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A Review: Polymeric *In-situ* Gel System

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Review Article

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ABSTRACT

Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered. *In-situ* gel structure occurs due to one or combination of different stimuli like pH change, temperature modulation and ionic exchange. The formation of gels depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets released in a sustained and controlled manner. Mainly *In-situ* gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. The *In-situ* gel forming polymeric formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery systems. The article presents a detailed review of these types of polymeric systems, their evaluation, advancements and their commercial formulations. From a manufacturing point of view, the production of such devices is less complex and thus lowers the investment and manufacturing cost.

INTRODUCTION

Over the past two decades, extensive research has been performed in the design of polymeric drug delivery systems among them, are a new series of thermoplastic, biodegradable, hydrogels based on star shaped poly (ether-ester) block copolymers can be used for drug delivery having improved biocompatibility, mass transport, biodegradability and process ability and thus can provide a better way of drug delivery at the site of infection. Polymeric compounds have been widely used in designing the implantable controlled release delivery systems due to various advantages such as predictability of drug release profile, ease of administration and ease of fabrication etc, which they provide over the conventional formulation. The *In-situ* setting semisolid drug depots are being developed as alternative delivery systems. These systems are made of biodegradable products, which can be injected via a syringe into the infected area and once injected; solidify to form a semisolid depot.

Advantage

This novelty has been sparked by the advantages shown by *In-situ* forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort.

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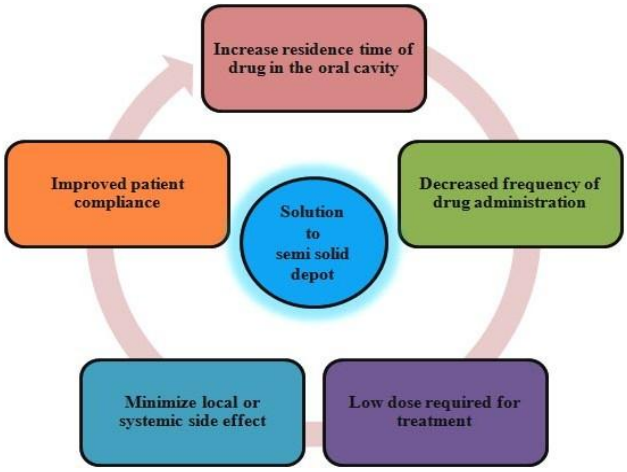
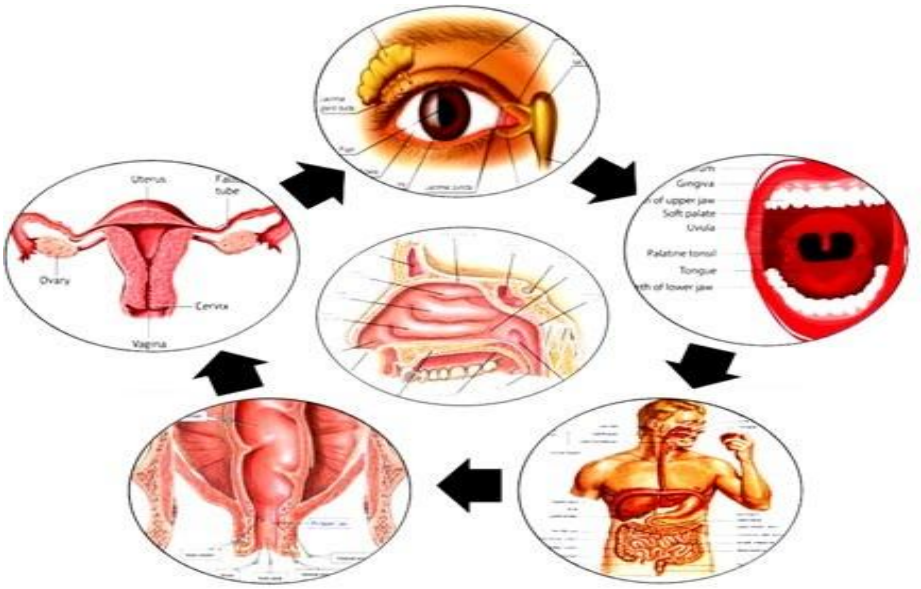


Route of Administration

In-situ gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes.



