FORMULATION AND EVALUATION OF ANTIBACTERIAL HYDROGEL

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ABSTRACT

Hydrogels are a unique class of cross-linked polymeric three-dimensional networks that can accommodate a significant fraction of aqueous solvents and biological fluids within their structures. Hydrogels now have attracted a growing interest from most of the scientists in various research fields. Currently, hydrogels with an antibacterial function are a main focus in biomedical research. Many advanced antibacterial hydrogels are developed, each possessing unique qualities, namely high water swellability, high oxygen permeability, improved biocompatibility, ease of loading and releasing drugs, and structural diversity. This review paper looks at the description of classification, methods of synthesis and applications.

KEYWORDS: Hydrogels, Cross-linking agents, complex coacervation.

INTRODUCTION

The term hydrogel describes as a three-dimensional cross linked polymeric network obtained from synthetic or natural polymers which has the capacity to hold water within its porous structure. (1,2) The water holding capacity of the hydrogels arise mainly due to the presence of hydrophilic groups, viz. amino, carboxyl and hydroxyl groups, in the polymer chains. These polymeric materials do not dissolve in water at physiological temperature and pH but swell considerably in an aqueous medium. Hydrogels can be made from virtually any water-soluble polymer, encompassing a wide range of chemical compositions and bulk physical properties. Further, more, hydrogels can be formulated in a variety of physical forms including slabs, microparticles, nanoparticles, coatings, and films. (3) Hydrogels have been widely used as drug carrier due to its ease in manufacturing and self-application in clinical and fundamental applications. Applications of hydrogels in the biomedical field include contact lenses, artificial corneas, wound dressing, coating for sutures, catheters, and electrode sensors. (4)
Classification

1. On the basis of the nature of the cross-linked junctions
   a. Permanent / chemical gel: they are called ‘permanent’ or ‘chemical’ gels when they are covalently cross-linked (replacing hydrogen bond by a stronger and stable covalent bonds) networks. They attain an equilibrium swelling state which depends on the polymer-water interaction parameter and the crosslink density.(1,5,6)

   b. Reversible/physical gel: they are called ‘reversible’ or ‘physical’ gels when the networks are held together by molecular entanglements, and / or secondary forces including ionic, hydrogen bonding or hydrophobic interactions. In physically cross-linked gels, dissolution is prevented by physical interactions, which exist between different polymer chains. All of these interactions are reversible, and can be disrupted by changes in physical conditions or application of stress.(1,5,6)

2. On the basis of origin
   a. Natural Polymers
      Biocompatible, Biodegradable, Supports Cellular Activities. Does not possess sufficient mechanical properties. May contain pathogen. Evoke immune and Inflammatory responses (1).

      Examples: Proteins like collagen and gelatine, Polysaccharides like alginate and agarose.

   b. Synthetic polymers
      Inherent bioactive properties absent. (1)

      Examples: Acrylic acid -Hydroxyethyl methacrylate (HEMA), Vinyl acetate, Methacrylic acid (MAA)

3. On the basis of preparation, they are classified in to (7)
   a. Homo polymer
      Homopolymers are referred to polymer networks derived from single species of monomer. It is the basic structural unit and comprising of any polymer network. Homopolymers may have cross-linked skeletal structure depending on the nature of the monomer and polymerization technique. Cross-linked homopolymers are used in drug delivery system and in contact lenses.

   b. Copolymer
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. (9)

c.Semi interpenetrating network
If one polymer is linear and penetrates another cross-linked network without any other chemical bonds between them, it is called a semi-interpenetrating network. (10)

d.Interpenetrating network
IPNs are conventionally defined as intimate combination of two polymers, at least one of which is synthesized or cross-linked in the immediate presence of the other. (11) This is typically done by immersing a pre polymerised hydrogel into a solution of monomers and a polymerisation initiator. IPN can overcome thermodynamic incompatibility occurs due to the permanent interlocking of network segments and limited phase separation can be obtained. The main advantage of IPNs are relatively dense hydrogel matrices can be produced which feature stiffer and tougher mechanical properties controllable physical properties and more efficient drug loading compared to other hydrogels. (7)

Methods of preparation
The various preparation techniques adopted are physical cross-linking, chemical cross-linking, grafting polymerisation, and radiation cross-linking such modifications can improve the mechanical properties and visco-elasticity for applications in biomedical and pharmaceutical fields. (12)
To produce physical and chemical gels the general methods are described below:

1.Physical cross-linking
There has been an increased interest in physical or reversible gels due to relative ease of production and the advantage of not using cross-linking agents. These agents affect the integrity of substances to be entrapped (e.g. cell, proteins, etc.) as well as the need for their removal before application. The various methods reported in literature to obtain physically cross-linked hydrogels are:

1.1 Heating/Cooling a polymer Solution
The gel formation is due to helix-formation, association of the helices, and forming junction zones. Carrageenan in hot solution above the melting transition temperature is present as random coil conformation. Upon cooling it transforms to rigid helical rods. In presence of salt (K+, Na+, etc.), due to screening of repulsion of sulphonic group (SO–3), double helices further aggregate to form stable gels. Some of the examples are polyethylene oxide-
polypropylene oxide, polyethylene glycol-polylactic acid hydrogel. (13)

1.2 Complex coacervation
Complex coacervate gels can be formed by mixing of a polyanion with a polycation. The underlying principle of this method is that polymers with opposite charges stick together and form soluble and insoluble complexes depending on the concentration and pH of the respective solutions. One such example is coacervating polyanionic xanthan with polycationic chitosan. Proteins below its isoelectric point are positively charged and likely to associate with anionic hydrocolloids and form polyion complex hydrogel. (14)

1.3 Ionic interaction
Ionic polymers can be cross linked by the addition of di or tri-valent counterions. This method underlies the principles of gelling a polyelectrolyte solution with the multivalent ion of opposite charges. Some other examples are chitosan-glycerol phosphate salt, chitosan-dextran hydrogels.

2. Chemical cross-linking
Chemical cross-linking involves grafting of monomers on the backbone of the polymers or the use of a cross-linking agent to link two polymer chains. The cross-linking of natural and synthetic polymers can be achieved through the reaction of their functional groups (such as OH, COOH, and NH2) with cross-linkers such as aldehyde (e.g. glutaraldehyde, adipic acid dihydrazide). Cross-linkers such as glutaraldehyde, epichlorohydrin etc have been widely used to obtain the cross-linked hydrogel. One such example is hydrogel prepared by cross-linking of corn-starch and polyvinyl alcohol using glutaraldehyde as a cross-linker. Hydrogels can also be synthesized from cellulose in NaOH/urea aqueous solutions by using epichlorohydрин as cross-linker and by heating and freezing methods. (15)

3. Grafting cross linking
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 that 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. A variety of polymeric supports have been used for the synthesis of hydrogel by grafting techniques. Starch grafted with acrylic acid by using N-vinyl-2-pyrrolidone is an example of this kind of process. (16)

4. Polymerization through irradiation (17)
Ionizing high energy radiation, like gamma rays and electron beams, has been used as an
initiator to prepare the hydrogels of unsaturated compounds

\[
\text{Irradiation of aqueous polymer} \\
\text{Radicals} \\
\text{Radiolysis of water molecules} \\
\text{Hydroxy radicals} \\
\text{Macro radicals} \\
\text{Recombination of macro radicals} \\
\text{Covalent bonds} \\
\text{Cross – linked structures}
\]

**Examples:** poly (vinyl alcohol), poly (ethylene glycol), and poly (acrylic acid)

**Advantages of hydrogels**

- Their degree of flexibility extremely similar to natural tissue which is due to their remarkable water content.
The environmentally sensitive hydrogels can sense the changes in temperature, pH or themetabolite concentration and sensing these changes they release the load.

They are biocompatible, biodegradable and are also injectable.

Entrapment of microbial cells within hydrogel beads has the advantage of low toxicity.

Timed release of growth factors and other nutrients to ensure proper tissue growth.

Hydrogels have good transport properties. (7,17,18)

Disadvantages of hydrogels

- They are non-adherent and may need to be secured by secondary dressing.
- They may cause a sensation similar to that which is felt by movement of maggots.
- They can be hard to handle.
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Applications

1. **Drug delivery in the oral cavity**

   Drug delivery to the oral cavity has versatile applications in local treatment of diseases of the mouth, such as periodontal disease, stomatitis, fungal and viral infections, and oral cavity cancers. For example, a bioadhesive tablet developed which is commercially available under the brand name Aftach. This product is composed of a double layer, with a bioadhesive layer made of hydroxypropyl cellulose and poly (acrylic acid) and a lactose non-adhesive backing layer. It is a local delivery system of triamcinolone acetonide for the treatment of ulcers. (19)

