

**OPHTHALMIC MUCOADHESIVE POLYMERS - A LITERATURE REVIEW****V.S. Kashikar***

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ABSTRACT

Delivery of drugs to the eye is complicated by the efficient removal mechanisms in the precorneal area which serve to maintain a good refractive surface. The absorption of drugs into the eye requires a prolonged precorneal residence time and good corneal permeation. However, for most drugs corneal permeation is low. Since the precorneal drug concentration acts as the driving force for passive diffusion, the corneal epithelium and conjunctival membranes act as reservoirs for potential absorption into the eye and surrounding structures. The mucus layer covering the cornea and conjunctiva is an important target to improve drug retention by mucoadhesion of a polymer excipient, especially one that specifically attaches to the corneal rather than to conjunctival mucin. The attached polymer-mucin bond can then be used to entrap soluble, colloidal and particulate material on the eye surface. This review includes literature on various temperature, pH, and ion induced in situ-forming polymeric systems used to achieve prolonged contact time of drugs with the cornea and increase their bioavailability.

Keywords: Mucoadhesive polymers, Poloxamer, Xyloglucan, Cellulose derivative, Chitosan, Gallen gum, Pseudolatexes, Carbomer.

INTRODUCTION

The eye is a specialized sensory organ that is relatively secluded from systemic access by the blood-retinal, blood-aqueous, and blood-vitreous barriers; as a consequence, the eye exhibits some unusual pharmacodynamic and pharmacokinetic properties. The rapid turnover of lacrimal fluid and efficient drainage apparatus profoundly affect the bioavailability of topically applied ophthalmic drugs. The amount of drug reaching the anterior chamber of the eye is dependent on two competing processes: the rate of drug loss from the precorneal area and the rate of drug uptake by the cornea. When an ophthalmic solution is instilled into the lower cul-de-sac, the reflex action of blinking causes a substantial portion of the drop to be lost to the drainage apparatus and some may spill over onto the cheek. Removal of the instilled volume continues until the total tear volume returns to the normal resident volume. A further consideration is the effect of turnover rate of lacrimal fluid on the concentration and amount of drug remaining on the eye. As the precorneal volume (lacrimal and instilled) gets smaller, the turnover rate of lacrimal fluid will have a greater influence on the residual drug concentration. An optimum volume is required to allow the maximum amount of drug to be in contact with the eye for the maximum period of time, with a minimum of drug loss. The precorneal drug concentration acts as a driving force for drug uptake. If this concentration falls below the epithelial surface concentration, drug reflux into the cornea ceases. The rapid clearance from the ocular surface and the relatively slow absorption through the cornea pose significant problems in drug delivery. Only a small fraction of the instilled drug survives the numerous loss processes experienced in the precorneal area and becomes available for absorption into the cornea. In summary, the success of any topical ocular

drug delivery system depends on good corneal penetration plus retention at the site of drug absorption. Ophthalmic research has been directed towards improving the topical route of administration, primarily to increase the amount of drug at the site of absorption and to increase its duration of contact with the target site. Several drug delivery systems have been developed in an attempt to increase drug bioavailability including polymeric solutions, ointments, soluble and insoluble inserts, and phase transition systems. Dosage forms that adhere to mucous membranes have been investigated as a method of optimizing drug delivery. It has been proposed that mucoadhesion occurs after wetting of the adhesive surface, by the interpenetration of the adhesive molecules and mucus glycoprotein followed by the formation of secondary chemical bonds. The concept of mucoadhesion in the eye is to seek polymers that will attach to corneal or conjunctival mucin, via non-covalent bonds, and remain in contact with precorneal tissues until mucin turnover causes elimination of the polymer: in other words, the weaker bond is the mucin-mucin bond rather than the mucin-polymer bond. This would substantially improve ocular drugs in terms of ocular drug bioavailability. While several polymers will attach to mucin through both covalent and non-covalent bonds, non-covalent bonding is preferred as the strength of attachment in many cases is sufficiently strong to be considered essentially irreversible. However, if the bond is too strong, the polymer offers resistance to blinking and eye movement and will feel uncomfortable in the eye; an ideal mucoadhesive system for ophthalmic use should exhibit only weak adhesive properties. Mucoadhesive polymers both water-soluble and water-insoluble can be placed in front of the eye and attach to the mucin coating. Water-soluble mucoadhesives slowly dissolve in the tear film whereas water-insoluble



