimethacrylate). The whole system was high sound sensitive that it showed the

pulsatile release of insulin just in one minute when got exposed to the ultrasonic exposure that resulted in disruption of the ordered methylene chain hence, controlled release of insulin.

HYDROGEL PREPARATION TECHNIQUES[8]

1) Bulk polymerization:

Many vinyl monomers can potentially be used for the production 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. 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. 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.

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.

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.

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

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.

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.

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) Grafting to a support:

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 shown in fig.(ii).

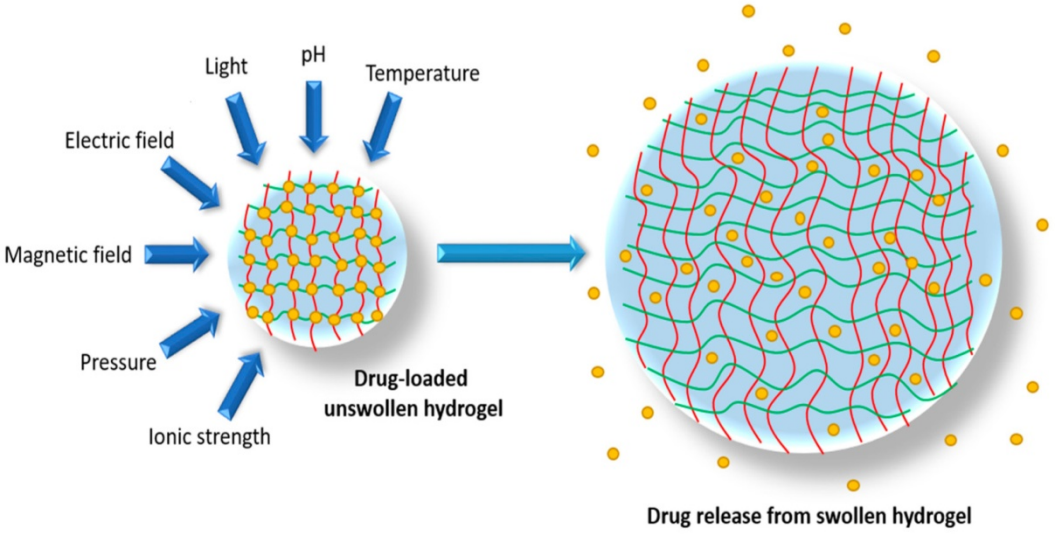

Fig. (i): Smart hydrogels

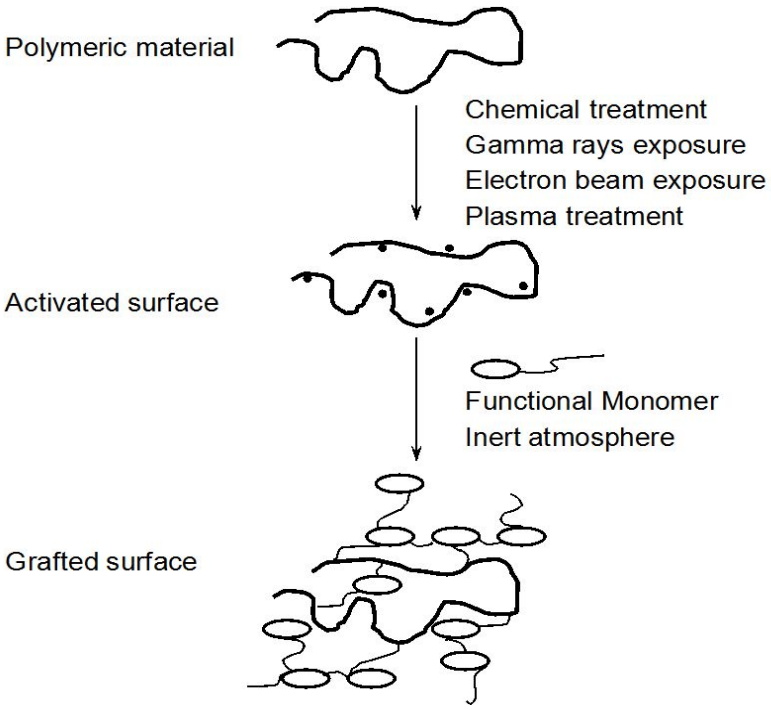

Fig. (ii): Grafting of monomer on preformed polymeric backbone, leads to branching and crossinking.

APPLICATIONS[9,10]

- **Drug delivery applications:**

Hydrogels, and smart hydrogels in particular, can be a very interesting solution in reaching a sustained and targeted release of pharmaceuticals, both increasing the effect of the drug itself and lowering side effects at the same time.

