Stimuli-sensitive hydrogels in controlled and sustained drug delivery

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Summary. *Recently, controlled and sustained drug delivery has become the standard in modern pharmaceutical design and an intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. In this regard, many polymers are very useful with majority of hydrogels, which undergo reversible volume and/or sol-gel phase transitions in response to physiological (temperature, pH and present of ions in organism fluids, blood glucose level) or other external (electric current, light) stimuli. This article reviews the main stimuli-sensitive hydrogels and the use of these hydrogels in parenteral, ocular, peroral, rectal, vaginal, nasal, dermal and transdermal drug delivery.*

Introduction

Over the past 30 years greater attention has been focused on development of controlled and sustained drug delivery systems. The goal in designing these systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of the action, decreasing the dose required or providing uniform drug delivery.

Polymers have historically been the keys to the great majority in drug delivery systems. Hydrogels preformed by chemical or physical crosslinking form three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluid (1). They resemble natural living tissue more than any other class of synthetic biomaterials due to their high water content; furthermore, the high water content of the materials contributes to their biocompatibility. In this regard, the phase-change polymers, which may trigger drug release in response to external stimuli, are the most investigated. Hydrogels providing such 'sensor' properties can undergo reversible volume phase transitions or sol-gel phase transitions upon changes in the environmental condition. These "intelligent" or "smart" polymers play important role in drug delivery since they may dictate not only where a drug is delivered, but also when and with which interval it is released (2). 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 (biomolecules) ones (3).

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 delivery research. These hydrogels are able to swell or deswell 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 (1, 3).

Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST) and contract upon heating above the LCST. Copolymers of (*N*-isopropylacrylamide) (PNIAAm) are usually used for negative temperature release. Hydrogels show an on-off drug release (2) with on at a low temperature and off at high temperature allowing pulsatile drug release. LCST systems are mainly relevant for controlled release of drugs, and of proteins in particular (4). Thermosensitive polymers may be fixed on liposome membranes, in that case liposomes exhibit control of their content release (5).

A positive temperature-sensitive hydrogel has an upper critical solution temperature (UCST), such hydrogel contracts upon cooling below the UCST. Polymer networks of poly(acrylic acid) (PAA) and polyacrylamide (PAAm) or poly(acrylamide-co-butyl methacrylate) have positive temperature dependence of swelling (3).

The most commonly used thermoreversible gels are these prepared from poly(ethylene oxide)-*b*-poly(pro-

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pylene oxide)-*b*-poly(ethylene oxide) (Pluronics®, Tetronics®, poloxamer) (3, 4). 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. In some cases, if lowering the amount of thermogelling polymer is necessary, it may be blended with a pH-sensitive reversibly gelling polymer. Recently new series of biodegradable triblock copolymers were designed. The polymers consisting of poly(ethylene glycol)-poly-(DL-lactic acid-co-glycolic acid)-poly(ethylen glycol) (PEG-PLGA-PEG) (6) or PLGA-PEG-PLGA (7) were investigated for sustained injectable drug delivery systems. Some natural polymers like xyloglucan may also form thermoreversible gels (8).

Cappello et al. (9) developed novel "protein polymers" ProLastins, which undergo an irreversible sol-gel transition. When injected as a solution into the body, the material forms a firm, stable gel within minutes. It remains at the site of injection providing absorption times from less than one week to many months.

Electric signal-sensitive hydrogels

Hydrogels sensitive to electric current are usually made of polyelectrolytes such as the pH-sensitive hydrogels (3). Electro-sensitive hydrogels undergo shrinking or swelling in the presence of an applied electric field. S. Ramanathan and L. H. Block (10) evaluated and characterized the use of chitosan gels as matrices for electrically modulated drug delivery. In electrification studies, release-time profiles for neutral (hydrocortisone), anionic (benzoic acid) and cationic (lidocaine hydrochloride) drug molecules from hydrated chitosan gels were monitored in response to different milliamperages of current as a function of time. Likewise, chondroitin 4-sulphate hydrogels were examined by Jensen et al. (11) as potential matrices for the electro-controlled delivery of peptides and proteins.

Light-sensitive hydrogels

Light-sensitive hydrogels can be used in the development of photo-responsive artificial muscle (3) or as the *in situ* forming gels for cartilage tissue engineering (12). In the last study (12) gels that may undergo transdermal photopolymerization after subcutaneous injection were found to be applicable for drug release devices. T. Matsuda (13) developed novel tissue adhesive technology based on photocrosslinkable gelatin, which allows *in situ* drug-incorporated gelatinous gel formation on diseased tissue and sustained drug release. In situ photopolymerizable hydrogel systems for barriers and local drug delivery in the control of wound healing were also studied (14).

pH-sensitive hydrogels

All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH (3). The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups.