polymers would be retained until the mucin is replaced (estimated to be 15-20 h in man) or more commonly until the shear force of blinking dislodges the mucoadhesive system. Most water-insoluble mucoadhesive polymers have hydrophilic groups that interact with water molecules and expand the polymer network to a more flexible and mobile state. The stretched and entangled mucoadhesive polymer in contact with the hydrophilic mucus substrate matches its active adhesive sites to those on the substrate to form adhesive bonds¹. A new approach is to try to combine advantages of both

solutions and gels, such as accuracy and facility of administration of the former and prolonged residence time of the latter. Thus in situ hydrogels can be instilled as eye drops and undergo an immediate gelation when in contact with the eye. In situ-forming hydrogels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. Three methods have been employed to cause phase transition on the surface: change in temperature, pH, and electrolyte composition (**Table 1**).

Table 1: Stimuli sensitive polymers²⁻⁷

Stimuli	Mechanism	Examples
Temperature	Formulation is liquid at room temperature (20-25°C) which undergoes gelation in contact with body fluid (35-37°C). Temperature increases degradation of polymer chains which leads to formation of hydrophobic domains & transition of an aqueous liquid to hydrogel network.	Poloxamer/ Pluoronic Xyloglucan Cellulose derivative
Ionic interactions	Formulation undergoes liquid- gel transition under influence of an increase in ionic strength Gel formation takes place because of complexation with polyvalent cations (like Ca ²⁺) in lacrimal fluid.	Chitosan Gallen gum/Gelrite Alginate
pH change	Sol to gel transition when pH rose from 4.2 to 7.4. At higher pH polymer forms hydrogen bonds with mucin which leads to formation of hydrogel network	Pseudolatexes Carbomer (Acrylic acid) Cellulose acetate phthalate latex (CAP- Latex) Polyox

REVIEW OF PAST WORKDONE ON THE POLYMERS

Qian Y *et al*⁸, in this study, a thermosensitive in situ gelling vehicle was prepared to increase the precorneal resident time and the bioavailability of methazolamide. The optimum concentrations of poloxamer analogs for the in situ gel-forming delivery system were 21% (w/w) poloxamer 407 and 10% (w/w) poloxamer P188. In vitro release studies demonstrated a diffusion-controlled release of MTA from the poloxamer solutions over a period of 10 hours. In vivo evaluation indicated that the poloxamer solutions had a better ability to retain drug than MTA eyedrops did.

Ammar HO *et al*⁹, utilized Poloxamer 407 with its thermoreversible gelation and surface active properties to formulate a novel dorzolamide hydrochloride in situ gel nanoemulsion (NE) delivery system for ocular use. The optimum formulation of in situ gel NE consisted of Triacetin (7.80%), Poloxamer 407 (13.65%), Poloxamer 188 (3.41%), Miranol C2M (4.55%), and water (70.59%). Biological evaluation of the designed dorzolamide formulation on normotensive albino rabbits indicated that this formulation had better biological performance, faster onset of action, and prolonged effect relative to either drug solution or the market product. The formula showed a superior pharmacodynamic activity compared to the in situ gel dorzolamide eye drops. This indicated the effectiveness of the in situ gel properties of

poloxamer 407, besides formulating the drug in an NE form for improving the therapeutic efficacy of the drug.

Cao F *et al*¹⁰, developed new method for ophthalmic delivery of azithromycin by poloxamer/carbopol-based in situ gelling system. Addition of Carbopol 974P (CP 974P) to the gelling systems could increase the solubility of ATM by salt effect and enhance the mucoadhesive property of the systems. Gelation temperature of these systems ranged from 31.21-36.31 degrees C depending on the ratio of P407 and P188. Mucoadhesion force of the system composed of P407/P188/CP 974P (21/5/0.3%, w/v) was 2.3-fold that without carbopol 974P. The formulation exhibited a 24-h sustained release of ATM.

