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Review

A Review on Smart Hydrogels: An Innovative Approach in New Drug Delivery Carriers

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ABSTRACT

In recent years, significant advancements in the field of advanced materials and hydrogel engineering have enabled the design and fabrication of smart hydrogels and nanogels that exhibit sensitivity to specific signals or pathological conditions, leading to a wide range of applications in drug delivery and disease treatment. Amongst the various novel routes of drug delivery, the field of ocular drug delivery is one of the most interesting and challenging .As an isolated and delicate organ, eye is very difficult to study from a drug delivery point of view. Despite this limitation, improvements have been made with the objective of maintaining the drug in the biophase for prolonged period of time. A major problem facing in ocular therapeutics is the attainment of an optimal drug concentration at the site of action. To achieve effective ophthalmic therapy, an adequate amount of active ingredient must be delivered and maintained within the eye. The most frequently used conventional dosage forms, i.e. eye solutions, ointments, gels, and suspensions are compromised in their effectiveness by several limitations leading to very poor ocular bioavailability and residing time. Ophthalmic use of viscosity-enhancing agents, penetration enhancers, cyclodextrins, prodrug approaches, and ocular inserts, and the ready existing drug carrier systems along with their application to ophthalmic drug delivery are common to improve ocular bioavailability. Amongst these stimuli sensitive hydro gels are important, which undergo reversible volume and/or sol-gel phase transitions in response to physiological (temperature, pH, ions, enzyme substrate) or other external (electric current, light) stimuli. They help to increase in precorneal residence time of drug to a sufficient extent that an ocularly delivered drug can exhibit its maximum biological action. The concept of this innovative ophthalmic delivery approach is to decrease the systemic side effects and to create a more pronounced effect with lower doses of the drug. The present article describes applications and results obtained by using stimuli sensitive hydrogel systems in ophthalmic drug delivery.

Keywords: Hydrogel, *In-situ* gel, instillation, ocular, stimuli sensitive

INTRODUCTION:

"Smart" hydrogels, or stimuli-sensitive hydro gels, are very different from inert hydro gels in that they can "sense" changes in environmental properties such as pH and temperature and respond by increasing or decreasing their degree of swelling. The volume-changing behavior of "smart" hydro gels is particularly useful in drug delivery applications as drug release can be triggered upon environmental changes. These "intelligent" or "smart" can dictate not only where a drug is delivered, but also when and with which interval it is released.

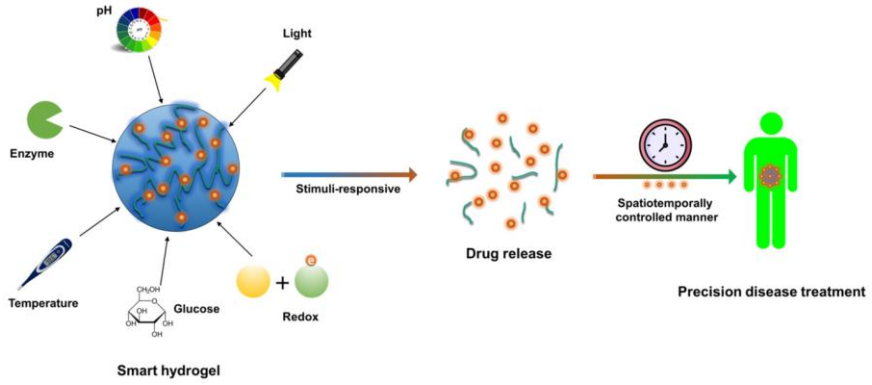

Figure 1. An overview of stimuli-responsive / Smart hydrogels

There are many mechanisms have been employed to cause reversible sol-gel phase transition by different stimuli in physiological environmental conditions of human body.