Polymeric *In-situ* System

Indrajeet Gonjari1 *et al.*, studied the potential of various mucoadhesive polymers on the retain ability of the ophthalmic gel of fluconazole in the intraocular therapy. Ocular delivery of topically applied drugs such as fluconazole is hampered by elimination of the solution due to tear turnover, so an *In-situ* gelling thermoreversible mucoadhesive gel was formulated. Thermosensivity mucoadhesive gels were prepared using the cold method along with poloxamer 407 and different mucoadhesive polymers such as hydroxy ethyl cellulose (HEC), hydroxy propyl methyl cellulose (HPMC) K4M, and polyvinyl pyrrolidone (PVP) K30[1].

Harish Nairy Matapady *et al.*, designed an *In-situ* gel formulation of fluconazole with mucoadhesive properties for prolonging buccal residence time and thereby better therapeutic effects. In addition, they afford intimate contact between a dosage form and the absorbing tissue, which may result in high drug concentration in local area. The *In-situ* formulation will have better patient acceptability since the formulation will be applied in the form of sols, which upon contact will form the corresponding gels causing less irritation or pain[2].

Joseph Jagur Grodzinskia., proposed that hydrogel system are formed when a three-hdimensional polymeric network is loosely crosslinked. They are swollen by water but not dissolved in it. Hydrogels may display reversible sol-gel transitions, induced by changes in the environmental conditions such as temperature, pH, ionic strength, phase separation, wave length of light, crystallinity, etc. Hydrogel is described as smart, when sharp transition is induced by small change in such conditions. For the shape memory hydrogels,soln-gel reversible change in shape may also be induced by such stimuli like ion,pH,temperature reverse[3].

Basavaraj Nanjawade *et al*., made an attempt of ophthalmic drug delivery for sustaining the drug delivery in the ocular cavity using *In-situ* hydrogels. The conventional ophthalmic drug delivery systems like solutions, suspensions, and ointments show drawbacks such as increased precorneal elimination, high variability inefficiency, and blurred vision respectively. *In-situ*-forming hydrogels are liquid before administration and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel depot and this provides a response to environmental changes. In the past few years, an impressive number of novel temperature induced, pH sensitive, and ion induced *In-situ*-forming systems have been reported for sustain ophthalmic drug delivery[4].

Sudipta Ganguly *et al*., investigated a novel chitosan-glyceryl monooleate (GMO) *In-situ* gel system for sustained drug delivery and targeting. The delivery system consisted of 3% (w/v) chitosan and 3% (w/v) GMO in 0.33 M citric acid. *In-situ* gel was formed at a biological pH. In vitro release studies were performed in Sorensen's phosphate buffer pH 7.4 [5].

Wataru Kubo *et al*., has studied the effect of gellan gum (1.0% w/v) and sodium alginate (1.5% w/v) containing ca^{++} ions in a complexed form on the sustainability of para amino phenol delivery by the formation of hydrogels in the stomach of rabbit and rat after oral administration. It resulted in the formation of *In-situ* gel depots in rabbit and rat stomachs as a consequence of the release of the calcium ions in the acidic environment. In vitro studies demonstrated diffusion-controlled release of para amino phenol from the gels over a period of 6h[6].

Lee *et al*., prepared the formulation for the local delivery of vancomycin with the use of pluronic F127 for the effective treatment of otitis media caused by methicillin resistant *Staphylococcus aureus* (MRSA).The phase transition property of pluronic F127, which is liquid at room temperature and becomes solid at body temperature [7].

El Hady., proposed that mebeverine hydrochloride (MbHCl) suffers from extensive first pass effect and the bioavailability of it can be superior and its absorption can be restricted to lower rectum only by using rectal solution having gelation temperature range of 30-37 C. Mixtures of Pluronic 407 and Pluronic 188 were used for the temperature sensitive gelation property. The cold method was used for the preparation of rectal solutions. Hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), methyl cellulose (MC) and polyvinylpyrrolidone K-25 (PVP K-25) were used to modulate gel strength and to impart bioadhesive force to MbHCl-poloxamer rectal solution. Addition of 10% MbHCl in rectal solution was found to increase gelation temperature of Pluronic mixtures while the effect was reversed upon the addition of bioadhesive polymers [8].