The most of anionic pH-sensitive polymers are based on PAA (Carbopol®, carbomer) or its derivatives (2). Likewise polyvinylacetal diethylaminoacetate (AEA) solutions with a low viscosity at pH 4 form hydrogel at neutral pH condition (15).

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 (16, 17). While κ-carrageenan forms rigid, brittle gels in reply of small amount of K^+, ι-carrageenan forms elastic gels mainly in the presence of Ca^{2+}. Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes *in situ* gelling in the presence of mono- and divalent cations, including Ca^{2+}, Mg^{2+}, K^+ and Na^+. Gelation of the low-methoxy pectins can be caused by divalent cations, especially Ca^{2+}. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e. g. Ca^{2+} due to the interaction with guluronic acid blocks in alginate chains.

Glucose-sensitive hydrogels

Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion (18). Another approach is based on competitive binding of insulin or insulin and glucose to a fixed number of binding sites in concanavalin A (19), where insulin is displaced in response to glucose stimuli, thus functioning as a self-regulating insulin delivery system. An alternative route through phenylborate-poly(vinyl alcohol) polymers was discussed by I. Hisamitsu et al. (20).

Applications of environment-sensitive hydrogels in drug delivery

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 (21). The suitability of poloxamer gel alone or with the addition of hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (CMC) or dextran was studied for epidural administration of drugs *in vitro* (22). The compact gel depot acted as the rate-limiting step and significantly prolonged the dural permeation of drugs in comparison with control solutions. J. M. Barichello et al. (23) evaluated Pluronic F127 gels which contained either insulin or insulin-PLGA nanoparticles with conclusion, that these formulations could be useful for the preparation of a controlled delivery system. Likewise, poloxamer gels were tested for intramuscular and subcutaneous administration of human growth hormone (24) or with the aim to develop a long acting single-dose injection of lidocaine (21). J. R. DesNoyer and A. J. McHugh (25) invented a new class of injectable controlled release depots of protein which consisted of blends of Pluronics with poly(D, L-lactide)/1-methyl-2-pyrrolidone solutions.

Some other termosensitive hydrogels may also be used for parenteral administration. ReGel® (triblock copolymer PLGA-PEG-PLGA) was used as a drug delivery carrier for the continuous release of human insulin (7). Steady amounts of insulin secretion from the ReGel® formulations up to day 15 of the subcutaneous injections were achieved. B. Jeong et al. (26) reported the synthesis of a biodegradable poly(ethylene oxide) and poly(L-lactic acid) hydrogel, which exists in a form of sol at an elevated temperature (around 45°C) and forms a gel after subcutaneous injection and subsequent rapid cooling to body temperature. A. Chenite et al. (27) developed novel thermally sensitive combinations of chitosan/polyol salts, which turn into gel implants, when injected *in vivo*. The authors presume that formulations may be a prototype for a new family of thermosetting gels highly compatible with biological compounds. Hydrogels formed by xyloglucan were also evaluated as a sustained release vehicle for the intraperitoneal administration of mitomycin (28).

PAA/polymethacrylic acid forms a pH-sensitive complex with PEG in situ, possessing the potential to release drug substances subcutaneously over a period of a few days (29). Alternatively, an aqueous solution containing MC in combination with polymethacrylate yields a reversible gel due to the change of temperature and pH shortly after parenteral administration.

Ocular delivery

The efficacy of ophthalmic hydrogels is mostly based on an increase of ocular residence time via enhanced viscosity and mucoadhesive properties. Since resulted swollen hydrogel is aqueous based, it is very comfortable in the human eye. Among these polymers, *in situ* gels are preferred since they are conveniently dropped in the eye as a solution, where undergo transition into a gel. Thermosensitive, specific ion sensitive or pH- sensitive hydrogels have been examined for their potential as vehicles for ocular drugs.

Poloxamers as thermogelling polymers could be applicable for the development of effective ophthalmic drug delivery (30). In order to reduce the concentration of polymer and/or to achieve a phase transition temperature higher than room temperature (25°C) and gelling at precorneal temperature (35°C), the combining Pluronic® analogs (30) or the addition of further polymer, e. g. PEG (31), PAA (32), methylcellulose (MC), HPMC, CMC (33) is often necessary. An alternative *in situ* gelling material of natural origin, xyloglucan, was evaluated for the sustained ocular delivery of pilocarpine (34) and timolol (35).

Ion-sensitive polymers belong to the mainly used in situ gelling materials for ocular drug delivery. Slightly viscous gellan gum solutions in low concentrations (<1%) show markedly increase in apparent viscosity, when introduced into presence of a physiological level of cations, without requiring more ions than 10–25% of those in tear fluid (36). The precorneal contact times for drugs can thus be extended up to 20-h (37). Gellan containing formulations of pilocarpine HCl allowed reduction of drug concentration from 2% to 0.5% obtaining the same bioavailability (38). The ability of gel formation at physiological Ca^{2+} levels was used in case of alginic acid as well. Presence of this polymer significantly extended the duration of the pressure reducing effect of pilocarpine to 10-h (39) and carteolol to 8-h (40) allowing only once a day administration in case of carteolol.