The stimuli that induce various responses of the hydrogel systems include-

1. Physical: Change in temperature, electric fields, light, pressure, sound, and magnetic fields.
2. Chemical: Change in pH and ion activation from biological fluid.
3. Biological/biochemical (bimolecular) : Change in glucose level

In ophthalmic drug delivery three types of stimuli-sensitive hydrogels - Temperature sensitive, pH sensitive and Ion-sensitive hydrogels are mainly used. Details are discussed further.

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 de-swell as a result of changing in the temperature of the surrounding fluid. For convenience, temperature-sensitive hydrogels are classified into negatively thermo sensitive, positively thermo sensitive and thermally reversible gels.[9]

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 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. Thermo sensitive polymers may be fixed on liposome membranes; in that case liposomes exhibit control of their content release.[10] 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.

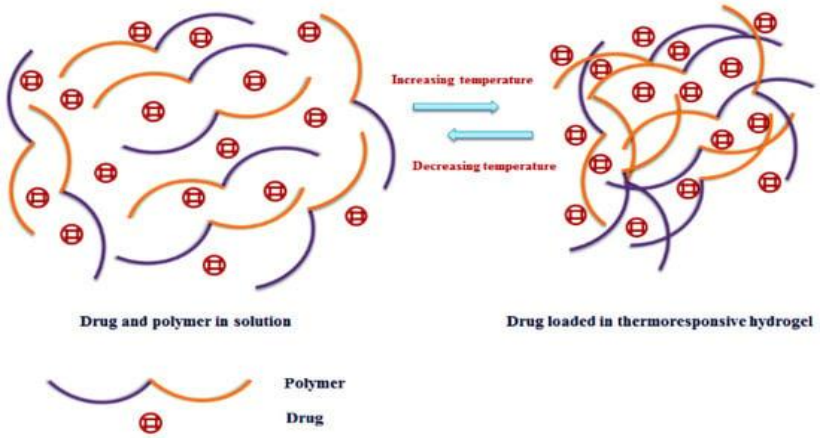

Figure 2 - Thermo responsive hydrogel formation using temperature as a trigger.

The most commonly used thermo reversible gels are these prepared from poly (ethylene oxide)-*b*-poly (propylene oxide)-*b*-poly (ethylene oxide) (Pluronics®, Tetronics®, poloxamer)[11] 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 thermo gelling 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 (ethylene glycol) (PEGPLGA- PEG)[12] or PLGA-PEG-PLGA[13] were investigated for sustained inject able drug delivery systems. Some natural polymers like xyloglucan may also form thermoreversible gels.[14]

Poloxamers are thermo reversible gels that seem to fulfill the aforementioned conditions. Poloxamers are a broad group of compounds that were introduced in the early 1950s as food additives and for pharmaceutical preparations. These water-soluble surfactants are triblock co-polymers[15] prepared from poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) commercially available as Pluronic® are the most commonly used thermosetting polymers and could be applicable for the development of effective ophthalmic drug delivery.[16]

Three principal mechanisms have been proposed to explain the liquid-gel phase transition after an increase in temperature, including:

1. Gradual desolvation of the polymer,
2. Increased micellar aggregation, and
3. The increased entanglement of the polymeric network.

pH-sensitive hydrogels:

These hydrogels respond to changes in pH of the external environment. These gels have ionic groups (which are readily ionizable side groups) attached to impart peculiar characteristics. Some of the pH sensitive polymers used in hydrogels' preparations are polymethyl methacrylate (PMMA), polyacrylamide (PAAm), polyacrylic acid (PAA), poly dimethylaminoethylmethacrylate (PDEAEMA) and polyethylene glycol. These polymers though in nature are hydrophobic but swells in water depending upon the pH prevalent in the external environment. Any change in pH of the biological environment causes changes in the swelling behavior, for example, the hydrogel of caffeine is prepared with poly-mer PDEAEMA at pH below 6.6. As the polymer shows high swellability but when pH changes to higher side, the polymer showed shrinkage leading to drug release. The other pH-sensitive hydrogels are copolymer of PMMA and polyhydroxy ethyl methyl acrylate (PHEMA), which are anionic copolymers, swell high in neutral or high pH but do not swell in acidic medium. It was also observed that pH and ionic strength determines kinetics of swelling of PHEMA and guar gum [17,18]

