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HYDROGEL IN PHARMACEUTICALS: A REVIEW

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Abstract:
Hydrogel products constitute a group of polymeric materials, the hydrophilic structure of which renders them capable of holding large amounts of water in their three-dimensional networks. Extensive employment of these products in a number of industrial and environmental areas of application is considered to be of prime importance. As expected, natural hydrogels were gradually replaced by synthetic types due to their higher water absorption capacity, long service life, and wide varieties of raw chemical resources. Literature on this subject was found to be expanding, especially in the scientific areas of research. However, a number of publications and technical reports dealing with hydrogel products from the engineering points of view were examined to overview technological aspects covering this growing multidisciplinary field of research. The primary objective of this article is to review the literature concerning classification of hydrogels on different bases, its merits and demerits. It also involved technologies adopted for hydrogel production and its application in drug delivery.
Key words: Hydrogel, drug delivery, cross-linking.

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INTRODUCTION:

Over the decade, Controlled drug delivery and site specific delivery have made rapid advances in drug development. The interest of using natural and chemically modified polysaccharides as a part of drug development has increased in past two decades and great attention has been focused on biopolymer based hydrogel as potential carriers in controlled drug delivery [1]. The number of references published under the research topic of "hydrogel" has increased exponentially during the last decade. According to SciFinder®, the first reference on hydrogel appeared in 1894. Although the hydrogels described during that time period was a colloidal gel of inorganic salts, which are not exactly the same type of hydrogels we are dealing with nowadays [2]. The hydrogel can be defined as a 3-dimensional cross linked polymeric network obtained from synthetic or natural polymers which has the capacity to hold water within its porous structure. 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 [3]. These polymeric materials do not dissolve in water at physiological temperature and pH but swell considerably in an aqueous medium. Hydrogels have been widely used as a drug carrier due to its ease in manufacturing and self-application in clinical and fundamental applications. Various combinations of polymers are made into hydrogel formulations to investigate their potentiality. The combination of natural and synthetic polymers may provide mechanical stability and biological acceptability, acquiring from synergistic properties of both materials. Then the hydrogels were found stable and resilient [4]. Additionally, there are numerous applications, particularly in the medical and pharmaceutical sectors. Because Hydrogels resemble natural living tissue more than any other class of synthetic biomaterials. This is due to their high water contents and soft consistency which is similar to natural tissue. Furthermore, the high water content of the materials contributes to their biocompatibility. Thus, hydrogels can be used as contact lenses, membranes for biosensors, linings for artificial hearts, materials for artificial skin, and drug delivery devices [5].

BENEFITS

- Bio-compatible.
- Can be injected.
- Easy to modify.
- Timed release of growth factors and other nutrients to ensure proper tissue growth.
- Low toxicity.
- Natural hydrogel materials are being investigated for tissue engineering, which includes agarose, methylcellulose, hylaronan, and other naturally derived polymers.

LIMITATIONS

- High cost.
- Low mechanical strength
- Difficult to load
- Difficult to sterilize
- Non-adherent
- In contact lenses - lens deposition, hypoxia, dehydration and red eye reactions.

CLASSIFICATION

1. **On the basis of the nature of the cross linked junctions**

a. Permanent / Chemical Gels: Chemically/ covalently cross linked networks having permanent junctions.

b. Reversible / Physical gels: Physical networks are held by molecular entanglements or physical interactions viz. ionic interactions, hydrogen bonds or hydrophobic interactions.

2. **On the basis of orgin:**

Class	Advantages	Disadvantages	Examples
Natural Polymers	-Biocompatible -Biodegradable -Supports Cellular Activities	-Does not possess sufficient mechanical properties -May contain pathogen -Evoke immune and Inflammatory responses	-Proteins like collagen and gelatin -Polysaccharides like alginate and agarose.
Synthetic polymers	Inherent bioactive properties absent	————————	Acrylic acid -Hydroxyethylmethacrylate (HEMA) -Vinyl acetate -Methacrylic acid(MAA)