2. **Drug delivery in the GI tract**

   The GI tract is unquestionably the most popular route of drug delivery because of the facility of administration of drugs for compliant therapy, and its large surface area for systemic absorption. It is, however, the most complex route, so that versatile approaches are needed to deliver drugs for effective therapy. Like buccal delivery, hydrogel-based devices can be designed to deliver drugs locally to the specific sites in the GI tract. For example, stomach-specific antibiotic drug delivery systems for the treatment of Helicobacter pylori infection in peptic ulcer disease. For localized antibiotic delivery in the acidic environment of the
stomach, they developed cationic hydrogels with pH-sensitive swelling and drug release properties.\cite{20} Recently, oral insulin delivery using pH-responsive complexation hydrogels was reported. The hydrogels used to protect the insulin in the harsh, acidic environment of the stomach before releasing the drug in the small intestine were cross-linked by copolymers of PMAA with graft chains of polyethylene glycol.\cite{21}

3. Rectal delivery

The rectal route has been used to deliver many types of drugs for local treatment of diseases associated with rectum, such as haemorrhoids. This route is more convenient, prevent the first pass metabolism and that drugs absorbed from the lower part of the rectum drain into the systemic circulation directly. Conventional suppositories are adapted as dosage forms for rectal administration are solids at room temperature, and melt or soften at body temperature. A problem associated with conventional suppositories is that drugs diffusing out of the suppositories in an uncontrolled manner are unable to be sufficiently retained at a specific position in the rectum, and sometimes migrate upwards to the colon. This often leads to a variation of the bioavailability of certain drugs. In this context, hydrogels may offer a valuable way to overcome the problem in conventional suppositories, provided that they are designed to exhibit a sufficient bioadhesive property following their rectal administration. For example, among the muco-adhesive polymeric compounds tested, polycarbophil and sodium alginate provided the largest muco-adhesive force and the smallest intra-rectal migration to the suppositories, resulting in the largest bioavailability of propranolol.\cite{22}

4. Ocular delivery

The conventional ophthalmic preparations like eye drops they tend to be eliminated rapidly from the eye, and the drugs administered exhibit limited absorption, leading to poor ophthalmic bioavailability. Additionally, their short-term retention often results in a frequent dosing regimen to achieve the therapeutic efficacy for a sufficiently long duration. These challenges have motivated researchers to develop drug delivery systems that provide a prolonged ocular residence time of drugs. Certain dosage forms, such as suspensions and ointments, can be retained in the eye, although these sometimes give patients an unpleasant feeling because of the characteristics of solids and semi solids. Due to their elastic properties, hydrogels can also represent an ocular drainage-resistant device, they may offer better feeling, with less of a gritty sensation to patients. In particular, in-situ-forming hydrogels are attractive as an ocular drug delivery system because of their facility in dosing as a liquid, and their long-term retention property as a gel after dosing. For example, an in-situ-gelling system of alginate with high guluronic acid contents for the ophthalmic delivery of pilocarpine. This system significantly extended the duration of the pressure reducing effect of pilocarpine to 10 h, compared to 3 h when pilocarpine nitrate was dosed as a solution.\cite{23}
5. **Wound healing**

Hydrogels which are cross linked materials, have the ability to hold water and drug in them and due to this 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. (24)

6. **Hydrogels for transdermal drug delivery**

Hydrogels when utilized by topical transdermal have several advantages like they bypass the hepatic metabolism, which increases the bio-availability and drug efficacy. Transdermal drug delivery system is used to achieve a constant drug release. Hydrogels are swollen and resemble living tissues hence they can be easily removed rather than the other dosage forms like patches, ointments. Poloxamer 407 based novel hydrogels containing gentamycin are more effectual in treating skin infections, whereas the gentamycin parental administration causes serious disorders. (25,26)

**CONCLUSION**

Hydrogels are polymer crosslinked networks that absorb significant amounts of aqueous solutions. The hydrogel are more resemble natural living tissue than any other type of synthetic biomaterial because of their high-water content. various methods of preparation for hydrogels are adopted which include physical cross-linking, chemical cross-linking, radiation cross-linking and grafting polymerization these modifications may improve mechanical properties and visco-elasticity for pharmaceutical applications. Hydrogels have a unique combination of features that make them useful in drug delivery applications. Hydrogels used in wound healing, drug delivery, transdermal systems, dental materials, implants, ophthalmic applications, injectable polymeric systems, encapsulated living cells because of their high-water absorption capacity and biocompatibility.

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