Review Article

Topical ophthalmic in situ gels for ocular delivery: A recent Update

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Abstract: Ocular drug delivery is challenging field to pharmaceutical scientists owing to the underlying anatomical, physiological and dynamic constraints put forth by the eye. Nonetheless, there is increasing need to overcome these barriers for the treatment of sight threatening ophthalmic ailments. Novel drug delivery strategies are being explored while intravitreal injections are still a standard treatment for the efficient treatment of ocular disorders. Topical ophthalmic in situ gels could be viable platform to increase mucoadhesivity, pre-corneal residence and thereby ocular bioavailability of drugs. In this review, various topical in situ gel formulations exploited for ocular delivery are summarized.

Keywords: Ocular delivery, topical in situ gels, ocular absorption and bioavailability, retinal delivery, ocular pharmacokinetics.

INTRODUCTION

Ocular delivery of drugs through topical route remains elusive, it is established that typically, only 1-5% or less of a topically instilled dose reach anterior segment, and a negligible amount to the posterior segment. Oral or systemic administration of drugs needs higher doses because of blood aqueous and retinal barriers, limiting the entry of drugs into the eye [1, 2]. Intravitreal injection is most promising method for localized posterior ocular delivery. However, this method of administration is too invasive technique and may lead to retinal detachment, cataract, endophthalmitis and increased intraocular pressure [3]. Different routes of administration comprising topical, systemic, intraocular, and periocular (including subconjunctival, sub-Tenon and retrobulbar) are widely used to deliver the drugs to posterior ocular tissues. Depending upon the ophthalmic disease state, complexity and origin delivery systems may vary from simple topical solutions to advanced formulations, such as intraocular implants and intravitreal injections [4, 5].

Topical solutions are better in terms of safety, patient compliance and non-specific systemic exposure. However, it is reported that ocular bioavailability of topically instilled drugs range from 5-10% of total dose due to various precorneal factors such as tear reflex, tear drainage and various physiological factors. In situ gels would be less viscous as to that of topical solutions at the room temperature and transform into gel following phase transition, which would be enough to withstand the shear forces in cul-de-sac. The external stimulus for phase transition could be obtained using wide range of excipients which increase precorneal residence. The ability of gelation and sustaining the drug release from the formulation can improve ocular bioavailability of topically instilled drugs. Literature reports demonstrated that in situ gels can be administered using various invasive and non-invasive routes to reduce systemic absorption and need for frequent dosing, thus improving patient compliance and adherence. However, various gel formulations prepared from a range of synthesized polymers have been reported in the literature apart from the in situ gel, however higher viscosity of these formulations may decrease patient compliance and adherence to the formulation. Those gels have been demonstrated to sustain the release of drugs over prolonged periods than the in situ gels [6, 7]. In the present review, recent updates on ophthalmic gels have been discussed.

Opthalmic in situ gels

In situ gel systems aroused interest in the researchers over the past few years which undergo sol-gel phase transition once administered into the ocular milieu in response to specific change in parameters such as pH, temperature, and ionic strength, UV absorption and solvent exchange mechanisms. Polymers such as pluronics, polyacrylamide (PAAm) (e.g N-isopropyl acrylamide), poly (acrylamide-co-butyl methacrylate) undergo thermoreversible gelation in response to temperature in the eye (34°C-37°C). Xyloglucan is tamarind seed polysaacharide which undergo gelation at lower concentrations (1.5% w/v) than pluronics (20-30% w/v). Polymers such as poly acrylic acid (PAA) or its derivatives, mixtures of poly (methacrylic acid)

(PMA) and poly (ethylene glycol) (PEG), undergo sol-gel phase transition with pH induced stimuli. Certain natural polysaccharides include carrageenan, gellan gum, pectin, and sodium alginate gelate in the presence of monovalent and divalent cations such as k^+, Ca^{+2}, Mg^{+2}, and Na^+ [7, 8]. Kang derwent *et al.* developed thermos responsive hydrogels of poly (N-isopropylacrylamide) (PNIPAAm), cross-linked with poly (ethylene glycol) diacrylate (PEG-DA). Proteins were then encapsulated into the hydrogels such as bovine serum albumin (BSA), immunoglobulin G (IgG), bevacizumab and ranibizumab and administered as intravitreal injection. Sustained release profile of the proteins was observed until 3 weeks in the vitreous cavity [9]. Wang evaluated the biocompatibility and biodegradability of RGD peptide hydrogel in the posterior segment of rabbit eye following injection into the vitreous cavity and suprachoroidal space. The results showed that RGD peptide hydrogel was well tolerated with lifetime of 25.7 ± 2.65 and 14.3 ± 3.3 days in the vitreous cavity and supra choroidal space respectively [10].

Gao *et al.* tested thermosensitive gel made of triblock polymer PLGA-PEG-PLGA (poly-(DL-lactic acid co-glycolic acid)-polyethylene glycol-poly-(DL-lactic acid co-glycolic acid) as an ocular delivery carrier for 0.1% w/v dexamethasone acetate (DXA). C_{max} and AUC were increased by 7 to 8 folds with *in situ* gel compared to topical solution at an equivalent dose [11, 12]. pH-triggered acetazolamide loaded polymeric nanoparticulate *in situ* gel was prepared by singh *et al.* The optimized formulation was dispersed in carbopol 934 P to form nanoparticulate *in situ* gels. *Ex vivo* transcorneal permeation study demonstrated significantly higher permeation with nanoparticles $(93.5\pm2.25\,mg/cm^2)$ than eye drops $(20.08\pm3.12\,mg/cm^2)$. Modified Draize test with zero score indicated nonirritant characteristics. Nanoparticles caused significant decrease in IOP $(p<0.05)$ in comparison to eye drops [13, 14]. Curcumin cationic nanostructured lipid carriers loaded into thermosensitive *in situ* nanogels by Liu *et al.* for prolonging ocular retention properties. Transcorneal permeability was increased by 1.56-fold and the ocular bioavailability (AUC) was enhanced by 9.24-fold, respectively when compared to curcumin solution $(p<0.01)$ [15, 16].

