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Research Article

**IN-SITU GEL SYSTEM BASED ON TEMPERATURE AND pH
ACTIVATION FOR SUSTAINED OCULAR DELIVERY**Arvind^{*1}, H.S. Lamba¹ and Asgar Ali²¹H.R. Institute of Pharmacy, Ghaziabad.²Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, New Delhi.**Received:** 20 February 2016**Accepted:** 10 March 2017**Published:** 16 March 2017**Abstract:**

The aim of the present investigational work was to develop an in-situ gel system based on chitosan and poly vinyl alcohol for ocular delivery of sparfloxacin. The hydrogel was developed by utilizing various concentration of chitosan and poly vinyl alcohol. The prepared hydrogel was characterized for pH, tonicity, viscosity, swelling and in-vitro drug release profile. Developed hydrogel underwent transition from solution to non-flowing hydrogel upon getting change of pH. In-vitro release of drug was observed spectrophotometrically which was upto 94% during six hours. The observed findings indicate that the proposed in-situ gelling system has substantial potential as ocular drug delivery.

Keywords: *In-situ gel system, Ocular delivery, Sparfloxacin, Chitosan, PVA.***Corresponding Author:****Arvind^{*},**

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INTRODUCTION:

Recently, drug delivery systems with modified release are the demanding avenue globally. Significant efforts have been carried out to enhance product efficacy as well as reliable safety. Ocular drug delivery is one of the important route which have been attracted the researchers worldwide. Conventional, liquid ophthalmic formulations such as eye drops, ointments depict poor bioavailability and consequently poor therapeutic response because of high turnover of lachrymal secretion produced, metabolism of the drug in eye environment, limited corneal area provided for drug absorption, poor permeability, binding with lachrymal proteins, and rapid clearance of the drug from the site of absorption [1, 2]. Dose administered is drained from the eye within 5 min and this short precorneal residence time is the main cause owing to that only 1-10% of bioavailability is achieved by normal ophthalmic solutions [3].

Increase in dosing frequency and amount of drug administered are not suitable approach to improve the drug action because increase in dosing frequency will cause patient non-compliance and increase in dose may also results in undesirable adverse effects if the drug is absorbed from the nasolacrimal duct [4].

To improve the efficacy in terms of increased bioavailability and reduced patient in-compliance many novel delivery systems like aqueous gels, suspensions, ointments and inserts have been mentioned [5]. These systems provide advantage of better retention and may be good enough for increasing bioavailability upto some extent but at the same time these systems are associated with some inherent limitations such as poor reproducibility in dose measurement with gel, irritation and clearance of large percentage of drug particles from the eye surface before dissolution and absorption with suspensions [6], blurred vision with ointments and minor surgery requirement in ocular inserts, all result in poor patient compliance. Increasing the precorneal residence time upto one or two hrs may be a promising approach to improve bioavailability, reduce dose and dosing frequency with improved patient acceptability [3].

Considering various inventions regarding ocular drug delivery, a liquid formulation with good retain

ability at the site of absorption may be an ideal system which may satisfactorily increase residence time. *In-situ* gel system has distinctive property of sol to gel phase transformation which is convenient to deliver and at the same time illustrate good retention due to gel form. Sol to gel transformation may be pH dependent, temperature-dependent or ion-activated [7].

In the present work, a clear *in-situ* gel system was developed comprising chitosan and PVA as formulation component. Chitosan has been reported as nontoxic [8], biodegradable [9], biocompatible [10], mucoadhesive [11] and penetration enhancer by transient widening of the tight junctions [12]. Biocompatibility [13] and adhesive property [14] of PVA and pH [15] and thermosensitivity [16] of chitosan and PVA blend is also available in the literature.

The purpose of the present work was to investigate the utility of the chitosan and PVA *in-situ* gel system for ocular delivery with better efficacy as an alternative to liquid ocular formulations.

MATERIALS AND METHODS:**Materials**

Chitosan and Poly vinyl alcohol were purchased from local supplier, Ghaziabad. Sparfloxacin was obtained as a gift sample. All other chemicals and solvents used were of analytical grade.

Drug polymer interaction studies

Aqueous solutions of chitosan, PVA and sparfloxacin were prepared separately and in combinations. Interactions, before and after autoclaving were determined spectrophotometrically using double beam UV-Visible spectrophotometer by comparing spectra for any possible sign of interaction.

Preparation of *in-situ* gelling system

A clear solution of chitosan having different concentration (1%, 2%, 3%, 4%, 5% w/v) was prepared in acetic acid solution and chilled in an ice bath for 15 min. Different concentration solutions (1%, 2%, 3% and 4% w/v) of PVA were prepared separately in preheated distilled water followed by chilling on ice bath. Chitosan and PVA solutions were mixed under magnetic stirring for 10 min to make different formulation from F1 to F5 (Table-1).