Gonjari and Kasture., designed a nasal controlled release formulation of a model drug propranolol hydrochloride restricted within liposomes separate in a thermoreversible gel by using polymer like poloxamer 407 and combination of poloxamer 407 with bioadhesive polymer like carbopol 934P. Liposomes were formulated by reverse phase evaporation method using soya lecithin and cholesterol in different ratios. The combination of soya lecithin and cholesterol showing maximum percentage setup was used for further spreading into gel prepared by using thermoreversible polymer and thermoreversible gel containing a mucoadhesive [9].

Dongkai., designed a thermosensitive nasal gel system of dextromethorphan hydrobromide and also in vitro drug release studies. The thermo induced polymer used for the preparation of nasal drop was Pluronic 407. Vertical diffusion cell was used for in vitro drug release study. The Pluronic solution of 20% w/w concentration and 2.5% w/w PEG 6000 is liquid at room temperature, and then undergoes a phase transition to a semisolid gel when being heated up to 33°C. Higuchi equation kinetics(r>0.99) is followed by drug release form Pluronic vehicle. This formulation thus prove to be efficient than traditional nasal preparations [10].

Majithiya *et al*., investigated a thermoreversible mucoadhesive gel formulation for intranasal delivery of sumatriptan using thermoreversible polymer poloxamer F127 and mucoadhesive polymer carbopol 934P. Preparation were developed so as to have gelation temperature below 34°C so that gelation will be at physiological temperature after intranasal administration [11].

Pisal, Reddy., designed a thermoreversible pluronic gel system for nasal administration of Melatonin for use in case of sleep disorders. With the use of cold method, aqueous poloxamer gels containing drug (0.5 mg/0.1ml), PEG 400 and PEG 15000 were studied for gelation and gel melting. Melatonin shifted gelation range to higher temperature while PEG narrowed the gel range. It was observed that increase in poloxamer concentration, flux of diffusion decreased. Bimodal pattern was observed with pluronic gel (20%w/w, 1mg/0.1 ml) showing a desired peak flux (0.248µg/min./cm^2) at 300min. Nasal cavity gels prepared show fast onset of action and induced sleep within fifteen minutes. They proved that melatonin gels can be used in the treatment of circadian cycle sleep disorders [12].

Charrueau *et al*., evaluated the use of Pluronic 407 for rectal administration of short chain fatty acids. Five thermogels were prepared with Pluronic 407 at concentrations ranging from 17% to 20% and viscosities were precise at room temperature and 37°C, and their gelling temperatures were determined. From the threshold concentration of 17.5%, the solutions show sign of Newtonian character at room temperature (50-80 mPa.s), gelled at 37°C.The higher the concentration & the higher the viscosity (1750 to 49,000 mPa.s), the

lower the gelling temperature (27.6°C to 23.4°C), and the stronger the work of adhesion (2.2 to 4.5 mJ). Short chain fatty acid release from the 18% polymer gel was decreased by 60% compared to the rectal solution. The 18% Pluronic 407 concentration provided a solution that was liquid at room temperature that gelled at 37°C, possessed adhesive properties, and controlled short-chain fatty acid release [13].

Zhou and Donovan., designed a system used putative bioadhesive polymers such as methylcellulose, SCMC, HPMC, CP 934P, chitosan glutamate and poloxamer F127 for the study of mucociliary clearance with the use of rat model. The mucociliary clearance for these polymer gels from nasal cavity was determined by following removal of microspheres which are fluorescently labeled and incorporated in the formulation. It was found that the poloxamer F127 and other polymer gel formulations have longer residence times and hence decrease mucociliary clearance [14].

Bochot A., intended at providing an ophthalmic delivery system based on the dispersion of liposomes into a thermosensitive gel made of a copolymer of ethylene oxide and propylene oxide (Pluronic 407). At high concentration of 20-30% and temperature of about 20°C, Pluronic 407 passes from a solution to a gel. In place of stabilization of liposomes in the gel, PEG2000-DSPE was introduced in their composition. Adsorption studies investigated by size and ζ-potential measurements have exposed that the adsorption was higher for positively charged or neutral non-sterically stabilized liposomes. Pluronic 407 adsorbed to a lower extent with negatively charged or PEG-DSPE containing liposomes. Moreover using a fluorescent aqueous marker, it was shown that liposome permeability was dramatically reduced in the presence of Pluronic 407 when PEG-DSPE was incorporated into the liposomes. This data suggests that Pluronic 407 could adsorb, at different extents, to all types of vesicles but that bilayer destabilization by the copolymer was reduced when liposomes were sterically stabilized. This was explains by the poor accessibility of the Pluronic to the phospholipidic which is the possible consequence of the steric repulsion effect induced by polyethylene glycol. Finally, it was shown that the thermosensitivity of Pluronic 407 was maintained after introducing the liposomes into the gel [15].