Gratieri *et al.* evaluate the potential an *in situ* gel-forming system comprised of poloxamer/chitosan for ocular delivery of fluconazole to treat fungal keratitis. *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 poloxamer/chitosan formulation presented superior *vivo* performance and

showed sustained release of the drug into the ocular tissues [17].

Pluronic F127-based thermoresponsive diclofenac sodium loaded ophthalmic in situ gels were prepared and evaluated by Rathapon *et al.* An optimized formulation was investigated for physicochemical properties pre and post moist heat sterilization, eye irritation potency in SIRC cells and in vivo ocular distribution in rabbits. Physicochemical properties of the respective formulation changed following sterilization. The optimized formulation exhibited phase transition temperature of $32.6\pm1.1\,°C$ with pseudoplastic behavior. The formulation delivered significant concentration into the aqueous humor when compared to control solution at an equivalent dose [18].

Ion-activated *in situ* gel-forming estradiol (E_2) solution eye drops using gellan gum was developed for prevention of age-related cataracts. The solution eye drops resulted in an i*n-situ* phase change to gel-state when mixed with simulated tear fluid (STF). The formulations appeared to be clear, isotonic and have storage stability for 6 months. *In vitro* results demonstrated that developed formulation is suitable for targeting the inner ocular tissues [19].

In situ gel formulations were prepared based on a blend of two hydrophilic polymers namely poloxamer 407 (P407) and poloxamer 188 (P188) for a sustained ocular delivery of ketorolac tromethamine. The respective gel formulation exhibited a pseudoplastic behaviour at different concentrations. *Ex vivo* permeation experiments indicated that the in situ gels was able to prolong and control the release profile from the formulation. In addition, the non-irritancy of KT loaded in situ gels was confirmed in the studies. MTT assay on corneal epithelial cells revealed that in situ gel formulations loaded with KT demonstrated good cell viability when compared to control solution [20, 21].

Ion induced nanoemulsion-based in situ gel for ocular delivery of acetazolamide was developed by Morsi *et al.* The nanoemulsion based in situ gels showed a significantly sustained drug release in comparison to the nanoemulsion. Gellan/xanthan and gellan/HPMC possessed good stability and showed higher therapeutic efficacy and significant reduction in intraocular pressure relative to that of commercial eye drops [22].

In situ gels of brimonidine tartarate were developed by Pang *et al.* using Carbopol 974P and HPMC E4M polymers. *In vitro* residence time studies demonstrated that the gels exhibited a better precorneal residence time in comparison to topical eye drops. The gels significantly reduced intraocular pressure (IOP)

when compared to the eye drop. Results from the study demonstrated that 0.1% ophthalmic gel has a potential to improve therapeutic efficacy and reduce the systemic toxicity [23].

Novel microemulsion in situ electrolyte-triggered gelling system for ophthalmic delivery of cyclosporine A was formulated by Gan *et al.* Viscosity of the microemulsion increased significantly on dilution with artificial tear fluid exhibiting pseudo-plastic rheology. In vivo results demonstrated that drug levels in the cornea with microemulsion gel system were approximately three-fold greater than control emulsion and were maintained until 32 hours post topical application. In situ electrolyte-triggered gelling system demonstrated an alternative approach to sustain and prolong the Cyclosporine delivery into the ocular tissues [24, 25].

Terbinafine hydrochloride was formulated as *in situ* nanoemulsion gels for ocular delivery by Tayel *et al.* Sterilized *in situ* NE gel was thermodynamically stable with hydrodynamic radius less than 30 nm. The gels were transparent, pseudoplastic, mucoadhesive and exhibited zero order kinetics. *In situ* gel did exert slight ocular irritation and significantly increased ocular bioavailability [26].

A novel thermosensitive in situ gel was prepared where a copolymer namely poly (*N*-isopropylacrylamide)–chitosan (PNIPAAm–CS) was used therein and tested for targeting the eye. Ocular concentrations of the model drug (timolol) in aqueous humor with the formulation was two-fold higher than that of the conventional eye drop and was able to maintain the intra-ocular pressure (IOP) lowering effect over a period of 12 h [27].

Light-responsive *in situ* forming injectable implants (ISFIs) were being developed as drug delivery carriers targeting posterior ocular tissues. Photoactivable polycaprolactone dimethacrylate (PCM) and hydroxyethyl methacrylate (HEMA) based gel network was developed to sustain the release of bevacizumab for suprachoroidal delivery by Tyagi *et al.* [28]. Bevacizumab release from cross-linked gel was sustained for ~4 months in the rabbit eye model [29, 30]. Topical gel formulation of brinzolamide was developed for posterior ocular delivery by Smith suing a pentablock co-polymer and tested in dogs for IOP lowering effect. The respective formulation could lower the IOP significantly with less dosing frequency of once a day [21].

CONCLUSION
Significant and considerable confrontations are encountered in the ocular drug delivery which needs to be addressed with viable formulation platforms to present additional possibilities. While the challenges pose to be significant, the data presented in the literature hold promise for novel therapies. Multidisciplinary integration of fields such as biomedical engineering and nanotechnology could explore new avenues in niche of topical ocular drug delivery in the near future.

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