Hydrogels have attracted noticeable interest for their use in drug delivery due to their unique physical properties. The high porosity that characterizes hydrogels can easily be adjusted by controlling the density of cross-links in their matrix and the affinity to water. Their porous structure also allows drugs to be loaded and then released. The advantages offered by hydrogels for drug delivery applications include the possibility for sustained release, which results in maintaining a high local concentration of an active pharmaceutical ingredient over a long period. The drug can be loaded into a hydrogel and then its release may proceed through several mechanisms: diffusion controlled, swelling controlled, chemically controlled and environmentally-responsive release.

- **Hydrogels as soft contact lenses:**

Hydrogel are mostly useful as soft contact lenses. Due to high permeability for oxygen and comfortable fit silicone hydrogel (SiHy) lenses have become prevalent on the market.Contact lens surfaces should also have excellent wettability in order to avoid tear-film deposits. The SiHy lenses have been made to compensate the hydrophobicity of silicone and to improve its wettability.

Hydrophobic monomer like tert-butyl acrylate(TBA) can act as strengthening agents when copolymerized with hydrophilic monomers such as 2-hydroxyethyl methacrylate(HEMA), or N-vinyl-2-pyrrolidone (NVP). The soft contact lenses made from these monomers combined with HEMA or NVP are large enough to cover the whole cornea and present good oxygen permeability.
The silicone hydrogel lenses can be designed to release ophthalmic drugs for an extended period varying from 10 days to a few months. The transport of timolol and dexamethasone in the silicone gels is diffusion limited, but the release profiles are complex particularly for dexamethasone which is the evidence of complex microstructure of the gels. The silicone hydrogels may also be suitable for other drug delivery applications such as puncta plugs, ophthacoils, retinal implants, transdermal patches, wound healing patches, etc.

- **Injectable hydrogels:**

Injectable hydrogel-drug system emerges as a powerful tool for noninvasive and in-situ controlled-release of drugs. Minimal invasive procedures using endoscopes, catheters and needles have been developed considerably in the last few decades. In the field of tissue engineering and regenerative medicine, there is a need for advancement over the conventional scaffolds and pre-formed hydrogels. In this scenario, injectable hydrogels have gained wider appreciation among the researches, as they can be used in minimally invasive surgical procedures. Injectable gels with their ease of handling, complete filling the defect area and good permeability have emerged as promising biomaterials. Hydrogel injections alone have been shown to attenuate the decline in cardiac function and left ventricular remodelling typically seen after myocardial infarction in both large and small animal models. Furthermore, hydrogels have also been shown to improve cell retention when co-injected for cellular cardiomyoplasty and to prolong release of therapeutics when used as a delivery vehicle.

- **Wound healing applications:**

Wound healing is the promise of a new way to heal damaged skin tissue with high biocompatible and bioactive materials. Skin burned, diabetic ulcer, are problems that at the state of the art are very expensive to treat. Prosthetic-tissue engineered skin are been made, unfortunately they are not ready-to-use; they are expensive and have many needs that are not always matched by patients. Theoretically, in wound healing applications a crucial parameter to assess is the wound contraction that can be evaluated in this way, remembering that A_0 is the original burn wound area, and A_t is the burn wound area at the time of biopsy:

$$\text{Wound Contraction [\%]} = \frac{A_0 - A_t}{A_0} \times 100$$

Many systems has been studied, with or without chemicals to aid the skin regeneration. Hyaluronic-acid and gelatin are both two promising materials for the aim because of their natural presence inside human extra cellular membrane of the skin tissues. Healing systems can be made from cellulose , alginate- chitosan copolymers , chitosan-gelatin-honey copolymers and new biphasic gelatin-silk. Most of the products already on the market use a combination of selected materials and proper seeding of cells from various origins (allogenic or autogenic).

- **Tissue Engineering applications:**

Hydrogels are three dimensional polymer scaffolds used in several applications of tissue engineering. A particularly important group of techniques is the so called *in-vivo* tissue regeneration. In this case, a patient's own cells are combined with the polymer, and held *in-vitro* until ready to be implanted. The hydrogel acts as a natural extra-cellular matrix that subsequently promotes cell proliferation and tissue re-growth. The pseudo-extra-cellular matrix, comprised of growth factors, metabolites and other materials, brings cells together and controls tissue structure with the ultimate goal of replacing the natural tissue that was lost or damaged.

CONCLUSION

Hydrogel based networks have been designed and tailored to meet the needs of different applications. The main property that makes it unique from another delivery system is its quick responsiveness towards different stimuli which is nowadays is of significant consideration for pharmaceutical engineers. Hydrogel matrices comprise a wide range of natural and synthetic polymers held together by a variety of physical or chemical crosslinks. With their capacity to embed pharmaceutical agents in their hydrophilic crosslinked network, hydrogels form promising materials for controlled drug release and tissue engineering.

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