Gupta, Singh., investigated a pH mediated *In-situ* gelling system using prilocaine for periodontal anesthesia using combination of chitosan ad hydroxyl propyl methylcellulose. The gel so developed can be used as anesthetic in lengthy dental surgery. The gel was evaluate for many parameters like gelation P^H, viscosity, physiochemical properties, In vitro release, sterility and stability.gel with chitosan (0.25%w/v) and HPMC (0.25%) was establish to have good gelatin near ph 7.4 (P^H of mucous) with prolong action [16].

Qi *et al*., discussed on the problems of regular ophthalmic solutions often eliminate rapidly after administration and cannot provide and maintain an adequate application of the drug in the precorneal area. To solve these problems, they developed a thermosensitive *In-situ* gelling and mucoadhesive ophthalmic drug release system containing puerarin based on poloxamer analogs (21% (w/v) poloxamer 407/5% (w/v) poloxamer 188) and carbopol (0.1% (w/v) or 0.2% (w/v) carbopol 1342P NF). The combined solutions would transfer to firm gels under physiological condition and attach to the ocular mucosal surface for a relative long time. The incorporation of carbopol 1342P NF not only did not affect the pseudoplastic behavior with hysteresis of the poloxamer analogs solution and leaded to a higher shear stress at each shear rate, but also improved the mucoadhesive force significantly. In vitro release studies established diffusion-controlled release of puerarin from the combined solutions over a period of 8 h [17].

Shi-lei Cao *et al*., studied a novel *In-situ* system for nasal delivery of MF and study its efficacy on allergic rhinitis model. An ion-activated *In-situ* gel was developed and characterized with gellan gum as a carrier. The system was stable kept at 40 ± 2 °C for 6 months, and the micrographic results showed that *In-situ* gel was safety without mucosa irritation [18].

Noha Cao *et al*., investigated to develop a mucoadhesive *In-situ* gel with reduced nasal mucociliary clearance in order to improve the bioavailability of the antiemetic drug, metoclopramide hydrochloride (MCP HCl). The *In-situ* gelation upon contact with nasal mucosa was conferred via the use of the thermogelling poloxamer 407 whereas mucoadhesion and drug release enhancement were modulated via the use of mucoadhesive and polyethylene glycol (PEG) polymers respectively. The results revealed that the different mucoadhesives augmented the gel viscosity but reduced its sol-gel transition temperatures ($T_{sol-gel}$) and the drug release. The inclusion of PEG counteracted the effect of the mucoadhesive polymers whereby it decreased the gel consistency and increased the $T_{sol-gel}$ as well as the *in vitro* drug release. The formulations with favorable sol-geltransition temperatures (25-32 °C) and high *in vitro* drug release (100% release in 60 min) were also rheologically stable upon storage. The mucoadhesiveness test was performed *in vivo* in rats, results showed that the carbopol-containing *In-situ* gel prolonged the mucociliary transport time from 10 min (control solution) to 52 min (mucoadhesive gel) and maintained nasal mucosal integrity after 14-days application. The bioavailability study in rabbits revealed that the absolute bioavailability of MCP HCl was significantly increased from 51.7% in case of the oral drug solution to 69.1% in case of the nasal *In-situ* gel. The study point to the potential of mucoadhesive nasal *In-situ* gel in terms of ease of administration, accuracy of dosing, prolonged nasal residence and improved drug bioavailability [19].

Ju Young Lee *et al*., examined a poly (ethylene glycol)-b-polycaprolactone (MPEG-PCL) diblock copolymer gel as an injectable drug depot for paclitaxel (Ptx). The copolymer solution remained liquid at room temperature and rapidly gelled in vivo at body temperature. In vitro experiments showed that Ptx was released from MPEG-PCL copolymer gels over the course of more than 14 days.