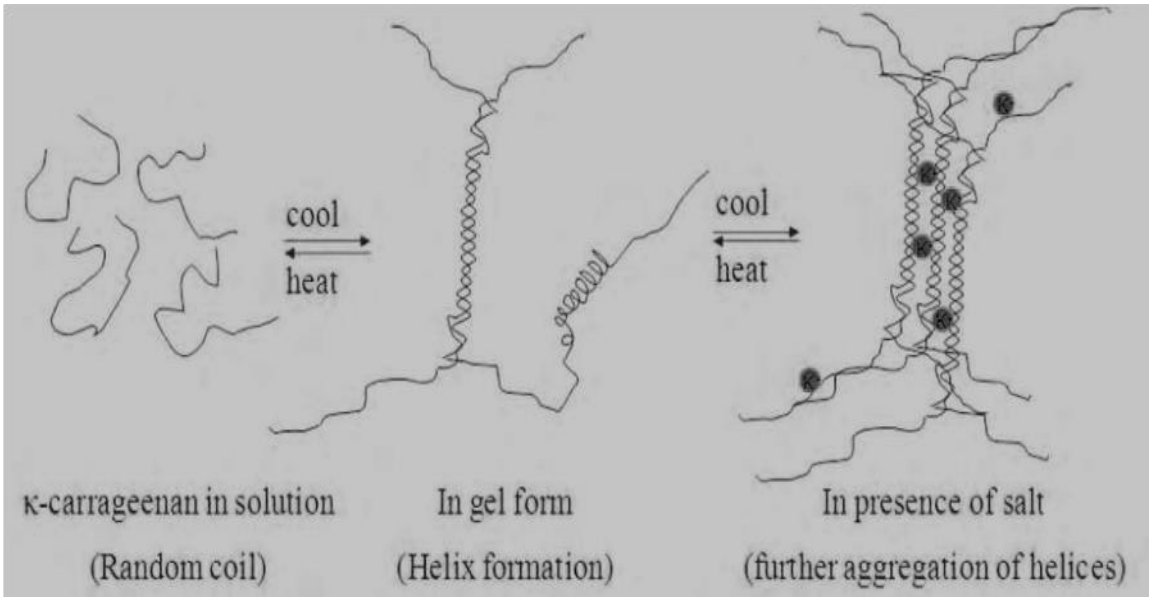


Fig 1: Gel Formation Due to Aggregation of Helix upon Cooling a Hot Solution of Carrageenan.

METHOD OF PREPARATION:

Cross-linked networks of Synthetic polymers such as Polyethylene oxide (PEO), Polyvinyl pyrollidone (PVP) , Polylactic acid (PLA) , Polyacrylic acid (PAA), Polymethacrylate (PMA), Polyethylene glycol (PEG) ,or Natural biopolymers such as Alginate, Chitosan, Carrageenan, Hyaluronan, and Carboxy methyl cellulose (CMC) have been reported. 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 [6]. The general methods to produce physical and chemical gels are described below.

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:

Heating/Cooling a Polymer Solution

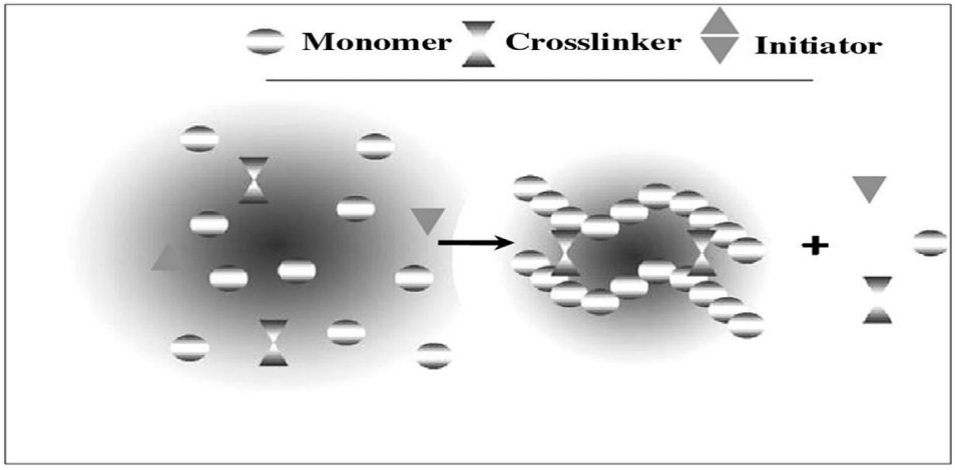
The gel formation is due to helix-formation, association of the helices, and forming junction zones . Carrageenan in hot solution above the melting transition temperature is present as random coil conformation. Upon cooling it transforms to rigid helical rods. In presence of salt (K+, Na+, etc.), due to screening of repulsion of sulphonic group (SO–3), double helices further aggregate to form stable gelsSome of the examples are polyethylene oxide-polypropylene oxide, polyethylene glycol-polylactic acid hydrogel [7].

