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ISSN: 0975-7538
Research Article

Investigation of pH dependent *in situ* gel forming solutions of imidazoline drug for ocular administration

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ABSTRACT

Imidazoline drugs which are antihistamines indicated for the treatment of ocular allergy are presently available as drops and has to be instilled 4-5 times a day. Hence to overcome all these disadvantages, an investigation with the purpose to increase the residence time of a solution in the cul-de-sac of the eye by increasing the viscosity of the vehicle which decreases the drainage rate thereby slowing drug release from the delivery system and minimizing the pre-corneal drug loss in *in situ* forming solutions of ophthalmic drugs. The current study includes the *in vitro* studies for the prepared formulations. The phase transition was induced by a shift in pH at physiological temperature condition. For the study, naphazoline hydrochloride was chosen. The polymers used Carbopol 940 and HPMC k_4M. All the formulations FF17, FF18, AA15 and AA20 were found to have satisfactory drug release ranging from 75 to 80 % over a time duration of 8 h. Stability studies indicated that there are no significant changes in pH, visual appearance, clarity, gelation, drug content, and *in vitro* release during two month of study period.

Keywords: *In Situ* gelling solution; Naphazoline Hydrochloride; Carbopol 940; HPMC K_4M

INTRODUCTION

The commercial liquid ophthalmic preparations show low bioavailability because of the constant lacrimal secretions and rapid naso lacrimal drainage. It is obvious that immediately after instillation of these ocular preparations, normal drainage of the instilled dose takes place and is completed within a couple of minute. Hence the advantage taken from such dosage forms are very minimal ophthalmic bioavailability will be minimal due to the abort of the precorneal residence time of the ophthalmic solution. Hence need for the frequent instillation of ophthalmic solutions.

The low bioavailability and ocular residence time exhibited by the topical conventional liquid ophthalmic formulations because of spillage by overflow, dilution of drug by tear turn over, nasolacrimal drainage and systemic absorption may be overcome by the use of *in situ* forming systems which is an improved ocular drug delivery system prepared in such a way that they are instilled as liquid drops into the cul-de-sac of the eye, where they transform into a gel or semisolid phase. The *in situ* gels are formed when liquid vehicles undergo a viscosity increase upon instillation in the eye, thus favouring precorneal retention. However, these appears to be only by a change in temperature, pH or electrolyte composition.

Ocular therapy would be significantly improved if the precorneal residence time of drugs could be increased. Successful results were obtained with inserts and collagen shields, although these preparations involve some disadvantages, such as non-compliance, especially by elderly people and also patient acceptance.

In situ gelling system is an improved ocular drug delivery system designed in such a way that it is a liquid before instilling to the eyes and when instilled, it falls as a drops and undergoes phase transition in the ocular cul-de-sac to form gel which prevents the washing of the instilled drops and hence increase the retention time.

An ideal *in situ* formulation would enhance bioavailability by sustaining drug release, while remaining in contact with the front of eye for prolonged periods of time without disturbing the vision. It must also have good rheological properties like viscosity, gelling capacity.

Sol-gel transition may be dependent on polymer concentration or pH or temperature. The critical gelling concentration is the concentration below which no macroscopic gel is formed under the prevailing experimental conditions; rather, sol is formed by the polymer and solvent. This concentration depends on polymer-polymer and polymer-solvent interactions, the hydrophilic-lipophilic character of the polymer, and the molecular weight and flexibility of the chain. An aqueous solution of Carbopol [polyacrylic acid (PAA)]

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Received on: 09-01-2012
Revised on: 24-01-2012
Accepted on: 25-01-2012

low viscosity acidic solutions that transform into gels upon an increase in the pH. A reduction in the PAA concentration without compromising the *in situ* gelling properties as well as the overall rheological behaviour of the system is achieved by adding a suitable viscosity-enhancing polymer (Sandeep K *et al.,* 1995).

Using such ocular polymers, it is possible to develop an ocular novel drug delivery system which comprises of *In situ* gelling system of ocular decongestants like imidazolines drugs Naphazoline, Hydrochloride and Antazoline. Phosphate Three methods have been employed to cause phase transition on the eye surface: change in viscosity can be triggered by a change in temperature, pH, or electrolyte composition (Hong-Ru Lin *et al* 2001).

