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PREPARATION AND EVALUATION OF INDOMETHACIN IN-SITU OCULAR GEL

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Abstract: The main objective of current study is to evaluate the in-situ gel prepared by using poloxamer and methyl cellulose. Methyl cellulose improves its adhesion property. The optimized formulation (PM-3) transparent and clear in appearance with 92.89 % drug content. The sol gel transformation of in-situ gel was found 33.70±0.30 ^{o}C with 84.63 % drug release in 5 hr. Viscosity of optimized formulation before gelation at 10, 20, 50, 100 rpm was found 1750, 1160,830,430 cps and after gelation 3980, 2010, 1470, 580 cps respectively. 6 weeks of stability studies reveal that there was no change in visual appearance and clarity with slight changes in pH, but it was in acceptable limits (±0.5). Finally, on the basis of current data, it can be concluded that in-situ gel were a promising enhance ocular bioavailability and patient compliance.

Keywords: Indomethacin, In-situ gel, Gelling capacity, In- vitro drug release.

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INTRODUCTION

Nasolacrimal drainage is the major factor for precorneal drug loss that leads to poor ocular bioavailability[1]. The short pre-corneal contact time combined and corneal impermeability results in low bioavailability, and due to this, frequent dosing is usually needed[2]. Although various ophthalmic drug delivery systems such as inserts, ointments and suspensions have been developed to overcome this problem, they have not been accepted by patients due to several drawbacks i.e., difficultly in administration of inserts, blurred vision due to use of ointments and dosage heterogeneity of suspensions[3]. In-situ gel forming system has been developed to prolong the pre-corneal residence time of a drug and improve ocular bioavailability. These systems consist of polymers that exhibit sol-to-gel phase tansititions due to change in specific physicochemical parameter[4,5]. hydrogel is mostly based on an increase of ocular residence time via enhanced viscosity and mucoadhesion properties[6].

MATERIAL AND METHODS:

Indomethacin (SGPTC Pvt. Ltd.), Polaxamer (BASF Aktiengesellschaft), Methyl cellulose (Merck India ltd.).

Method:

CALIBRATION CURVE OF INDOMETHACIN IN STF: For this purpose, stock solutions of drug samples were prepared in the simulated tear fluid (STF). 10 mg of indomethacin was accurately weighed and transferred to a 100 ml volumetric flask volume was made upto Simulated tear fluid 100 ml. so as to obtain a stock solution dilution for subsequent concentration (4,8,12..) was made with STF, and the sample was scanned between 200 nm to 400 nm on a double beam UV/Visible spectrophotometer (Shimadzu 1800) against STF as blank.

PREPARATION OF SIMULATED TEAR FLUID (STF):sodium chloride 0.67 g, sodium bicarbonate 0.20 g,calcium chloride dehydrate 0.008 g in distilled water q.s. to 100 ml[7].

PREPARATION OF IN-SITU GEL: Polaxmer solutions prepared by weighing the polymer in cold water. The solutions kept in a refrigerator for at least 24 h to ensure complete dissolution.. In case of methyl cellulose, it initially dissolved in hot water about 60^{o}C after this the MC solution mixed in polaxmer solution[8].

Table 1. Composition of in-situ gel formulations at various concentration of Polaxamer

Formulation no.	Drug (%w/v)	Polaxamer (%w/v)	STF
F-0	1	17	q.s
F-1	1	18	q.s.
F-2	1	19	q.s.
F-3	1	20	q.s.
F-4	1	21	q.s.
F-5	1	22	q.s.
F-6	1	23	q.s

Table 2. Composition of in-situ gel formulations at various concentration of methyl cellulose.

Formulation no.	Drug (%w/v)	Polaxamer (%w/v)	Methyl cellulose (%w/v)	STF
PM-1	1	19	0.25	q.s.
PM-2	1	19	0.50	q.s.
PM-3	1	19	0.75	q.s.
PM-4	1	19	1.00	q.s.

FOURIER-TRANSFORM INFRARED SPECTROSCOPY:

The FTIR spectra were obtained by using an FTIR spectrometer.The samples were previously ground and mixed thoroughly with potassium bromide. The scanning range was from 4000 to 400 cm^{-1}.