Cellulose acetate phthalate (CAP) latex, cross linked acrylic, and derivatives such as carbomer are used. Cellulose acetate derivatives are the only polymer known to have a buffer capacity that is low enough to gel effectively in the cul-de-sac of the eye. The pH change of about 2.8 units after instillation of the native formulation (pH 4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into viscous gel.

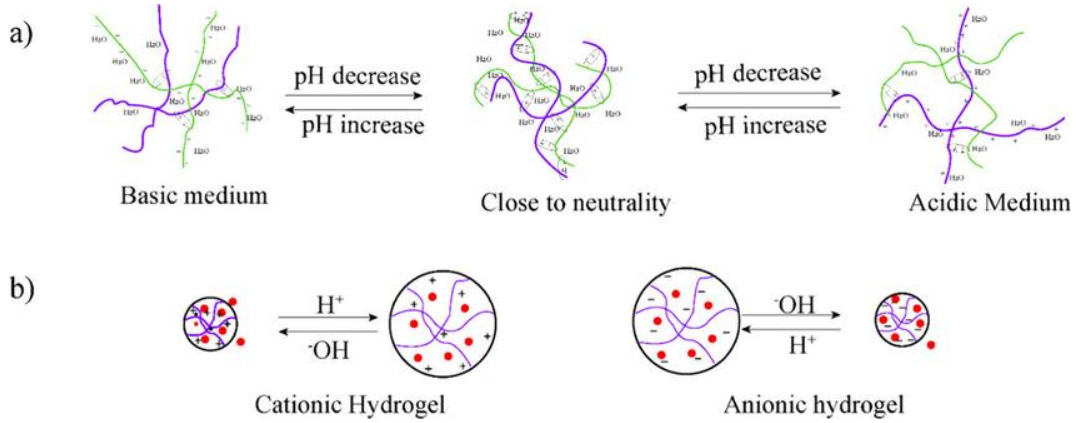

Figure 3- An Overview of the pH-sensitive structural change

Ion-sensitive hydrogels:

Ion-sensitive polymers belong to the mainly used *in situ* gelling materials for ocular drug delivery. Gelling of the instilled solution is also triggered by change in ionic strength. It is assumed that the rate at which electrolytes from the tear fluid is absorbed by the polymer will depend on the osmotic gradient across the surface of the gel. It is therefore likely that the osmolality of the solution might have an influence on the rate of the sol-gel transition occurring in the eye. One example is Gelrite, an anionic extra cellular polysaccharide, low acetyl Gellan gum secreted by pseudomonas elodea. Gelrite formulations in aqueous solutions form a clear gel in the presence of the mono or divalent cations typically found in the tear fluids. The electrolyte of the tear fluid and especially Na+, Ca++, and Mg++ cations are particularly suited to initiate gelation of the polymer when instilled as a liquid solution in to the cul-de-sac. Gelrite has been the most widely studied and seems to be preferred compared to the pH sensitive or temperature setting systems. The polymeric concentration is much lower compared to previously described systems.[19] 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.[20] The precorneal contact times for drugs can thus be extended up to 20-h.[21] Gellan-containing formulations of pilocarpine HCl allowed reduction of drug concentration from 2% to 0.5% obtaining the same bioavailability.