MATERIALS AND METHODS

CHARACTERIZATION AND EVALUATION

Infrared Spectra

Sample preparation: - Samples and potassium bromide were taken in the ratio of 1:100. It was triturated using motor and pressed, due precaution was taken not to come in contact with the moisture, which may interfere with the test. The sample along with blank (KBr), Reference standard drug were placed in order on the disk provided. Peaks obtained in FTIR are compared to that of Standard peaks for any significant change in the peaks of the respective drug. FTTR spectra of coded samples of naphazoline hydrochloride, carbopol 940, HPMC K_4M separately and combinations were taken and studied for any interactions between the drug and the excipients (Chunjie Wu, 2006; Moffat AC, 1986; Abashzadeh S, 2011).

Formulation of naphazoline hydrochloride *in situ* gelling solution formulations

The formulation was prepared by dispersing carbopol in distilled water with continuous stirring (Thermostatic hot plate with magnetic stirrer) until completely dissolved and allowed to hydrate overnight. For the preparation of solution, HPMC K_4M was added in distilled water and allowed to hydrate. Then Carbopol 940 solution was added uniformly into HPMC solution mixed well. After complete hydration of the polymers a separate solution of naphazoline hydrochloride and sodium chloride was added to the polymeric added to the polymeric solution. The resultant solution was thoroughly mixed. benzalkoonium chloride and sodium metabisulphite were then added mixing was continued until uniform and clear solutions were formed. Final volume was made up to 100 ml by adding required volume of distilled water and filtered through 0-2mm filter paper. All the solutions were adjusted to about pH 5.5 by 0.5 M sodium hydroxide. Sterilization was done by ultrafiltration.

Estimation of drug content

The assay was carried out by diluting 1 ml of the formulation (0.1% w/v) in 100 ml of distilled. From this stock solution 20 ml which corresponds to 20 μg/ml is taken and the drug content was estimated by UV visible spectrophotometer (Jasco V-530) for naphazoline hydrochloride using distilled water as blank. The absorption maximum was recorded at 276 nm.

Determination of pH, visual appearance and clarity

The pH of the gel forming ophthalmic solution was measured using pH meter. The developed formulations were then evaluated for visual inspection by placing them under fluorescent light against a white and black background in well-lit cabinet for appearance and clarity (Lekhraj Verma, 2011 and Ilva D 2011).

Determination of gelling capacity

The gelling capacity was determined by placing a drop of the system in a vial containing 2 ml of simulated tear fluid freshly prepared and equilibrated at 37^{o}C and visually assessing the gel formation and noting the time for gelation and the time taken for the formed gel to dissolve. The following grades are given based on gelling capacity. These grading helps in optimization of polymer concentration.

- No gelation

+ Gels after a few minutes, dissolves rapidly

++ Gelation immediate remains for few hours

+++ Gelation immediate remains for extended period

++++ Stiff gel formation.

Determination of viscosity

Viscosities of all the formulation was determined by using Brook Field's DV II viscometer at 10 RPM using spindle no.2. Both solution as well as the gel was measured for viscosity. 100ml of the developed formulations were taken in the beaker and the angular velocity increased gradually from 10 to 100 rpm. The hierarchy of the angular velocity was reversed. The average of the two reading was used to calculate the viscosity. The formulations were then poured into a beaker and the pH was raised to 7.4 by adding simulated lachrymal fluid. The viscosity was measured for the *in situ* gels (Estherlobel 2001).

EVALUATION OF NAPHAZOLINE HYDROCHLORIDE *IN SITU* GELLING SOLUTION

The formulations as given in the Table 1 were prepared as per the methodology. All the solution formulations and gelled formulations had an acceptable pH. Appearance and clarity and viscosity. All the selected formulations were shear thinning exhibiting pseudoplastic behaviour. All the formulations were liquid at room temperature and underwent rapid gelation upon raising the pH to 7.4.