Table 1: Formulation components of the developed *In-situ* gel formulation

Ingredients	Formulations				
	F1	F2	F3	F4	F5
Chitosan (% w/v)	1	2	3	4	5
PVA (% w/v)	4	3	2	1	-
Sparfloxacin (% w/v)	0.3	0.3	0.3	0.3	0.3
Benzalkonium chloride (% w/v)	0.05	0.05	0.05	0.05	0.05
Glycerol	qs.	qs.	qs.	qs.	qs.
Citrophosphate buffer (pH 6.0)	qs.	qs.	qs.	qs.	qs.

Preparation of medicated formulation

A drug solution in citrophosphate buffer was used in medicated formulations. A 0.05% of benzalkonium chloride (BKC) was added in the formulations as preservative. Formulations were made isotonic by adding glycerol and osmolarity of the formulations was examined by osmometer. Formulations were transferred into amber-colored bottles fitted with dropper having teat followed by sterilization (autoclaving at 121°C for 20 min).

Evaluation of the formulation

Viscosity

Viscosity of the prepared formulations was determined in both sol and the gel form using Brookfield viscometer in the small volume adaptor [17].

Degree of swelling

Degree of swelling was carried out in artificial tear fluid (ATF), pH 7.4. Gel of fixed weight was taken in ATF and it was allowed to swell until equilibrium swelling within ATF. Degree of swelling was determined by dividing the weight gained by the original weight taken [18].

In-vitro release studies

Formulation was filled in the egg sac (separated by egg shell), this filled sac was suspended in release media (Artificial tear fluid (ATF), pH 7.4). Release media was maintained at 37°C with continuous magnetic stirring at 50 rpm. Sampling was carried out at different time points by taking aliquots and release media was replaced with fresh media to maintain the constant volume. Aliquots were filtered, diluted and analyzed for drug content by UV-Visible spectrophotometer [19].

Results and Discussion

The major requirement for the ocular dosage form is their sterility which should be maintained throughout the period of their utilization. Among various methods available for sterilization, autoclaving is the method of choice for terminal sterilization. Therefore, the prepared formulations were exposed for autoclaving and checked for any measurable change by comparing UV spectra before and after autoclaving. No change in physical appearance was observed. Results reveal that the formulation can be autoclaved without any sign of degradation. The formulations were found to be clear when tested against light and black background and also found to have pH and osmolarity appropriate for utilization (Table 2).

Table 2: Physicochemical characteristics of the developed formulations

Parameter checked	Inference
Clarity	Clear solution
pH	6.0
Osmolarity	290-310 mOsmol

(Mean \pm SD, n=5)

The formulation showed conversion into gel after

getting stimulation by change in pH from (6.0 to 7.5). The solution form was free flowing while after converting into gel, it was not free flowing.

Chitosan is a polymeric material with solubility in acidic solutions. In acidic solution, i.e. pH below its pKa value (6.2) it gets solubilized and free amino group which are present on the surface converted into protonated form. In acidic solution, presence of protonated amino groups makes chitosan as a weak acid. Presence of this positive charge cause electrostatic repulsion between the chains. Increased pH will lead to deprotonation resulting in decreased electrostatic repulsion. At lower temperature, decrease in electrostatic repulsion will lead to the formation of hydrogen bonding between chitosan, poly vinyl alcohol and water due to hydrophilicity of poly vinyl alcohol, which results in dissolution of chitosan chains and reduced mobility also prevents the association of chitosan chains. However, at higher temperature hydrogen bonding interactions are reduced and the energized water molecules around the chitosan chains are removed. Removal of water molecules will lead to association of chains as a result, gel is formed.

Viscosity

The viscosity of the prepared formulation was observed from 21.66 \pm 1.52 to 61.66 \pm 5.03 at pH 6.0 but it was increased to 107.33 \pm 4.50 to 237.33 \pm 3.51 upon getting converted into gel at pH 7.4. The viscosity at both pH was minimum for F5 while it was maximum for F1. Decrease in viscosity was observed from F1 to F5 which simply reveal that high concentration of PVA will provide high viscosity for the formulation.

Degree of swelling

Degree of swelling studies was conducted in ATF (pH 7.4) maintaining the temperature constant at 37°C. The formulations were allowed to swell until equilibrium swelling. The maximum degree of swelling (%) was shown by F3 (chitosan 3%, PVA 2%) while minimum degree of swelling was shown by F5 (chitosan 5%, PVA 0%). Hydrogel are the substances with distinctive characteristics of absorbing water from the mucosa, which results in temporary dehydration of the mucosal membrane along with transient widening of tight junctions.