EVALUATION PARAMETERS:

PHYSICAL APPEARANCE: Physical appearance of the formulations was visually observed .

pH: The pH of the prepared in situ gelling system after addition of all the ingredients was measured using pH meter. pH of all the formulations were adjusted to 7.4 [9,10].

CLARITY: The clarity of the all formulations before and after gelling is to be determined by visual inspection of the formulations under light, alternatively against white and black backgrounds[9,11].

GELLING CAPACITY TEST: Gelling capacity of the representative formulations was determined by placing a drop of the sample into a test tube containing 2ml of pH 7.4 simulated tear fluid (STF) equilibrated at 35±1°C. The visual assessment of gel formation and dissolution with time record was performed in triplicate[12].

DRUG CONTENT: The drug content of formulation was determined by taking 1 ml of the formulation and diluting it to 10 ml with STF was determined at 320 nm by using UV-Visible spectrophotometer[13].

VISCOSITY: Viscosity of the instilled formulation is an important factor in determining residence time of drug in the eye. The solutions were allowed to gel in the STF and then the viscosity determinations were carried out by using Brooke field viscometer, angular velocity ran from 10-100 rpm. Viscosity of the formulations increased with increase in polymer concentration. The hierarchy of shear rate was reversed and average of two readings was used to calculate viscosity[14].

IN VITRO RELEASE STUDIES:

In vitro release studies of in-situ gel were performed by dialysis tubing cellophane membrane using. Cellophane membrane, previously soaked overnight in the dissolution medium, was tied to one end of opening was tied to the mouth of a PVC test tube (1cm diameter) and dipped in a 100 ml beaker containing STF (pH 7.4, 50 ml). The entire system was placed in beaker (250 ml) containing distilled water maintained at 37±0.5 ◦C by used hot plate.

A small magnetic bead was placed in the beaker and was stirred at 100rpm on a magnetic stirrer (Remi India Ltd.). In-situ gel 1-ml volume, were withdrawn hourly intervals and replaced by an equal volume medium. The aliquots were diluted with the receptor medium and analyzed under UV spectrophotometry[15] .

ACCELERATED STABILITY STUDIES:

According to ICH guideline, the accelerated stability studies were carried for prepared in situ gelling systems. All the Formulations were analyzed for visual appearance, clarity, pH and drug remaining for 6 weeks of stability studies[16].

RESULT & DISCUSSION

CALIBRATION CURVE INDOMETHACIN IN STF

The λmax for drug in STF is 320 nm.

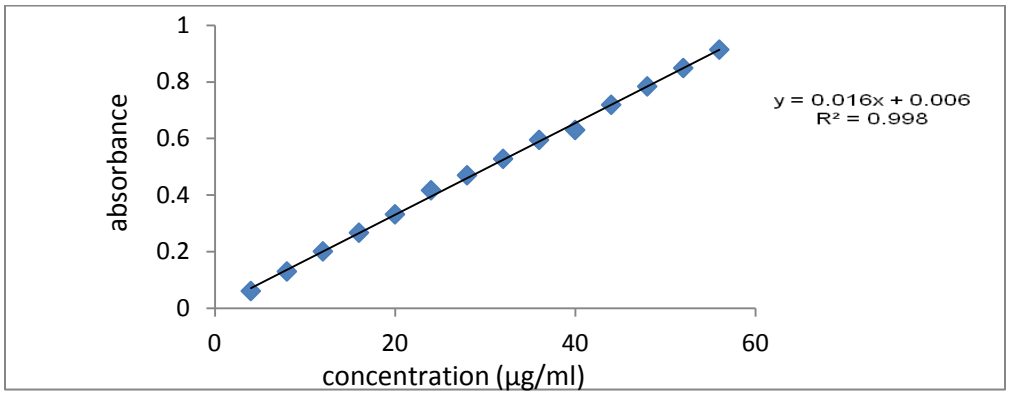

Fig. 1. Calibration curve of indomethacin in simulated tear fluid.