Shastri DH *et al*¹¹, formulated an in situ gelling thermoreversible mucoadhesive gel of an antibacterial agent, Moxifloxacin HCl using a combination of poloxamer 407 and poloxamer 188 with different mucoadhesive polymers such as Xanthan gum and Sodium alginate with a view to increase gel strength and bioadhesion force and thereby increased precorneal contact time and bioavailability of the drug. Formulations were found transparent, uniform in consistency and had good spreadability within a pH range of 6.8 to 7.4. The order of drug release was in order: Xanthan gum > Sodium alginate.

Bhowmik M *et al*¹², studied effect of salts on gelation and drug release profiles of methylcellulose-based ophthalmic



thermo-reversible in situ gels. The gel temperature of 1% w/v methylcellulose (MC) was 60 degrees C. It was found that 5-7% w/v sodium chloride (NaCl), 8-9% w/v potassium chloride (KCl), or 5% w/v sodium bicarbonate (NaHCO₃) was capable of decreasing the gel temperature below physiological temperature, i.e. 37 degrees C. It can be concluded that the salted MC solutions were a better alternative than the MC solution to enhance the ocular bioavailability of the drug.

Liu Y *et al*¹³, studied in situ gelling gelrite/alginate formulations as vehicles for ophthalmic drug delivery of matrine. It was found that the optimum concentration of Gelrite solution for the in situ gel-forming delivery systems was 0.3% (w/w) and that for alginate solution was 1.4% (w/w). The mixture of 0.2% Gelrite and 0.6% alginate solutions showed significant enhancement in gel strength at physiological condition. In vivo pharmacological studies indicated that the Gelrite/alginate solution had the better ability to retain drug than the Gelrite or alginate solutions alone.

Gratieri T *et al*¹⁴, formulated a poloxamer/chitosan in situ forming gel with prolonged retention time for ocular delivery. The results showed that chitosan improves the mechanical strength and texture properties of poloxamer formulations and also confers mucoadhesive properties in a concentration-dependent manner. After a 10-min instillation of the poloxamer/chitosan 16:1 formulation in human eyes, 50-60% of the gel was still in contact with the cornea surface, which represents a fourfold increased retention in comparison with a conventional solution.

Gupta S *et al*¹⁵, studied dual-drug delivery system based on in situ gel-forming nanosuspension of forskolin to enhance antiglaucoma efficacy. By formulating Noveon AA-1 polycarboxyl/poloxamer 407 platforms, at specific concentrations, it was possible to obtain a pH and thermoreversible gel with a pH(gel)/T (gel) close to eye pH/temperature. Investigations successfully prove that the pH and thermoreversible polymeric in situ gel-forming nanosuspension with ability of controlled drug release exhibits a greater potential for glaucoma therapy.

Al-Kassas RS *et al*¹⁶, developed ophthalmic controlled release in situ gelling systems for ciprofloxacin based on polymeric carriers. Carbopol and alginates polymers were used to confer gelation properties to the formulations. Hydroxypropylmethylcellulose and methylcellulose were combined with carbopol to increase the viscosity of the gels and to reduce the concentration of the incorporated carbopol.

Singh SR *et al*¹⁷, used L-Carnosine: multifunctional dipeptide buffer for sustained-duration topical ophthalmic formulations. Specific utilisation of L-carnosine as a buffer in gellan gum carrying vehicles was characterised. Combinations of 7.5 mm L-carnosine with 0.06-0.6% (w/v) gellan gum were characterized rheologically. A unique formulation combining timolol (which lowers intraocular pressure) in L-carnosine-buffered gellan gum was compared with Timoptic-XE.

Functional synergy between excipients in gellan gum formulations buffered with L-carnosine has potential for topical ocular dosage forms with sustained precorneal residence.