Hence, stimuli-sensitive hydrogels are better alternative for ophthalmic drug delivery of pharmaceuticals; they show the following advantages[22]:

- Prolonged drug release
- Reduced systemic side effects
- Reduced number of applications
- Better patient compliance

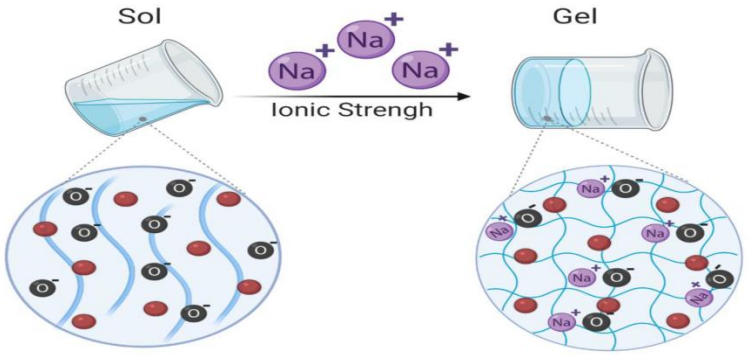

Figure 4: An Overview of the Ion-sensitive hydrogel

Applications in treating different diseases[23,24,25]

Comprehending the unique biological or pathological conditions of specific diseases is a fundamental requirement for the creation and application of smart hydrogels in drug delivery and therapy. With increasing insights into the distinct characteristics of each disease's microenvironment, researchers can tailor smart hydrogels with appropriate functional groups that can react to particular triggers like ph, temperature, redox reactions, enzymes, or disease-specific signals. We discussed the unique pathological or biological conditions of each disease and how to use them to design corresponding smart hydrogels.

- *Oral Disease:*

The physiological actions within the oral cavity, such as saliva production and chewing, play a substantial role in minimizing the stay of therapeutic medications in periodontal disease. This has resulted in significant interest in utilizing hydrogels for oral disease treatment due to their excellent bio adhesion, biocompatibility, and ease of administration. Smart hydrogels have been researched for addressing oral diseases such as periodontitis and implantitis. These responsive hydrogels can undergo reversible sol–gel transitions in situ and control drug release

upon exposure to varied triggers such as temperature, pH, ROS, or enzymes, which can significantly improve the efficacy of oral disease treatment.

- *Cancer:*

In spite of the availability of diverse treatments, achieving optimal efficacy in anti-cancer therapies remains challenging. The primary hurdles in effective cancer treatment involve the emergence of resistance in cancer cells to chemotherapy, compromised intracellular drug transport, deactivation of therapeutic agents, and pronounced systemic and organ toxicity. As a solution, hydrogels/nanogels have been harnessed as drug carriers, offering controlled drug release at tumor sites with reduced toxicity and a response to specific triggers, making them more suitable for cancer treatment compared to other carriers. These smart nanogels can respond to stimuli within the tumor microenvironment, such as changes in pH, temperature, light, redox, etc., enabling a precisely managed drug release for cancer therapy.

Moreover, tumor tissues generally possess a lower pH compared to normal tissues. This pH discrepancy can be exploited to devise pH-sensitive hydrogels that modulate the delivery and release of anti-tumor drugs specifically at tumor sites. Liu designed a pH-responsive peptide nanogel to concurrently release two anti-tumor drugs, gemcitabine and paclitaxel, at the same location to enhance the anti-tumor effect and prevent drug resistance. In vivo experimentation confirmed the nanogel's ability to reach the tumor site, ensuring gradual and continuous release of the two drugs in the tumor microenvironment.

- *Wound Healing and Topical Application:*

The wound healing process can be categorized into acute and chronic healing. Acute wounds, resulting from skin breakage or puncture, typically heal quickly and are categorized based on their causes, such as surgical incisions, thermal injuries, abrasions, lacerations, and gunshot wounds. In contrast, chronic wounds, often associated with conditions like diabetes and obesity, require a longer healing duration due to the disruption of the normal healing cascade caused by extensive inflammation, impaired angiogenesis, etc. Wound healing involves various cell types and distinct phases—homeostasis, inflammation, proliferation, and maturation. Traditional wound dressings like bandages, dumb hydrogels, and foams are insufficient in addressing the wound healing process. Smart hydrogels have emerged as wound dressings that can interact with wounds, detecting and responding to changes in the wound condition, facilitating effective healing.