In Vitro drug release

Table 1: Composition of in situ gelling solution of ocular formulations

Ingredients	Formulations			
	AA15	AA20	FF17	FF18
Naphazoline Hydrochloride (%w/v)	0.1	0.1	0.1	0.1
Carbopol 940 (% w/v)	1.0	1.0	0.5	0.6
HPMC K_4M (%w/v)	0.9	1.0	1.0	1.0
NaCl (% w/v)	0.9	0.9	0.9	0.9
Benzalkonium Chloride(% w/v)	0.02	0.02	0.02	0.02
Sodium metabisuphite (%w/v)	0.1	0.1	0.1	0.1
Distilled water(ml) to	100	100	100	100

Table 2: Drug content, viscosity and Gelling capacity of prepared formulations

Formulations	Viscosity(in cps)		Gelling capacity	pH		Drug Content in %
	Solution	Gel		Solution	Gel	
FF17	8.99	49.55	+ + +	5.09	7.32	96.05
FF18	9.79	50.25	+ + +	5.15	7.38	97.00
AA15	10.60	52.45	+ + +	5.34	7.40	95.10
AA20	12.41	55.00	+ + +	5.50	7.42	96.25

The *in vitro* releases of the drug from these formulations were studied through cellophane membrane using a modified *in vitro* permeation apparatus. The dissolution medium used was STF freshly prepared (pH 7.4). Cellophane membrane, previously soaked overnight in the dissolution medium, was tied to one end of a specifically designed glass cylinder (open at both ends and of 3.4 cm diameter). A 2-ml volume of the formulations was accurately pipetted into this assembly. The cylinder was attached to the metallic shaft and suspended in 50 ml of dissolution medium so that the membrane just touched the receptor medium surface and maintained at 37 $\pm$ 2°C at 50 RPM using magnetic stirrer. Aliquots, each of 1ml volume, were withdrawn an hourly intervals and replaced by an equal volume of the receptor medium. The aliquots were diluted with the receptor medium and analyzed by UV spectrophotometer at 276 nm for naphazoline hydrochloride using STF as blank (Des Noyer JR, 2003).

Drug Release Kinetics

To study the drug release kinetics the *in vitro* drug release data were plotted in kinetic models zero order, first order Higuchi square, Korsemeyer's Peppas models.

Stability Studies

The samples were stored at different storage conditions of elevated temperature such as 28°C/ 60% ± 5 % RH and 40°C/75% ± 5 % RH. The samples were withdrawn at one month time intervals for 3 months and evaluated for the pH, visual appearance, gelling capacity and *in vitro* drug release.

RESULTS AND DISCUSSION

Ophthalmic gel forming solution systems were developed for naphazoline hydrochloride with a view to deliver the drug in a sustained manner. The details of results and discussion were given in the following sections.

CHARACTERIZATION AND EVALUATION

Infrared Spectra

Determined the infrared absorption spectra of Naphazoline Hydrochloride in the potassium bromide Cup method under the FT Infrared Spectrophotometer, and compared these spectra: with the peak intensities found in a standard reference. Both spectra exhibited similar intensities of absorption at the same wave numbers. Principal peaks were found at wave numbers 1637, 721, 1399, 800, 1202, 817cm^{-1}.

From the spectral study, it was found that there were no interactions between drug and the excipient, hence the formulations prepared with naphazoline hydrochloride with polymer namely carbopol 940 and HPMC K_4M was compatible with each other

Drug content

Results obtained from these studies are given in Table : 2 .All the formulation had satisfactory drug contents Table -2

The initial drug contents of all the formulation was found satisfactory before the conducting the study for the drug release kinetic.

Estimation of drug content

The assay was carried out as per the methodology. The absorption maximum was recorded at 276 nm. Initial drug content for FF17, FF18, AA15, AA20 are given in Table 2.