Mayol L *et al*¹⁸, studied the influence of hyaluronic acid (HA) on the gelation properties of poloxamers blends with the aim of engineering thermosensitive and mucoadhesive polymeric platforms for drug delivery. The optimised systems were loaded with acyclovir and its release properties studied in vitro. By formulating poloxamers/HA platforms, at specific concentrations, it was possible to obtain a thermoreversible gel with a T(gel) close to body temperature. In vitro release experiments indicated that the optimized platform was able to prolong and control acyclovir release for more than 6h.

Mansour M *et al*¹⁹, developed ocular poloxamer-based ciprofloxacin hydrochloride in situ forming gels. The in situ forming gels were prepared using different concentrations of poloxamer 407 (P407) and poloxamer 188 (P188). Mucoadhesives such as hydroxypropylmethyl cellulose (HPMC) or hydroxyethyl cellulose (HEC) were added to the formulations to enhance the gel bioadhesion properties. Ciprofloxacin HCl in situ forming gel formulae composed of P407/P188/HPMC (18/13/1.5%, wt/wt), and P407/P188/HEC (18/13/0.5%, wt/wt) showed optimum release and mucoadhesion properties and improved ocular bioavailability as evidenced by an enhanced therapeutic response compared with the marketed conventional eye drops.

Jain SP *et al*²⁰, formulated in situ ophthalmic gel of ciprofloxacin hydrochloride for once a day sustained delivery. The in situ gelling system involves the use of polyacrylic acid (Carbopol 980NF) as a phase transition polymer, hydroxypropyl methylcellulose (Methocel K100LV) as a release retardant, and ion exchange resin as a complexing agent. Ciprofloxacin hydrochloride was complexed with ion exchange resin to avoid incompatibility between drug and polyacrylic acid. The developed formulation was stable, and nonirritant to rabbit eyes and in vitro drug release was found to be around 98% over a period of 24 hours.

Ma WD *et al*²¹, studied temperature-responsive, Pluronic-g-poly(acrylic acid) copolymers in situ gels for ophthalmic drug delivery. The in vivo experimental results, along with the rheological properties and in vitro drug release studies, demonstrated that in situ gels containing Pluronic-g-PAA copolymer may significantly prolong the drug resident time and thus improve bioavailability. The results showed that the Pluronic-g-PAA copolymer can be a promising in situ gelling vehicle for ophthalmic drug delivery.

Liu Z *et al*²², studied ocular pharmacokinetics of ion-activated in situ gelling ophthalmic delivery system for gatifloxacin by microdialysis. The conventional ophthalmic solution of gatifloxacin was used as reference. The developed formulation has a higher bioavailability



and longer residence time in aqueous humor than conventional ophthalmic solutions.

Gupta H *et al*²³, described formulation and evaluation of an ocular delivery system of timolol maleate based on the concept of both temperature and pH-triggered in situ gelation. Pluronic F-127 (a thermosensitive polymer) in combination with chitosan (pH-sensitive polymer also acts as permeation enhancer) was used as gelling agent. Developed formulation was clear, isotonic solution that converted into gel at temperatures above 35 degrees C and pH 6.9-7.0. The developed system is a viable alternative to conventional eye drops for the treatment of glaucoma and various other ocular diseases.

Cao Y *et al*²⁴, investigated a novel copolymer, poly(N-isopropylacrylamide)-chitosan (PNIPAAm-CS), for its thermosensitive in situ gel-forming properties and potential utilization for ocular drug delivery. The in vivo ocular pharmacokinetics of timolol maleate in PNIPAAm-CS solution were evaluated and compared to that in conventional eye drop solution by using rabbits according to the microdialysis method. Results suggest that PNIPAAm-CS is a potential thermosensitive in situ gel-forming material for ocular drug delivery, and it may improve the bio-availability, efficacy, and compliance of some eye drugs.