Furthermore, the concept of self-healing hydrogels has emerged, allowing them to autonomously repair themselves when damaged, thus enhancing their stability and resilience when promoting chronic wound healing.

- *Neurological Disorders:*

Drug resistance in neurological diseases is a significant challenge that occurs at various levels, including genomic and proteomic levels, affecting cellular transporters and disrupting signaling pathways. This resistance hinders the therapeutic effect of drugs and leads to severe health complications. Stimuli-responsive hydrogels exhibit the potential to mitigate drug resistance in neurological disorders by orchestrating controlled drug release and targeted delivery. These hydrogels can be fine-tuned to respond to distinct stimuli, like pH, temperature, or enzymes, ensuring precise drug release at designated sites. Another challenge in neurological disease treatment is the formidable blood–brain barrier, which shields the brain but also prevents many drugs from entering the brain. Hydrogels offer distinct advantages for treating neurological conditions, primarily due to their capability to deliver bioactive agents and cells across the blood–brain barrier. Consequently, hydrogels are emerging as promising candidates to address prevalent neurological diseases—ranging from Alzheimer's, Parkinson's, spinal cord injuries, and stroke to brain tumors. Furthermore, hydrogels can mimic the properties of the central nervous system's extracellular matrix, making them ideal carriers for drug delivery and tissue regeneration. Specifically, injectable hydrogels can minimize invasiveness during administration and can encapsulate exogenous cells and therapeutic molecules, while providing a permissive environment for cell survival and propagation.

- *Diabetes:*

Diabetes represents a substantial contemporary healthcare challenge, characterized by disrupted glucose metabolism leading to conditions such as hyperglycemia, glycosuria, and hyperlipidemia. The global annual cost for treating diabetes reaches billions of dollars. While multiple daily insulin injections are commonly used, they are invasive and

can lead to suboptimal patient compliance. Insulin delivery has evolved from direct injections to advanced hydrogel-based methods that respond to various stimuli, including glucose, pH, electric, or magnetic fields, triggering insulin release. For instance, glucose-sensitive hydrogels can mimic the behavior of pancreatic beta cells by releasing insulin upon changes in glucose levels. Similarly, pH-sensitive polymeric hydrogels can facilitate oral insulin delivery, shielding insulin from stomach acid degradation and enabling its release in the neutral pH of the intestine. Among these approaches, glucose-responsive hydrogels and artificial beta cell therapy stand out as the most promising solutions.

- *Cardiovascular and Cerebrovascular Diseases:*

Cardiovascular diseases (CVDs), including atherosclerosis, vascular inflammation, and rheumatic heart disease, have stood as the foremost global cause of mortality for many years. While stem cell transplantation and growth factor therapy hold promise in treating these diseases, their efficacy is impeded by the low survival rates of cells/growth factors at injury sites. To address this challenge, the emergence of smart hydrogels has opened new avenues for CVD treatment. Stimuli-responsive hydrogels offer a smart solution, enabling precise control over the spatiotemporal release of therapeutic agents, a capability absent in traditional hydrogels.

Challenges and Future Perspectives:

Smart hydrogels exhibit the potential to enhance therapeutic outcomes through their sensitivity to various stimuli. Nevertheless, there are limitations and obstacles that must be overcome in order to optimize these DDSs.

One significant limitation is the safety of newly developed materials. Given the growing utilization of newly synthesized polymers and chemical components in smart hydrogel construction, it is imperative to thoroughly assess and verify their safety prior to their utilization in clinical applications. Materials that have been approved by the FDA or those with a history of prolonged use without notable side effects are preferred choices for the fabrication of stimuli-responsive hydrogels.

