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Review Article

Hydrogels in Pharmaceutical Science

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Abstract

Recently, controlled release and sustained release drug delivery has become the standards in modern pharmaceutical design and an intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. The pharmaceutical applications of hydrogels are as a matrix for controlled drug delivery. Polymers are very useful with majority of hydrogels, which undergo reversible volume and sol-gel phase transitions in response to physiological (temperature, pH, ions present in fluids, blood glucose level) or other external (electric current, light) stimuli. These stimuli-sensitive hydrogels can be used for parenteral, ocular, vaginal, dermal and transdermal drug delivery.

Keywords: Hydrogels, pharmaceutical science.

1. Introduction

Over the past thirty years, greater attention has been focused on the development of controlled and sustained release drug delivery systems. The objective is in designing these systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, decreasing the dose required or providing uniform drug delivery[1]. Hydrogels were studied by scientists long before the existence of polymers was recognized. Wichterle and Lim proposed their use as contact lenses in 1960; this opened the door to other biomedical applications of hydrogels including drug delivery[2]. In drug delivery "hydrogels" is typically reserved for polymeric materials that can absorb a significant amount of water (>20% of its dry weight) while maintaining a distinct three-dimensional structure. Hydrogels thus defined are an important material in designing specialized drug delivery systems[3]. In recent years, there has been an explosion of interest in polymer based delivery devices.

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Such systems can-

- Enhance drug stability by protecting labile drugs from denaturants in the body.
- Control the release rate of therapeutic agents.
- Helps target release to chosen site in the body[4].

Hydrogels preformed by chemical and physical cross-linking form three-dimensional, hydrophilic, polymeric networks capable of imbibing large amount of water or biological fluids. They resembles natural living tissue more than the other class of synthetic biomaterials due to their high water content, furthermore, the high water content of the materials contributes their biocompatibility[5,6]. The more important feature is the high permeability of hydro gels to low molecular weight solutes. This allows the leaching of initiators, monomers and other impurities from the gel prior to use as drug delivery devices. Leaching of low molecular weight substances from biomaterials is known to be a leading cause of incompatibility. Under certain conditions, hydrogels even appear to be hydrophobic. This behavior is apparently due to the fact that the polymer chains have sufficient mobility to orient themselves with either hydrophilic or hydrophobic groups

exposed, depending on environment of the gel. An additional advantage of hydrogels, which has received considerable attention, recently is that they may provide desirable protection of labile drugs, peptides and proteins from potentially harsh environment in the vicinity of the release site[7]. Drug delivery systems based on chemically cross-linked hydrogels have been evaluated. A physically cross-linked poly (vinyl alcohol) gel has been used in a transdermal nitroglycerin product and morphine suppositories. ProstaglandinE_2 vaginal pessaries based on PEO hydrogels have been clinically evaluated. Lee has reported a controlled extraction process to immobilize a sigmoidal, non uniform initial drug profile in glassy hydrogel beads, which give rise to a zero order drug release behavior previously obtainable with only membrane reservoir delivery systems. If properly developed, this process can be utilized to rate programmed dosage forms to meet variety of therapeutic needs[8]. Hydrogels responsive to changes to their environment or external stimuli are also being applied to drug delivery problems and are the most investigated. Hyderogels providing such sensor properties can undergo reversible volume phase transitions and sol-gel transitions upon change in the environmental conditions. These 'intelligent' or 'smart' polymers play important role in the delivery, since they may dictate not only where a drug is delivered but also when and with which interval it is released[9]. The stimuli that induce various responses of the hydrogel systems include physical (temperature, electric fields, light, pressure, sound, magnetic fields), chemical (pH, ions) or biological / biochemical ones[10].