Liu Z *et al*²⁵, studied an alginate/HPMC-based in situ gelling ophthalmic delivery system for gatifloxacin. Alginate (Kelton) was used as the gelling agent in combination with HPMC (Methocel E50Lv) which acted as a viscosity-enhancing agent. Both in vitro release studies and in vivo pre-corneal retention studies indicated that the alginate/HPMC solution retained the drug better than the alginate or HPMC E50Lv solutions alone. These results demonstrate that the alginate/HPMC mixture can be used as an in situ gelling vehicle to enhance ocular bioavailability and patient compliance.

Yoo MK *et al*²⁶, studied release of ciprofloxacin from chondroitin 6-sulfate-graft-ploxamer hydrogel in vitro for ophthalmic drug delivery. The bioadhesive and thermally gelling of these graft copolymers will be expected to be an excellent drug carrier for the prolonged delivery to surface of the eye.

Lin HR *et al*²⁷, prepared in situ gelling of alginate/pluronic solutions for ophthalmic delivery of pilocarpine. The optimum concentration of alginate solution for the in situ gel-forming delivery systems was 2% (w/w) and that for Pluronic solution was 14% (w/w). The mixture of 0.1% alginate and 14% Pluronic solutions showed a significant increase in gel strength in the physiological condition; this gel mixture was also found to be free flowing at pH 4.0 and 25 degrees C. Both in vitro release and in vivo pharmacological studies indicated that the alginate/Pluronic solution retained pilocarpine better than the alginate or Pluronic solutions alone.

Balasubramaniam J *et al*²⁸, developed an ophthalmic delivery system of the NSAID indomethacin, based on the

concept of ion activated in situ gelation. Gelrite gellan gum, a novel ophthalmic vehicle, which gels in the presence of mono or divalent cations present in the lacrimal fluid, was used as the gelling agent. The developed formulations were therapeutically efficacious (in a uveitis induced rabbit eye model) and provided sustained release of the drug over an 8-hour period in vitro.

El-Kamel AH *et al*²⁹, developed Pluronic F127 (PF127) based formulations of timolol maleate (TM) aimed at enhancing its ocular bioavailability. The effect of isotonicity agents and PF127 concentrations on the rheological properties of the prepared formulations was examined. In an attempt to reduce the concentration of PF127 without compromising the in situ gelling capabilities, various viscosity enhancing agents were added to PF127 solution containing 0.5% TM. The viscosity of formulations containing thickening agents was in the order of PF-MC 3%>PF-HPMC 2%>PF-CMC 2.5%>PF127 15%. The slowest drug release was obtained from 15% PF127 formulations containing 3% methylcellulose.

Miyazaki S *et al*³⁰, formed in situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. In vitro release of pilocarpine from gels formed by warming xyloglucan sols (1.0, 1.5 and 2.0% w/w) to 34 degrees C followed root-time kinetics over a period of 6 h. The degree of enhancement of miotic response following sustained release of pilocarpine from the 1.5% w/w xyloglucan gel was similar to that from a 25% w/w Pluronic F127 gel.

Srividya B *et al*³¹, described sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system. Polyacrylic acid (Carbopol 940) was used as the gelling agent in combination with hydroxypropylmethylcellulose (Methocel E50LV) which acted as a viscosity enhancing agent. The developed formulation was therapeutically efficacious, stable, non-irritant and provided sustained release of the drug over an 8-h period. The developed system is thus a viable alternative to conventional eye drops.

Lin HR *et al*³², developed and characterized a series of carbopol- and pluronic-based solutions as the in situ gelling vehicles for ophthalmic drug delivery. It was found that the optimum concentration of carbopol solution for the in situ gel forming delivery systems was 0.3% (w/w), and that for pluronic solution was 14% (w/w). The mixture of 0.3% carbopol and 14% pluronic solutions showed a significant enhancement in gel strength in the physiological condition; this gel mixture was also found to be free flowing at pH 4.0 and 25 degrees C. The results demonstrated that the carbopol/pluronic mixture can be used as an in situ gelling vehicle to enhance the ocular bioavailability.