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Experiments employing intratumoral injection of saline (control), gel-only, Taxol, or Ptx-loaded gel into mice bearing B16F10 tumor xenografts showed that Ptx-loaded gel inhibited the growth of B16F10 tumors more effectively than did saline or gel alone. Further, intratumoral injection of Ptx-loaded gel was more efficacious in inhibiting the growth of B16F10 tumor over 10 days than was injection of Taxol. A histological analysis demonstrated an increase in necrotic tissue in tumors treated with Ptx-loaded gel. In conclusion, our data show that intratumoral injection of Ptx-loaded MPEG-PCL diblock copolymer yielded an *In-situ*-forming gel that exhibited controlled Ptx release profile, and that was effective in treating localized solid tumors [20].

Rathapon Asasutjarit *et al*., conducted to optimize and evaluate Pluronic F127-based thermoresponsive diclofenac sodium ophthalmic *In-situ* gels (DS *In-situ* gel). They were prepared by cold method and investigated their physicochemical properties i.e., pH, flow ability, sol-gel transition temperature, gelling capacity and rheological properties. An optimized formulation was selected and investigated its physicochemical properties before and after autoclaving, eye irritation potency in SIRC cells and rabbits. In vivo ophthalmic absorption was performed in rabbits. It was found that physicochemical properties of DS *In-situ* gels were affected by formulation compositions. Increment of Pluronic F127 content decreased sol-gel transition temperature of the products while increase in Pluronic F68 concentration tended to increase sol-gel transition temperature. In this study, Carbopol 940 did not affect sol-gel transition temperature but it affected transparency, pH, and gelling capacity of the products. The optimized formulation exhibited sol-gel transition at 32.6 ± 1.1 °C with pseudoplastic flow behavior. It was lost diclofenac sodium content during autoclaving. However, it was accepted as safe for ophthalmic use and could increase diclofenac sodium bioavailability in aqueous humor significantly. In conclusion, the optimized DS *In-situ* gel had potential for using as an alternative to the conventional diclofenac sodium eye drop. However, autoclaving was not a suitable sterilization method for this product [21].

Tofeeq Ur-Rehman., developed by exploiting the tendency of poloxamer solution to form gel at physiological temperatures and of chitosan (CT) to form iono tropic gel structures in the presence of sodium tri polyphosphate (TPP). Novel poloxamer gels containing CT-TPP complex formed *In-situ* during the administration were prepared by mixing poloxamer-CT and poloxamer-TPP solutions in double syringes. The micellization and gelation of poloxamer 407 in the presence of chitosan and/or TPP were studied using differential scanning calorimetry and tube inversion; both additives were found to reduce the critical micellization temperature and critical gelation temperature of poloxamer aqueous solution. The poloxamer gels containing CT-TPP complex formed *In-situ* were found to exhibit reduced dissolution rate and superior release characteristics with three different drugs – metoprolol, doxycycline and flufenamic acid. Furthermore, by varying the compositions of the two solutions independently, it is possible to control the pH in a way to suit the solubilization of a drug as well as the specific environment of a particular application site. By varying the concentrations of chitosan, TPP and poloxamer, the delivery system can be fine-tuned to afford gels with specific properties, ranging from nanoparticle suspensions to semisolid gels. These *In-situ* gels have the potential to increase the utility of thermo-reversible poloxamers in drug delivery [22].

Yuan Yuan *et al*., studied the thermo-sensitive gelling properties. Nevertheless, these gels possess inadequate poor bioadhesiveness and high permeability to water, which limited its' application as a thermoresponsive matrix. The main aim of the present investigation was to develop thermosensitive and mucoadhesive rectal *In-situ* gel of nimesulide (NM) by using mucoadhesive polymers such as sodium alginate (Alg-Na) and HPMC. These gels were prepared by addition of mucoadhesive polymers (0.5%) to the formulations of thermosensitive gelling solution containing poloxamer 407 (18%) and nimesulide (2.0%). Polyethylene glycol (PEG) was used to modify gelation temperature and drug release properties. The gelation temperature and drug release rate of the prepared *In-situ* gels were evaluated. Gelation temperature was significantly increased with incorporation of nimesulide (2.0%) in the poloxamer solution, while the addition of the mucoadhesive polymers played a reverse role on gelation temperature. The addition of PEG polymers increased the gelation temperature and the drug release rate. Among the formulations examined, the poloxamer 407/nimesulide/sodium alginate/PEG 4000 (18/2.0/0.5/1.2%) exhibited the appropriate gelation temperature, acceptable drug release rate and rectal retention at the administration site. Furthermore, the micrographic results showed that *In-situ* gel, given at the dose of 20 mg/kg, was safe for no mucosa irritation. In addition, it resulted in significantly higher initial serum concentrations, C_{max} and AUC of NM compared to the solid suppository [23].