Determination of pH, visual appearance and clarity

The pH of the gel forming ophthalmic solution was found to be satisfactory. The developed formulations were then evaluated for visual inspection by placing

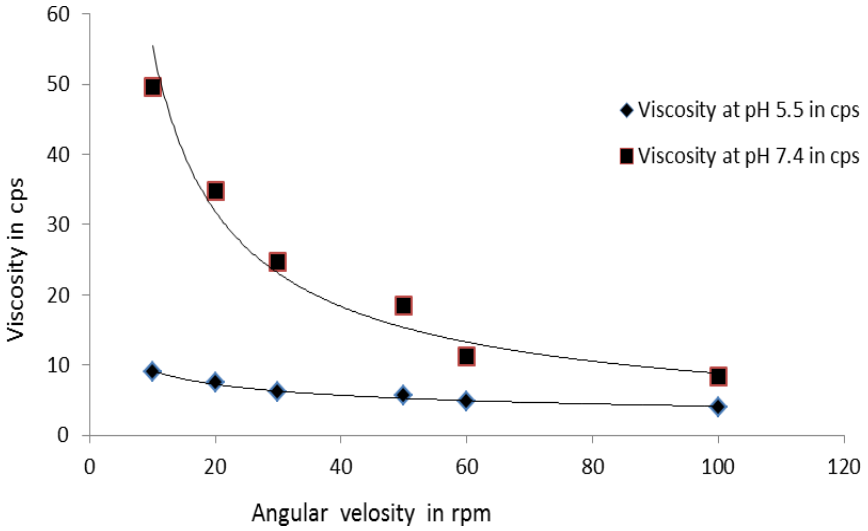

Figure 1: Trend of viscosity of formulation FF 17 at pH 5.5 and pH7.4

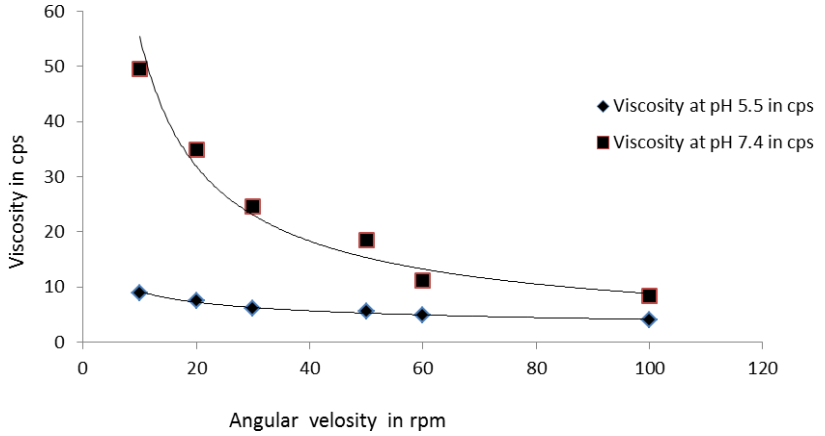

Figure 2: Trend of viscosity of formulation FF 18 at pH 5.5 and pH7.4

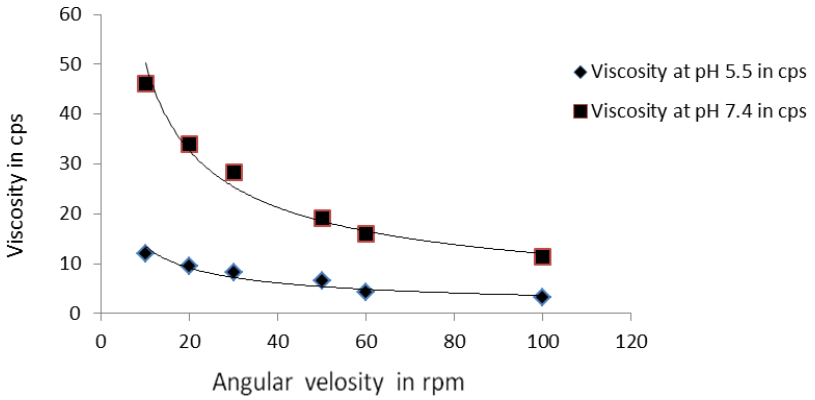

Figure 3: Trend of viscosity of formulation AA15 at pH 5.5 and pH7.4

them under fluorescent light against a white and black background in well-lit cabinet which appeared clear Table-2.