CONCLUSION

The development of ophthalmic drug delivery systems is easy because we can easily target the eye to treat ocular diseases and complicated at the same time because the eye has specific characteristics, which make the development of ocular drug delivery systems extremely difficult. The most widely developed drug delivery system is represented by the polymeric hydrogels. In situ 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. Over the last decades, an impressive number of novel temperature, pH, and ion induced in-situ forming solutions have been described in the literature. Each system has its own advantages and drawbacks. The choice of a particular hydrogel depends on its intrinsic properties and envisaged therapeutic use.

REFERENCES

- Jane L. Greaves and Clive G. Wilson., Treatment of diseases of the eye with mucoadhesive delivery systems. *Advanced Drug Delivery Reviews*, 11 (1993) 349–383
- Basavaraj K. Nanjawade ., F.V. Manvi , A.S. Manjappa., Review In situ-forming hydrogels for sustained ophthalmic drug delivery. *Journal of Controlled Release* 122 (2007) 119–134
- Hongyi Qi , Wenwen Chen et al., Development of a poloxamer analogs/carbopol-based in situ gelling and mucoadhesive ophthalmic delivery system for puerarin. *International Journal of Pharmaceutics* 337 (2007) 178–187
- Annick Ludwig., The use of mucoadhesive polymers in ocular drug delivery. *Advanced Drug Delivery Reviews* 57 (2005) 1595– 1639
- Lin C, Metters AT. Hydrogels in controlled release formulations: Network design and mathematical modelling. *Adv Drug Deliv Rev* 2006;58: 1379–1408.
- Garipey ER, Leroux GC. In situ-forming hydrogels—review of temperaturesensitive systems. *Eur J Pharm Biopharm* 2004;58: 409–26.
- Tomme SRV, Storm G, Hennink EW. *In situ* gelling hydrogels for pharmaceutical and biomedical applications. *Int J Pharm* 2008; 355:1–18.
- Qian Y, Wang F, Li R, Zhang Q, Xu Q., Preparation and evaluation of in situ gelling ophthalmic drug delivery system for methazolamide. *Drug Dev Ind Pharm*. 2010 Nov; 36(11):1340-7.
- Ammar HO, Salama HA, Ghorab M, Mahmoud AA., Development of dorzolamide hydrochloride in situ gel nanoemulsion for ocular delivery. *Drug Dev Ind Pharm*. 2010 Nov; 36(11):1330-9.
- Cao F, Zhang X, Ping Q., New method for ophthalmic delivery of azithromycin by poloxamer/carbopol-based in situ gelling system. *Drug Deliv*. 2010 Sep-Oct;17(7):500-7.
- Shastri DH, Prajapati ST, Patel LD., Design and Development of Thermoreversible Ophthalmic In Situ Hydrogel of Moxifloxacin HCl. *Curr Drug Deliv*. 2010 May 24.
- Bhowmik M, Bain MK, Ghosh LK, Chattopadhyay D., Effect of salts on gelation and drug release profiles of methylcellulose-based ophthalmic thermo-reversible in situ gels. *Pharm Dev Technol*. 2010 Apr 30.
- Liu Y, Liu J, Zhang X, Zhang R, Huang Y, Wu C., In situ gelling gelrite/alginate formulations as vehicles for ophthalmic drug delivery. *AAPS PharmSciTech*. 2010 Jun;11(2):610-20.
- Gratieri T, Gelfuso GM, Rocha EM, Sarmento VH, A poloxamer/chitosan in situ forming gel with prolonged retention time for ocular delivery. *Eur J Pharm Biopharm*. 2010 Jun;75(2):186-93.
- Gupta S, Samanta MK, Raichur AM., Dual-drug delivery system based on in situ gel-forming nanosuspension of forskolin to enhance antiglaucoma efficacy. *AAPS PharmSciTech*. 2010 Mar; 11(1):322-35.
- Al-Kassas RS, El-Khatib MM., Ophthalmic controlled release in situ gelling systems for ciprofloxacin based on polymeric carriers. *Drug Deliv*. 2009 Apr; 16(3):145-52.
- Singh SR, Carreiro ST, Chu J, Prasanna G, et. Al., L-Carnosine: multifunctional dipeptide buffer for sustained-duration topical ophthalmic formulations. *J Pharm Pharmacol*. 2009 Jun; 61(6):733-42.
- Mayol L, Quaglia F, Borzacchiello A, Ambrosio L, La Rotonda ML., A novel poloxamers/hyaluronic acid in situ forming hydrogel for drug delivery: rheological, mucoadhesive and in vitro release properties. *Eur J Pharm Biopharm*. 2008 Sep;70(1):199-206.
- Mansour M, Mansour S, Mortada ND, Abd Elhady SS., Ocular poloxamer-based ciprofloxacin hydrochloride in situ forming gels. *Drug Dev Ind Pharm*. 2008 Jul;34(7):744-52.
- Jain SP, Shah SP, Rajadhyaksha NS, Singh P S PP, Amin PD., In situ ophthalmic gel of ciprofloxacin hydrochloride for once a day sustained delivery. *Drug Dev Ind Pharm*. 2008 Apr;34(4):445-52.
- Ma WD, Xu H, Nie SF, Pan WS., Temperature-responsive, Pluronic-g-poly(acrylic acid) copolymers in situ gels for ophthalmic drug delivery: rheology, in vitro drug release, and in vivo resident property. *Drug Dev Ind Pharm*. 2008 Mar; 34(3):258-66.
- Liu Z, Yang XG, Li X, Pan W, Li J., Study on the ocular pharmacokinetics of ion-activated in situ gelling ophthalmic delivery system for gatifloxacin by microdialysis. *Drug Dev Ind Pharm*. 2007 Dec;33(12):1327-31.
- Gupta H, Jain S, Mathur R, Mishra P, Mishra AK, Velpandian T., Sustained ocular drug delivery from a temperature and pH triggered novel in situ gel system. *Drug Deliv*. 2007 Nov;14(8):507-15.
- Cao Y, Zhang C, Shen W, Cheng Z, Yu LL, Ping Q., Poly(N-isopropylacrylamide)-chitosan as thermosensitive in situ gel-forming system for ocular drug delivery. *J Control Release*. 2007 Jul 31; 120(3):186-94.
- Liu Z, Li J, Nie S, Liu H, Ding P, Pan W., Study of an alginate/HPMC-based in situ gelling ophthalmic delivery