Aqueous solutions of PAA that transform into gels upon increase in pH may be used as *in situ* gelling ophthalmic drug delivery systems. However, the amount of PAA required to form stiff gel upon instillation in the eye is not easily neutralized by the buffering action of tear fluid. Combination PAA with a suitable viscosity enhancing polymer e. g. HPMC (41) or MC (42) allows a reduction in the PAA concentration without comprising the *in situ* gelling properties. The formulation containing Carbopol®940 and Methocel E50LV (HPMC) afforded sustained release of ofloxacin over an 8-h period (41).

Peroral drug delivery

The pH-sensitive hydrogels have a potential use in site-specific delivery of drugs to specific regions of

the GI tract. Hydrogels made of varying proportions of PAA derivatives and cross-linked PEG allowed preparing silicone microspheres, which released prednisolone in the gastric medium or showed gastroprotective property (43). Cross-linked dextran hydrogels with a faster swelling under high pH conditions, likewise other polysaccharides such as amidaded pectins, guar gum and inulin were investigated in order to develop a potential colon-specific drug delivery system (1). W. Kubo et al. (44) developed the formulations of gellan and sodium alginate both containing complexed calcium ions that undergo gelation by releasing of these ions in the acidic environment of the stomach. Oral delivery of paracetamol was studied.

Rectal delivery

The rectal route may be used to deliver many types of drugs that are formulated as liquid, semi-solid (ointments, creams and foams) and solid dosage forms (suppositories). Conventional suppositories often cause discomfort during insertion. In addition, suppositories are unable to be sufficiently retained at a specific position in the rectum, sometimes they can migrate upwards to the colon, that makes them possible for drug to undergo the first-pass effect. H.-G. Choi et al. (45) developed novel *in situ* gelling liquid suppositories with gelation temperature at 30–36°C. Poloxamer 407 and/or poloxamer 188 were used to confer the temperature-sensitive gelation property. Bioadhesive polymers were used to modulate the gel strength and the bioadhesive force. Bioavailibility of acetaminophen was studied. C. Charrueau et al. (46) proposed 18% poloxamer 407 solution as a vehicle for short-chain fatty acid enemas. After gelation at 37°C it allows control release of short-chain fatty acids. S. Miyazaki et al. (8) investigated the potential use of thermoreversible xyloglucan gels for rectal drug delivery. A more sustained release of indomethacin was achieved in vitro in comparison with commercial suppositories.

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 ingredients such as nonoxynol-9, progestins, estrogens, peptides and proteins (47). J. Y. Chang et al. (48) have recently reported a mucoadhesive thermosensitive gel (combination of poloxamers and polycarbophil) which exhibited increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation.

Dermal and transdermal delivery

Thermally reversible gel of Pluronic F127 was evaluated as vehicle for the percutaneous administration of indomethacin (49). In-vivo studies suggest that 20% w/w aqueous gel may be of practical use as a base for topical administration of the drug. Poloxamer 407 gel was found suitable for transdermal delivery of insulin (50). The combination of chemical enhancers and iontophoresis resulted in synergistic enhancement of insulin permeation.

Nasal delivery

Nasal formulations of AEA with chlorpheniramine maleate and tetrahydrozoline hydrochloride were investigated (15). The findings suggest that liquid AEA formulations facilitate the instillation into the nose and the hydrogel formed on the mucous membrane provide controlled drug release.

Conclusions

Different types of functional polymers have been investigated for series of drugs in vitro or in vivo. As a result, new and interesting controlled and sustained delivery strategies have become available. 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. However, there is still a basic need for more details in this area.

Poveikiui jautrūs hidrogeliai vartojant kontroliuojamo ir nenutrūkstamo veikimo vaistus

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Raktažodžiai: poveikiui jautrūs polimerai, hidrogeliai, kontroliuojamas vaistų veikimas.

Santrauka. Dabartinėje farmacijoje kontroliuojamo ir nenutrūkstamo veikimo vaistai įprasti. Intensyvūs

moksliniai tyrimai vykdomi siekiant sukurti efektyvesnius, patikimesnius ir saugesnius vaistus. Tam gali būti labai naudingi polimerai, ypač galintys virsti hidrogeliais, kurie grįžtamai keičia savo tūrį ar iš solio virsta geliu, ir atvirkščiai, atsakydami į fiziologinius (temperatūra, organizmo skysčių pH ir juose esantys jonai, gliukozės kiekis kraujyje) ar kitus išorinius (elektros srovė, šviesa) veiksnius. Šiame straipsnyje apžvelgiami pagrindiniai veiksniams jautrūs hidrogeliai bei jų pritaikymas vartojant vaistus parenteraliai, į akis, per os, per rectum, vaginaliai, į nosį bei transdermaliniu būdu.

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