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 [8].

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 epichlorohydrin as cross-linker and by heating and freezing methods [9].



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 [10].

Radiation Cross-Linking

Radiation cross-linking is widely used technique since it does not involve the use of chemical additives and therefore retaining the biocompatibility of the biopolymer. Also, the modification and sterilisation can be achieved in single step and hence it is a cost effective process to modify biopolymers having their end-use specifically in biomedical application. The technique mainly relies on producing free radicals in the polymer following the exposure to the high energy source such as gamma ray, x-ray or electron beam. The action of radiation (direct or indirect) will depend on the polymer environment (i.e. dilute solution, concentrated solution, solid state) [11].

APPLICATIONS OF HYDROGEL IN DRUG DELIVERY:

A number of strategies have been proposed to achieve drug delivery systems for efficient therapy. Among them, hydrogels have attracted considerable attention as excellent candidates for controlled release devices, bioadhesive devices, or targetable devices of therapeutic agents. Hydrogel-based delivery devices can be used for oral, rectal, ocular, epidermal and subcutaneous application.

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 Aftachw. 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 [12].

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 [13]. 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 [14].

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 [15].

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 [16].

FUTURE PROSPECTS:

The specific requirements of advanced drug delivery could easily be met by hydrogels. Wide array of methods for the synthesis of these novel biomaterials has extended its application from drug delivery system to tissue engineering scaffolds, wound dressing material, bioseparators, gene delivery device and biosensors etc. Further delivery into the fundamentals of multi-polymer based hydrogel and their properties, may give raise a novel approach for implementing the biomaterials in the biomedical field in a better way [17].

CONCLUSION:

Controlled drug delivery and site specific delivery have made rapid advances in drug development. Especially the delivery of large molecular weight protein and peptide-based drugs due to the recent advances in the field of molecular biology has given us new ways to treat a number of diseases. So these synthetic hydrogels offer a possibly effective and convenient way to administer these compounds. The Hydrogels are hydrophilic, three-dimensional networks, which are able to imbibe large amounts of water or biological fluids, and thus resemble with natural living tissue more than any other class of synthetic biomaterials. This is due to their high water contents and soft consistency which is similar to natural tissue. Furthermore, the high water content of the materials contributes to their biocompatibility. . These materials can be synthesized to respond to a number of physiological stimuli present in the body, such as pH, ionic strength and temperature. There are various method of preparation techniques adopted for hydrogels which includes 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. Radiation cross-linking is widely used technique since it does not involve the use of chemical additives and therefore retaining the biocompatibility of the biopolymer. Also, the modification and sterilisation can be achieved in single step and hence it is a cost effective process to modify biopolymers having their end-use specifically in biomedical application. Now a days, Due to their high water absorption capacity and biocompatibility they have been used in wound dressing, drug delivery, agriculture, sanitary pads as well as trans-dermal systems, dental materials, implants, injectable polymeric systems, ophthalmic applications, hybrid-type organs (encapsulated living cells). And these have several interesting applications of such systems in the treatment of diabetes, osteoporosis, cancer or thrombosis have been discussed. Other hydrogels with great promise as drug delivery vehicles include neutral gels of PEO or PVA, and gels of star molecules and other complex structures.

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