- system for gatifloxacin. *Int J Pharm.* 2006 Jun 6;315(1-2):12-7.
26. Yoo MK, Cho KY, Song HH, Choi YJ, et al., Release of ciprofloxacin from chondroitin 6-sulfate-graft-poloxamer hydrogel in vitro for ophthalmic drug delivery. *Drug Dev Ind Pharm.* 2005 May;31(4-5):455-63.
27. Lin HR, Sung KC, Vong WJ., In situ gelling of alginate/pluronic solutions for ophthalmic delivery of pilocarpine. *Biomacromolecules.* 2004 Nov-Dec;5(6):2358-65.
28. Balasubramaniam J, Kant S, Pandit JK., In vitro and in vivo evaluation of the Gelrite gellan gum-based ocular delivery system for indomethacin. *Acta Pharm.* 2003 Dec;53(4):251-61.
29. Cho KY, Chung TW, Kim BC, et al., Release of ciprofloxacin from poloxamer-graft-hyaluronic acid hydrogels in vitro. *Int J Pharm.* 2002 Jul 8;241(1):47-55.
30. Miyazaki S, Suzuki S, Kawasaki N, Endo K, Takahashi A, Attwood D., In situ gelling xyloglucan formulations for sustained release ocular delivery of pilocarpine hydrochloride. *Int J Pharm.* 2001 Oct 23;229(1-2):29-36.
31. Srividya B, Cardoza RM, Amin PD., Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system. *J Control Release.* 2001 Jun 15;73(2-3):205-11.
32. Lin HR, Sung KC., Carbopol/pluronic phase change solutions for ophthalmic drug delivery. *J Control Release.* 2000 Dec 3;69(3):379-88.