Determination of gelling capacity

The gelling capacity also was good for all the formulation and is recorded in the Table-2.

Determination of Viscosity

In order to evaluate the rheological behaviour viscosity of the formulation before and after addition of simulated lacrimal fluid was evaluated by using Brookfield viscometer using increased shear stress and simultaneously varying the angular velocities. All the selected formulations were shear thinning exhibiting pseudo plastic behaviour. All the formulations were liquid at room temperature and underwent rapid gelation upon raising the pH to 7.4. The obtained results are plotted

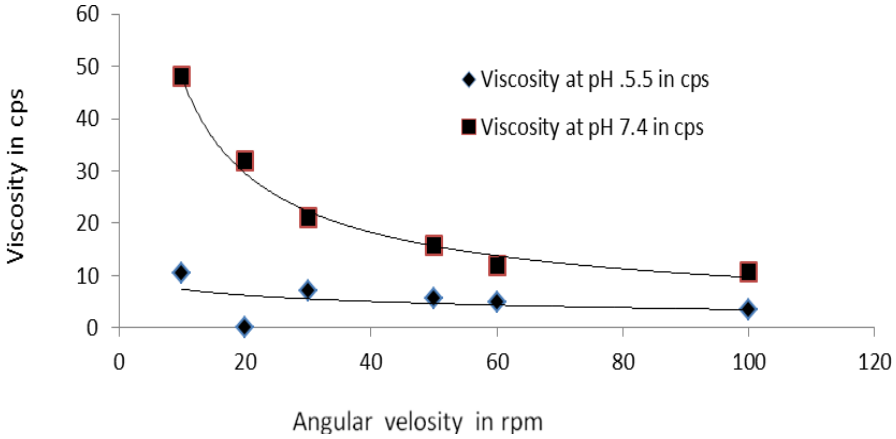

Figure 4: Trend of viscosity of formulation AA20 at pH 5.5 and pH7.4

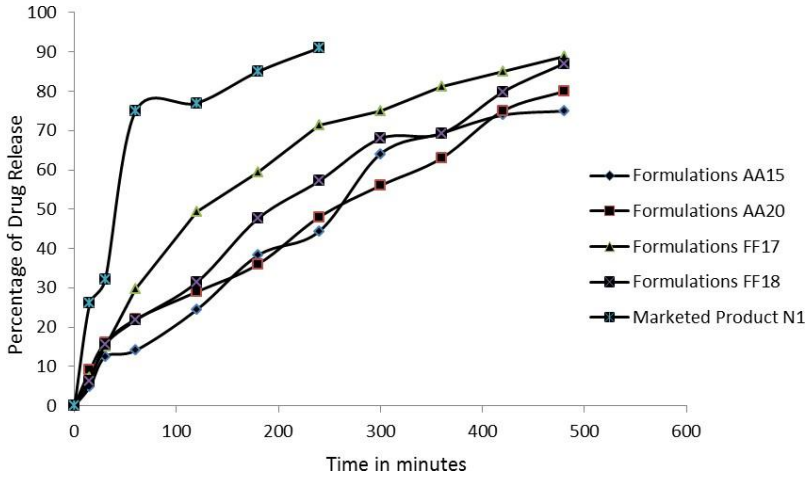

Figure 5: Comparative *in vitro* release profile of naphazoline hydrochloride *in situ* gel formulations with the marketed product N1

Table 3: Comparison of orders of *in vitro* release of naphazoline hydrochloride - FF17, FF18, AA15 and AA20