Feirong Kang., developed a single-dose insulin delivery system based on *In-situ* forming gel to provide basal insulin level for a prolonged period. The *In-situ* forming gel formulation was prepared by dissolving poly(d,l-lactic acid) (PLA) in hydrophobic (benzyl benzoate) and hydrophilic (benzyl alcohol) solvent mixtures. In vitro release was carried out in phosphate buffered saline (PBS) (pH 7.4) and the amount of released insulin was quantified by MicroBCA assay. In vivo biocompatibility study of *In-situ* forming gel system was based on the histological evaluation of the tissue samples retrieved from injection sites at different time points. The tissue reaction was evaluated over 12 weeks. Throughout this period, all formulations showed normal inflammatory and foreign body reactions characterized by the presence of macrophages, fibroblasts and foreign body giant cells. Neither necrosis nor tissue damage could be identified. At the end of 12 weeks, no distinct histological differences were observed in comparison to the control tissue samples. The comparable results between blank and insulin-loaded *In-situ* forming gel system indicated that the insulin itself did not induce additional inflammatory reactions. The results suggested that *In-situ* forming gel system was biocompatible [24].

Giovanna Pitarresi *et al*., prepared *In-situ* gel systems by linking polylactic acid (PLA) to a water soluble and poly functional polymer, such as α,β-poly (N-2-hydroxyethyl)-d,l-aspartamide (PHEA). Three graft copolymers PHEA-PLA with a different derivatization degree in PLA, have been synthesized and characterized. PHEA-PLA graft copolymer with the highest amount in PLA has been used to prepare solutions in organic solvents able to give rise to gel-like matrices when injected into phosphate buffered saline solution. The chemical degradation of these gels has been evaluated and in vitro tests have been performed to evaluate the cell compatibility of the hydrolysis products. The possibility to use these gels for drug release has been investigated by incorporating leuprolide as a peptide model drug and by evaluating its in vitro release. To improve the drug release profile, PHEA-PLA graft copolymer has been derivatized with pendant carboxylic groups that are able to form an ion pair with the leuprolide thus reducing the burst effect and prolonging its release [25].

Yanxia Cao *et al*., investigated for its thermosensitive *In-situ* gel-forming properties and potential utilization for ocular drug delivery. The thermal sensitivity and low critical solution temperature (LCST) were determined by the cloud point method. PNIPAAm-CS had a LCST of 32 ℃, which is close to the surface temperature of the eye. 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. The Cmax of timolol maleate in aqueous fluid for the PNIPAAm-CS solution was 11.2 μg/ml, which is two-fold higher than that of the conventional eye drop, along with greater AUC. Furthermore, the PNIPAAm-CS gel-forming solution of timolol maleate had a stronger capacity to reduce the intra-ocular pressure (IOP) than that of the conventional eye drop of same concentration over a period of 12 h. In addition, the MTT assay showed that there is little cytotoxicity of PNIPAAm-CS at concentration range of 0.5-400 μg/ml. These 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 [26].

Tais Gratieri *et al*., evaluated the potential of a chitosan solution as well as an *In-situ* gel-forming system comprised of poloxamer/chitosan as vehicles for enhanced corneal permeation and sustained release of fluconazole (FLU). For this, in vitro release and ex vivo corneal permeation experiments were carried out as a function of chitosan concentration from formulation containing the chitosan alone and combined with the thermosensitive polymer, poloxamer. Microdialysis was employed in a rabbit model to evaluate the in vivo performance of the formulations. The in vitro release studies showed the sustained release of FLU from the poloxamer/chitosan formulation. Ex vivo permeation studies across porcine cornea demonstrated that the formulations studied have a permeation-enhancing effect that is independent of chitosan concentration in the range from 0.5 to 1.5% w/w. The chitosan solutions alone showed the greatest ex vivo drug permeation; however, the poloxamer/chitosan formulation presented similar in vivo performance than the chitosan solution at 1.0%; both formulations showed sustained release and about 3.5-fold greater total amount of FLU permeated when compared to simple aqueous solutions of the drug. In conclusion, it was demonstrated that both the *In-situ* gelling formulation evaluated and the chitosan solution are viable alternatives to enhance ocular bioavailability in the treatment of fungal keratitis [27].

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