



Fabrication and Physicochemical Evaluation of *In-situ* Gel System for Sustained Ocular Delivery

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ABSTRACT

The aim of the present investigational study was to develop an *in-situ* gel system based on chitosan, poly vinyl alcohol and gellan gum for ocular delivery of sparfloxacin. The proposed system was inimitable and supposed to be activated by number of mechanism such as temperature, pH and ions present in biological milieu. Hydrogel was prepared and optimized by using different concentration of polymeric materials and evaluated for its clarity, osmolarity, pH and viscosity. The developed *in-situ* gel was sensitive enough which underwent instantaneous phase transition upon getting physiological stimulation. Obtained physicochemical findings confirm the suitability of the developed system as a potential alternative for sustained ocular delivery.

Keywords: Ocular delivery; *In-situ* gel system; Chitosan; PVA; Gellan gum

INTRODUCTION

Availability of the active molecule in proper concentration at the site of action is the prime requirement of any drug delivery strategy. The accessibility at the site not only improve the efficacy of the delivery by restricting its distribution to affected area but at the same time it may also reduce the chances of adverse effects and enhance patient compliance by reducing the dosing frequency. Various ocular pathological conditions like glaucoma, dry eye syndrome and conjunctivitis are some of them which require adequate retention of the drug at the corneal surface. The natural physiology of the ocular route i.e., blinking action and naso-lachrymal drainage provide a challenge in designing the carrier and also contribute in reduced drug efficacy [1]. Frequent dosing may be a mean to provide drug at the site of action but it may also cause side effects and patient incompliance due to overdose and repeated administration respectively. The only solution of this problem is designing a delivery system with good retention and sustained ocular delivery. Problems related to ocular delivery were taken as challenges by the scientific community globally and a number of strategies such as implantable systems [2], collagen shields [3], ocular inserts [4,5], colloidal carriers [6,7], nanoparticles [8-10] and nanocapsules [11,12] were explored worldwide. These strategies were successful upto some extent but also suffered with some limitations like poor patient compliance, need of surgery, difficulty in self-insertion [6] and rapid drainage by the site of application.

Among the novel formulations tried for ocular delivery, *in-situ* gel is a promising approach which is comparable in ease with available marketed formulations and longer retention at the corneal surface due to its unique property of sol to gel conversion upon physiological stimulation like temperature, pH or ionic interaction. *In-situ* gel system for ocular drug delivery is one of the novel approaches investigated thoroughly with a number of combinations of available polymeric materials [13-16]. In the present study, we proposed an *in-situ* gel system composed of chitosan, poly (vinyl alcohol) (PVA) and gellan gum. Chitosan and PVA based *in-situ* gel system has been evaluated successfully for surface property of the blend [17], rheological characterization [18] and its practical utility in drug

delivery [19]. Each component present in the system has its unique property which ultimately fortifies the system efficacy. Chitosan is a cationic polymer which acts as mucoadhesive and penetration enhancer [20] and it also reveals phase conversion upon change in pH and temperature. PVA is a polymer which provides gel strength [21] while gellan shows ion activated phase transition behavior.

Ocular site provides three major mechanism of bio-stimulation such as pH, temperature and ions. Therefore, the present work has been an attempt to explore a system which is supposed to be activated by a combination of triple mechanism (temperature, pH and ion activation) and its various aspects for the suitability of the present system in ocular delivery by considering sparfloxacin as model drug.

MATERIALS AND METHODS

Materials

Sparfloxacin was obtained as a generous gift from Dr. Reddy's Laboratories, Hyderabad. Chitosan and PVA were purchased from local supplier respectively. Gellan gum was obtained as a gift sample. All other chemicals and solvents used were purchased from local suppliers and of analytical grade.

Drug Polymer Interaction Studies

Aqueous solutions of all the polymeric materials i.e., chitosan, PVA and gellan and the drug, sparfloxacin were prepared separately and in combinations. The presence of any possible interactions was detected by comparing spectra obtained by double beam UV-Visible spectrophotometer before and after autoclaving of all the solutions individually and in combinations.

Fabrication of *In-situ* Gel

Blank *in-situ* gel was prepared by using different polymer ratios and suitable composition was identified by evaluating their gelling capacity (Table 1). Chitosan solution was prepared by dissolving weighed amount of chitosan in 1% v/v acetic acid while PVA and gellan gum solution were prepared separately by dissolving the weighed amount in preheated ultrapure water (80°C) with continuous stirring.