Regression equations	FF17	FF18	AA15	AA20
Zero Order	y = -x + 100 R^2 = 1	y = -0.9106x + 102.24 R^2 = 0.9878	y = -9.6712x + 93.467 R^2 = 0.9672	y = -8.9415x + 89.489 R^2 = 0.9944
First Order	y = -0.1156x + 1.9658 R^2 = 0.9944	y = -0.1017x + 2.0126 R^2 = 0.9753	y = -0.0812x + 2.0112 R^2 = 0.975	y = -0.0804x + 2.0013 R^2 = 0.9647
Higuchi model	y = 33.088x R^2 = 0.9683	y = 28.74x R^2 = 0.9688	y = 24.805x R^2 = 0.7112	y = 25.619x R^2 = 0.9621
Korsemeyer-Peppas model	y = 0.7039x + 1.388 R^2 = 0.9662 n=1.1309	y= 0.716x + 1.3116 R^2 = 0.9833 n=1.2278	y = 0.7789x + 1.2056 R^2 = 0.9794 n= 1.1198	y = 0.1003x + 0.6999 R^2 = 0.9452 n=1.0175

in Figures: 1 to 4 respectively for FF17, FF18, AA15, AA20.

DRUG RELEASE KINETICS

In vitro drug release is the most important evaluation study for the gel forming ophthalmic solution system and the results reveals the pattern of the drug release The drug release of a market conventional ocular solution was also compared with the release of the prepared formulations which is shown in figure: 5. The drug release kinetic study data is shown in Table: 3. All the prepared formulation of naphazoline hydrochloride *in situ* gelling solutions were found to be good than the marketed formulation N1 and had shown a drug re-

lease up to 8 h and followed the following release mechanisms.

1. Drug released from the formulation FF17 followed the zero order as the best fit model. Similarly, the release was in agreement with Higuchi and Korsemeyer-Peppas model as per the data obtained. Korsemeyer-Peppas model release mechanism is not well known, since more than one type of release phenomenon could be involved. However the slope of equation 'n' value could be used to characterize different release mechanisms as shown in Table-10. According to this the value of 'n' is calculated and shown in Table (6) and (7). It is seen that, value is greater than 1 and suggests that the formulation follows Super case II transport.

2. Drug release from the formulation FF18 followed zero order as the best fit model. The slope of the equation 'n' value is greater than 1 and suggests that the formulation follows Super case II transport.

3. Drug release from the formulation AA15 followed Korsemeyer-Peppas model as the best fit model. The slope of the equation 'n' value is greater than 1 and suggests that the formulation follows Super case II transport.

4. Drug release from the formulation AA20 followed zero order as the best fit model. The slope of the equation 'n' value is greater than 1 and suggests that the formulation follows Super case II transport.

Stability study showed all the formulations were stable for 3 months at 4°C, 28°C/ 60% ± 5 % RH, but gelled at higher temperature.

CONCLUSION

The gel forming ophthalmic solutions of Naphazoline Hydrochloride was successfully prepared by mechanism based on pH triggered using carbopol 940 as gel forming agent and HPMC K_4M as viscosity enhancing agents having a concentration of 0.1 % w/v of the drug. Prepared formulations were clear, transparent, and satisfactory regarding drug content. FTIR studies proved that there is no interaction between the drug and polymers based on the principle peaks. Rheological evaluation showed that the developed formulations obeyed pseudo plastic flow after addition to the STF. Gel forming ophthalmic solutions released drug (74%-87%) up to 8 h and was found to be better than the marketed conventional ocular solution of naphazoline hydrochloride. Release mechanism of the drug from the developed formulations was concluded as drug release from the formulation F17 followed zero order as the best fit model. The slope of the equation 'n' value is greater than 1 and suggests that the formulation follows Super case II transport.

Drug release from the formulation F18 followed zero order as the best fit model. The slope of the equation 'n' value is greater than 1 and suggests that the formulation follows Super case II transport. Drug release from the formulation AA15 followed Korsemeyer-Peppas model as the best fit model. The slope of the equation 'n' value is greater than 1 and suggests that the formulation follows Super case II transport. Drug release from the formulation AA20 followed zero order as the best fit model. The slope of the equation 'n' value is greater than 1 and suggests that the formulation follows Super case II transport. Stability studies at different conditions of temperature concluded that the suitable temperature for storage of the prepared *in situ* gelling solutions is 28°C/60% ± 5 % RH. All the four formulations are found to be satisfactory. Thus the objectives of present investigations are achieved for this drug and the results of the study indicated that the gel forming ophthalmic solution of Naphazoline Hydrochloride can be successfully prepared by pH triggered methods.

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