FOURIER-TRANSFORM INFRARED SPECTROSCOPY:

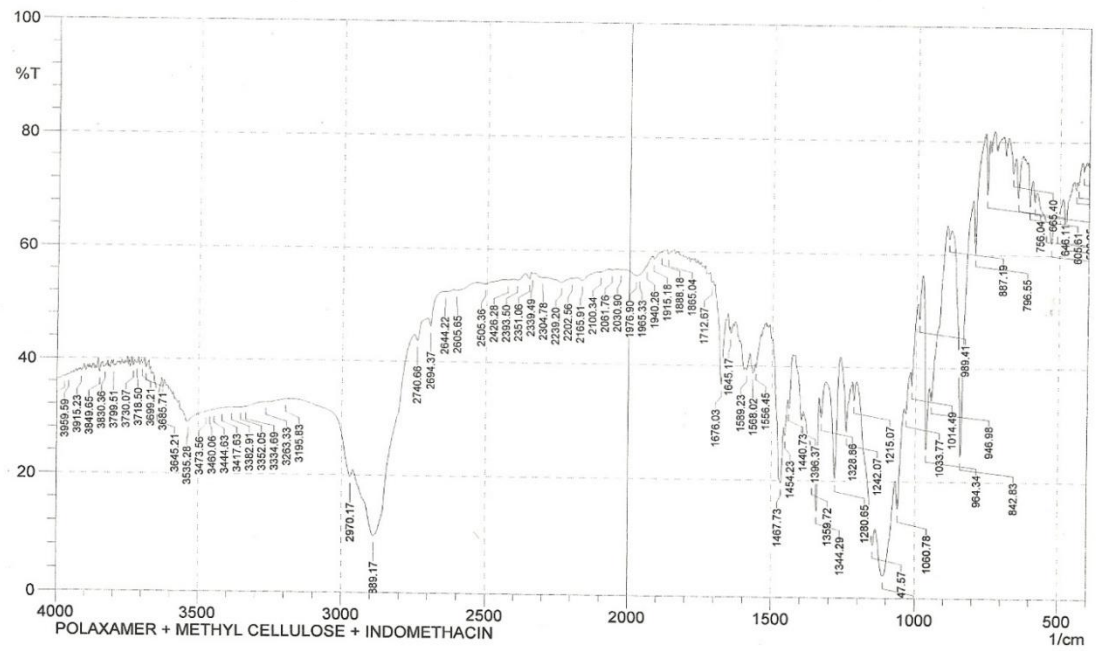

Fig. 2. FTIR of Polaxamer, methyl cellulose and indomethacin.

EVALUATION OF VISUAL APPEARANCE, CLARITY, PH, AND DRUG CONTENT:

Table 3. Evaluation of visual appearance, clarity, pH, and drug content

Formulation Code	Visual Appearance	Clarity	pH	%Drug content
F-0	Transparent	Clear	7.4	82.32
F-1	Transparent	Clear	7.4	86.43
F-2	**Transparent**	**Clear**	**7.4**	**92.63**
F-3	Transparent	Clear	7.4	89.68
F-4	Transparent	Clear	7.4	86.52
F-5	Transparent	Clear	7.4	84.98
F-6	Transparent	Clear	7.4	83.38
PM-1	Transparent	Clear	7.4	91.32
PM-2	Transparent	Clear	7.4	91.85
PM-3	**Transparent**	**Clear**	**7.4**	**92.89**
PM-4	Transparent	Clear	7.4	91.93

Table 4. Evaluation of thermoresponsive ophthalmic in-situ gel formulations.

Formulation Code	Tsol–gel (^{o}C)	In vitro gelation
F-0	38.50±0.70	+
F-1	38.20±0.30	++
F-2	**34.80±0.60**	+++
F-3	32.30±1.30	+++
F-4	30.50±1.60	+++

F-5	25.60±0.40	+++
F-6	22.80±0.30	+++
PM-1	35.50±0.90	+++
PM-2	34.80±0.30	+++
PM-3	**33.70±0.30**	**+++**
PM-4	32.60±0.40	+++

Gels after a few minutes, dissolves rapidly (+); Gelation immediate, remains for few hours (++); Gelation immediate, remains for extended period (+++).