In-vitro release studies

In-vitro release from the formulations was checked by employing egg membrane. The selection of the egg membrane was carried out because it is biological membrane and results obtained in-vitro may mimic in-vivo performance in a better way. Cumulative drug release (%) was obtained minimum for the formulation F5 (59.03 \pm 4.78) while it was maximum with formulation F3 (94.26 \pm 2.15) during 6 h release study.

Findings of the cumulative release were in accordance with the results obtained for degree of swelling i.e. more the degree of swelling, more the

release was observed from the prepared formulation. Hence, it may be predicted that the proposed gel shows swelling controlled release. Contributing factor in drug release may be the presence of chitosan which is widely considered as penetration enhancer which enhances penetration by transient opening of the tight junction of mucosal membrane.

CONCLUSION:

The developed *in-situ* gel formulations revealed a unique character of sol to gel conversion after getting bio-stimulation. Prepared formulations demonstrated satisfactory physicochemical characteristics. Based on the performance, the proposed system may be a suitable alternative of conventional solution dosage form and can be employed to treat eye disorders in a more better and effective manner,

REFERENCES:

- Gupta H, Velpandian T, Jain S. Ion-and pH-activated novel *in-situ* gel system for sustained ocular drug delivery. *J Drug Target*, 2010; 18: 499-505.
- 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.
- 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; 14: 507-515.
- Srividya B, Cardoza RM, Amin PD. Sustained ophthalmic delivery of ofloxacin from a pH triggered *in-situ* gelling system. *J Control Rel*, 2001; 73: 205-211.
- Miller SC, Donovan MD. Effect of poloxamer 407 gel on the miotic activity of pilocarpine nitrate in rabbits. *Int J Pharm*, 1982; 12: 147-152.
- Davies NM. Biopharmaceutical considerations in topical ocular drug delivery. *Clin Exp Pharmacol Physiol*, 2000; 27: 558-562.
- Ruel-Gariépy E, Leroux JC. *In-situ*-forming hydrogels--review of temperature-sensitive systems. *Eur J Pharm Biopharm*, 2004; 58: 409-426.
- Rao SB, Sharma CP. Use of chitosan as a biomaterial: studies on its safety and hemostatic

potential. *J Biomed Mater Res Part A*, 1997; 34: 21-28.

- Chenite A, Chaput C, Wang D, Combes C, Buschmann MD, Hoemann CD. Novel injectable neutral solutions of chitosan form biodegradable gels *in-situ*. *Biomaterials*, 2000; 21: 2155-2161.
- VandeVord PJ, Matthew HWT, DeSilva SP, Mayton L, Wu B, Wooley PH. Evaluation of the biocompatibility of a chitosan scaffold in mice. *J Biomed Mater Res Part A*, 2002; 59: 585-590.
- Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. *In-vitro* evaluation of mucoadhesive properties of chitosan and some other natural polymers. *Int J Pharm*, 1992; 78: 43-48.
- Sandri G, Rossi S, Ferrari F, Bonferoni MC, Muzzarelli C, Caramella C. Assessment of chitosan derivatives as buccal and vaginal penetration enhancers. *Eur J Pharm Sci*, 2004; 21: 351-359.
- Berger J, Reist M, Mayer JM, Felt O, Gurny R. Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. *Eur J Pharm Biopharm*, 2004; 57: 35-52.
- Therme F, Rozier A, Plazonnet B, Grove J. Bioadhesion: the effect of polyacrylic acid on the ocular bioavailability of timolol. *Int J Pharm*, 1992; 81: 59-65.
- Wang T, Turhan M, Gunasekaran S. Selected properties of pH sensitive, biodegradable chitosan-poly (vinyl alcohol) hydrogel. *Polym Int*, 2004; 53: 911-918.
- Agrawal AK, Gupta PN, Khanna A, Sharma RK, Chandrabanshi HK, Gupta N. Development and characterization of *in-situ* gel system for nasal insulin delivery. *Pharmazie*, 2010; 65: 188-193.
- El-Hefian EA, Nasef MM, Yahaya AH. Preparation and Characterization of Chitosan/Polyvinyl Alcohol Blends - A Rheological Study. *E- J Chem*, 2010; 7: S349-S357.
- Khafagy ES, Morishita M, Onuki Y, Takayama K. Current challenges in non-invasive insulin delivery systems: a comparative review. *Adv Drug Deliv Rev*, 2007; 59: 1521-1546.
- Tang YF, Du YM, Hu XW, Shi XW, Kennedy JF. Rheological characterisation of a novel thermosensitive chitosan/poly (vinyl alcohol) blend hydrogel. *Carbohydr Polym*, 2007; 67: 491-499.