Table 1: Formulation components of *in-situ* gel formulations

Ingredients	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Chitosan (% w/v)	0.25	0.5	1	0.25	0.5	1	0.25	0.5	1
PVA (% w/v)	2	2	2	2	2	2	2	2	2
Gellan gum (% w/v)	0.25	0.25	0.25	0.5	0.5	0.5	1	1	1
Sparfloxacin (% w/v)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Benzalkonium chloride (% w/v)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Glycerol (Tonicity adjustment)	q.s.								
Citrophosphate buffer (pH 6.0) q.s.	100	100	100	100	100	100	100	100	100
Gelling capacity	++	++	++	++	+++	+++	+++	+++	+++

The gelling capacity of the various combinations was checked in simulated tear fluid [22] by noting the time taken in phase conversion from sol to gel and time taken to formed gel to get completely dissolved.

Fabrication of Medicated *In-situ* Gel

Weighed amount of sparfloxacin was dissolved in citrophosphate buffer (pH 6.0) and added to the prepared *in-situ* gel to make the drug concentration, 0.3% w/v, in the final formulation. Benzalkonium chloride in the concentration of 0.05% w/v was used as preservative while glycerol was added in the formulation as a tonicity modifier. Final medicated formulation was dispensed in amber colored bottles fitted with dropper and subjected to sterilization by autoclaving at 121°C for 20 min at 15 psi [23-25].

Evaluation of the Formulation

Based on clear and transparent solution along with good gelling capacity, formulation F5 was selected as final formulation for further efficacy of the developed formulation. Formulation was characterized for its physicochemical characteristics and other parameters to justify its effectiveness as a suitable delivery mode for ophthalmic delivery.

Physicochemical Evaluation [8,13-16,19,23]

Developed *in-situ* gel formulation was evaluated for different physicochemical attributes.

Clarity

Clarity of the developed *in-situ* gel was checked by visual examination of both sol and gel form against white and black background.

Osmolarity

Osmolarity is the prerequisite for any developed ophthalmic product which was confirmed for the developed *in-situ* gel formulation by osmometer.

Gelation pH

Gelation pH is the point at which physiological change from sol to gel occur upon getting change in pH. The gelation pH was determined by adding 1M NaOH drop wise to the formulation and the gelation pH was determined as point at which sudden change in pH occur.

Viscosity

Viscosity of the developed *in-situ* gel was determined at both pH conditions i.e. at pH 6.0, sol form and at pH 7.4 the gel form using Brookfield viscometer.

RESULTS AND DISCUSSION

In the present research endeavour, a combination of chitosan, PVA and gellan gum was proposed for the development of novel *in-situ* gel as a carrier for sustained ocular drug delivery. Numerous reports are available about safety and utilization of chitosan as penetration enhancer. Besides the above mentioned properties, bio-adhesiveness and its ability to convert into hydrogel upon getting physiological stimulation (at pH >6.5) make this as a polymer of choice. PVA has also been reported for its biocompatibility as well as unique gelling characteristics which provide adhesive characteristic to this polymer. Gellan gum solution also reveals inimitable property of ion induced gelation and has been employed successfully for ocular delivery. Therefore, the presented combination was supposed to be activated by number of mechanisms which may also result in fortify activity in terms of quick response and better gel strength. The overlay UV spectra obtained for the individual component and combinations were found to be identical with no major additional peaks and without shifting the existing peaks. Findings obtained for compatibility assure the judicial selection of the formulation components. After getting confirmation regarding the compatibility between the formulation components, another prime requirement for ophthalmic product is its sterility which must be achieved and maintained throughout the shelf life. Autoclaving is a method of choice for ophthalmic preparations in which the sterility is achieved terminally in final containers. Identical spectral pattern, before and after autoclaving proves the autoclaving as a safe method of sterilization for the proposed system. *In-situ* gel system has inimitable property of sol to gel conversion which offer easy administration in sol form and prolong residence at the administration site in gel form. Formulation F5 (chitosan 0.5%, PVA 2% and gellan gum 0.5%) was selected as optimized formulation based on clear and transparent solution along with good gelling capacity. Formulation was iso-osmotic and instantaneous change to gel was found at pH >6.5. The observations are represented in Table 2.

Table 2: Physicochemical properties of developed *in-situ* gel

Parameters	Results
Clarity	Clear solution
pH	6.0 ± 0.1
Osmolarity	294 – 305 mOsmol
Gelation pH	>6.5
Viscosity (cps) (at pH 6.0)	61 ± 3.4
Viscosity (cps) (at pH>6.5)	210 ± 5.6

Values are represented as mean ± SD (n=5)

CONCLUSION

The proposed *in-situ* gel was sensitive enough to instantaneous gelation (sol to gel stimulation) and supposed to be due to combination of mechanisms such as temperature, pH and ionic interaction. Developed formulations revealed

acceptable physicochemical attributes. Based on the performance of the system as well as physicochemical characterization, this can be a better alternative over the conventional marketed solution dosage form.

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