Large scale production of hydrogels

Despite the growing number of publications and patents on hydrogels and their applications, very little information is available in the literature addressing large-scale production of hydrogel devices. The two methods, which gains commercial status for synthesis are-

1. Bulk/ solution polymerization.
2. Suspension polymerization.

Stimuli-sensitive swelling-controlled release systems

Temperature-sensitive Hydrogels

Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug research. These hydrogels are able to swell as a result of changing in the temperature of the surrounding fluid. For convenience, temperature-sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive and thermally reversible gels[11]. Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST) and contract upon heating above LCST. Copolymers of (*N*-isopropylacrylamide) are usually used for negative temperature release. The most commonly used thermoreversible gels are prepared from poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) (pluronics, poloxamer). Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature, such a system would be easy to administer into desired body cavity[12].

pH-sensitive Hydrogels

All the pH-sensitive polymers contain acidic or basic groups that either accept or release protons in response to changes in environmental pH. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decrease if polymer contains weakly basic (cationic) groups. The most of anionic pH-sensitive polymers are based on PAA (Carbopol, carbomer) or its derivative[13].

Ion-sensitive Hydrogels

Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones. Gellan gum is an anionic polysaccharide that undergo *in situ* gelling in the presence of mono and divalent cations, including Ca^+, Mg^{2+}, K^+ and Na^+. Likewise algenic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca^+ due to the interaction with glucoronic acid blocks in alginate chains[14].

Glucose-sensitive Hydrogels

Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymer containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in pulsatile fashion[15].

Electric signal-sensitive Hydrogels

Hydrogels sensitive to electric current are usually made of polyelectrolytes such as pH-sensitive hydrogels. Electro-sensitive hydrogels undergo shrinking or swelling in the presence of an applied field. Block L.H. has evaluated chitosan gels as matrices for electrically modulated drug delivery. In electrification studies, release-time profiles for neutral (hydrocortisone), anionic (benzoic acid), and cationic (lidocaine). Drug molecules from hydrated chitosan gels were monitored in response to different milliamperages of current as a function of time[16].

Applications of Stimuli-sensitive Hydrogels

Ocular Delivery

The efficacy of ophthalmic hydrogels is mostly based on an increase of ocular residence time via enhanced viscosity and mucoadhesive properties. Among these polymers, *in situ* gels are preferred since they are easily dropped in the eye as a solution, where undergo transition into a gel. Poloxamer as thermogelling polymers could be applicable for the development of effective ophthalmic drug delivery[17]. Ion-sensitive polymers belong to the mainly used in situ gelling materials for ocular drug delivery. Slightly viscous gellan gum solutions in low concentrations show markedly increase in apparent viscosity when introduced in presence of physiological level of cations, without requiring more ions than 10-25% of those in tear fluid. Aqueous solutions of polyacrylic acid that transform into gels upon increase in pH may be used as *in situ* gelling ophthalmic drug delivery systems.

Parenteral Delivery

One of the most obvious ways to provide sustained release medication is to place the drug in a delivery system and inject or implant the system into the body tissue. Thermoreversible gels mainly prepared from poloxamers are predominantly used. The suitability of poloxamer gel alone or with the addition of hydroxypropylmethyl cellulose (HPMC), sodium carboxymethyl cellulose (CMC) or dextran was studied for epidural administration of drugs *in vitro.* The compact gel depot acted as the rate-limiting step and significantly prolonged the dural permeation of drugs. Barichello et al. evaluated pluronic F127 gels, which contained either insulin or insulin-PLGA nanoparticles with conclusion, that these formulations could be useful for the preparation of controlled delivery system. Likewise, poloxamer gels were tested for intramuscular and subcutaneous administration of human growth hormone.

Vaginal Delivery

The vagina, in addition to being an important organ of reproductive tract, serves as a potential route for drug administration. Formulations based on a thermoplastic graft copolymer that undergo *in situ* gelation have been developed to provide the prolonged release of active ingredient such as nonoxynol, progestins, estrogen, peptides and proteins.

Dermal and Transdermal Delivery

Thermally reversible gel of pluronic F127 was evaluated as a vehicle for percutaneous administration of indomethacin*. In-vivo* studies suggest that aqueous gel may be of practical use as a base for topical administration of the drug. Poloxamer gel was found suitable for transdermal delivery of insulin. The combination of penetration enhancers resulted in synergistic enhancement of insulin permeation[18].

Conclusion

The fascinating properties of the stimuli-sensitive polymers seem promising in many future applications and offer possible use as the next generation of materials in biological, biomedical and pharmaceutical products.

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