Another limitation is the need for novel smart hydrogel systems that exhibit enhanced and precise stimuli responses in clinical trials. Despite numerous publications on stimuli-responsive hydrogel systems, only a handful have successfully transitioned to practical clinical use. The majority of published stimuli-responsive hydrogel systems are not suitable for product development. Take glucose-responsive hydrogels, for instance, where the primary issue is that most proposed systems exhibit sluggish responsiveness to fluctuations in blood-glucose levels. The second issue is the insufficient efficacy of glucose-responsive hydrogels in human clinical trials. Although certain smart hydrogels, like A1 and B29-oligofucosyl-insulin (MK-2640), have yielded promising outcomes in diabetic dog and minipig models, the successful evaluation of glucose-responsive insulin delivery systems in human clinical trials has not yet been achieved. This discrepancy is likely attributed to the incomplete understanding of quantitative differences across species, which complicates the prediction of clinical outcomes of glucose-responsive insulin's when translated to humans.

Addressing these limitations is vital to advancing the field of stimuli-responsive hydrogels. Future advancements rely on expanding their capabilities through the integration of innovative biomaterials and the utilization of cutting-edge fabrication techniques. The creation of more intricate hydrogel structures, closely mimicking the natural cellular microenvironment, can be achieved by harnessing micro fluidic systems or the revolutionary potential of 3D-printing technology. This opens up exciting possibilities for engineering hydrogels that can seamlessly adapt to the dynamic microenvironment within the human body. Concurrently, there is significant potential in the development of smart hydrogels with multi-stimuli responsiveness, which holds the key to achieving precision and personalization in drug delivery strategies.

Conclusion:

The main efforts in ocular drug delivery during the past two decades has been on the design of systems to prolong the residence time of topically applied drugs in conjunctival sac. The most widely developed drug delivery system is represented by the polymeric hydrogels. Hydrogels generally offer a moderate improvement of ocular drug bioavailability despite their favorable bio adhesive properties. One of the disadvantages is that hydrogel may result in blurred vision as well as foreign body sensation to patients. Stimuli activated gel-forming systems seem to be preferred as they can be administered in drop form and create significantly less problems with vision. Moreover, they provide good sustained release properties. Thus, 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, because as with non-viscous eye drops, accurate and precise sustained release properties with little or no eye irritation is possible. However, there is still a basic need for more details in this area.

References:

1. Saettone MS, Bucci P. Kinetics of topically applied drugs. In: Maurice DM, Saettone MS, Bucci P, Speiser P, editors. Ophthalmic drug delivery, biopharmaceutical, technological and clinical aspects, Fidia research series. Vol. 11. Padova: Livinia press; 1987. pp. 19–26.
2. Alfonso R, Gennaro. Remington pharmaceutical sciences. 18th ed. Pennsylvania: Mack Publishing Company; 1990. Ophthalmic Preparation; p. 1581.
3. Keister JC, Cooper ER, Missel PJ, Lang JC, Hager DF. Limits on optimizing ocular drug delivery. J Pharm Sci. 1991; 80:50–3. doi: 10.1002/jps.2600800113.
4. Shyamala B, Lakshmi PK, Harish GG. Topical ocular drug delivery-A Review. Indian J Pharm Sci. 2005;67:404–8.
5. Monem AS, Ali FM, Ismail MW. Prolonged effect of liposomes encapsulating pilocarpine HCL in normal and glaucomatons rabbits. Int J Pharm. 2000;198:29–38. doi: 10.1016/s0378-5173(99)00348-8.
6. Cohen S, Lobel E. A novel in situ forming ophthalmic drug delivery system from alginates undergoing gelation in the eye. J Controlled Release. 1997;44:201–8.
7. Patton TF, Robinson JR. Ocular evaluation of polyvinyl alcohol vehicle in rabbits. J Pharm Sci. 1975;64:1312–6. doi: 10.1002/jps.2600640811.
8. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev. 2001;53:321–39. doi: 10.1016/s0169-409x(01)00203-4.
9. Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm. 2000; 50:27–46. doi: 10.1016/s0939-6411(00)00090-4.
10. Kono K. Thermosensitive polymer-modified liposomes. Adv Drug Deliv Rev. 2001; 53:307–19. doi: 10.1016/s0169-409x(01)00204-6.
11. Bromberg LE, Ron ES. Temperature-responsive gels and thermogelling polymer matrices for protein and peptide delivery. Adv Drug Deliv Rev. 1998;31:197–221. doi: 10.1016/s0169-409x(97)00121-x.
12. Jeong B, Choi YK, Bae YH, Zentner G, Kim SW. New biodegradable polymers for injectable drug delivery systems. J Control Release. 1999; 62:109–14. doi: 10.1016/s0168-3659(99)00061-9.
13. Kim YJ, Choi S, Koh JJ, Lee M, Ko KS, Kim SW. Controlled release of insulin from injectable biodegradable triblock copolymer. Pharm Res. 2001; 18:548–50. doi: 10.1023/a:1011074915438.
14. Miyazaki S, Suisha F, Kawasaki A, Shirakawa M, Yamatoya K, Attwood D. Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. J Control Release. 1998;56:75–83. doi: 10.1016/s0168-3659(98)00079-0.
15. Alexandridis P, Hatton TA. Poly (ethylene oxide) Poly (propylene oxide)-poly (ethylene oxide) block co-polymer surfactants in aqueous solutions and at interface thermodynamic, structure, dynamic, and modeling. Colloids Surf A Physicochem Eng Asp. 1995;96:1–46.
16. Wei G, Xu H, Ding PT, Li SM, Zheng JM. Thermosetting gels with modulated gelation temperature for ophthalmic use: The rheological and gamma scintigraphic studies. J Control Release. 2002;83:65–74. doi: 10.1016/s0168-3659(02)00175-x.
17. Miller SC, Donovan MD. Effect of Poloxamer 407 gel on the miotic activities of pilocarpine nitrate in rabbit. Int J Pharm Sci. 1982;12:147–52.
18. Edsman K, Carlfors J, Petersson R. Rheological evaluation of poloxamers as an in situ gel for ophthalmic use. Eur J Pharm Sci. 1998;6:105–12. doi: 10.1016/s0928-0987(97)00075-4.
19. Ling HR, Sung KC. Carbopol/pluronic phase change solutions for ophthalmic drug delivery. J Control Release. 2000;69:379–88. doi: 10.1016/s0168-3659(00)00329-1.
20. Peppas LB, Peppas NA. Dynamic and equilibrium behavior of pH sensitive hydrogels containing 2-hydroxy ethyl methacrylates. Biomaterials. 1990;11:635–44. doi: 10.1016/0142-9612(90)90021-h.

21. Das A, Wadhwa S, Srivastava AK. Cross-linked guar gum hydrogels discs for colon-specific delivery of ibuprofen: Formulation and in-vitro evaluation. Drug Deliv. 2006;13:139–42. doi: 10.1080/10717540500313455.
22. Bhaskaran S, Lakshmi PK, Harish CG. Topical ocular drug delivery: A review. Indian J Pharm Sci. 2005;64:404–8.
23. Paulsson MH, Hägerström H, Edsman K. Rheological studies of the gelation of deacetylated gellan gum (Gelrite®) in physiological conditions. Eur J Pharm Sci. 1999;9:99–105. doi: 10.1016/s0928-0987(99)00051-2.
24. Carlfors J, Edsman K, Petersson RJ, Jörnving K. Rheological evaluation of Gelrite® in situ gels for ophthalmic use. Eur J Pharm Sci. 1998;6:113–9. doi: 10.1016/s0928-0987(97)00074-2.
25. Yulong Zhang,Benjamin M. Wu Current Advances in Stimuli-Responsive Hydrogels as Smart Drug Delivery Carriers

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