IN-VITRO RELEASE STUDY

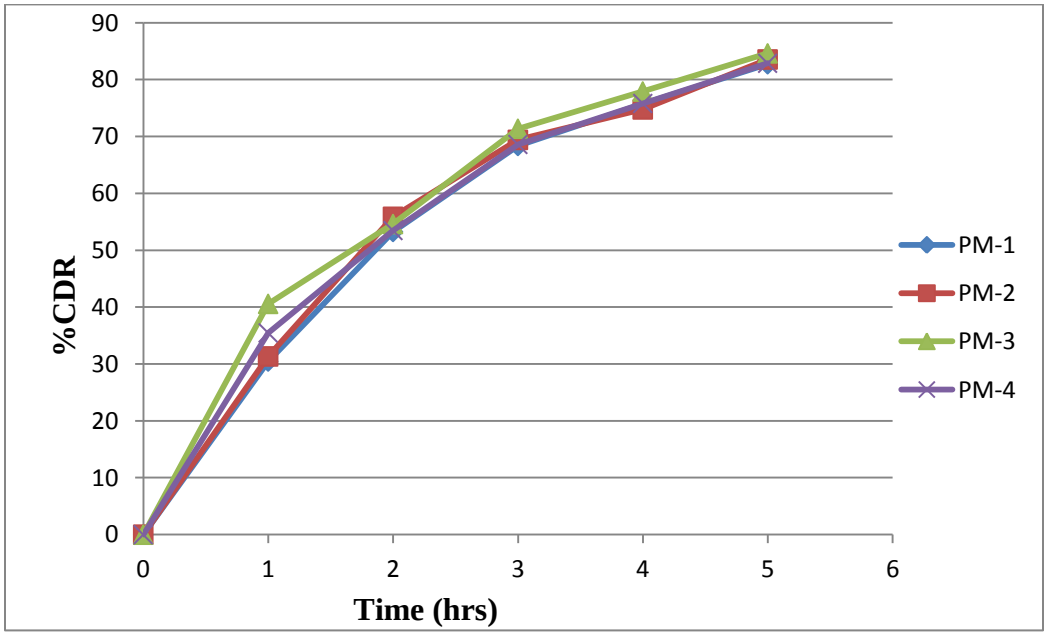

Figure 3. In-vitro release

KINETIC MODEL ANALYSIS:

Higuchi model

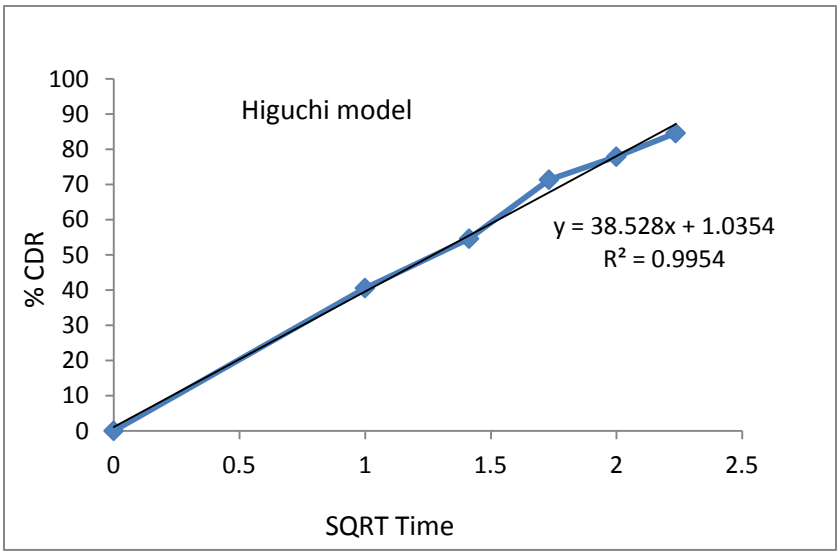

Figure 4. Higuchi model for release of in-situ gel

PM-3 optimized formulation follow the Higuchi model. This model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than drug solubility; (ii) drug diffusion takes place only in one dimension (edge effect must be negligible); (iii) drug particles are much smaller than system thickness; (iv) matrix swelling and dissolution are negligible; (v) drug diffusivity is constant; and (vi) perfect sink conditions are always attained in the release environment.

MEASUREMENT OF VISCOSITY:

Viscosity of optimized formulation was measured by Brookfield viscometer.

Table 5.Measurement of viscosity of in-situ gel

Viscosity (cps) at rpm (before gelation)				Viscosity (cps) at rpm (after gelation)			
10	**20**	**50**	**100**	**10**	**20**	**50**	**100**
1750	1160	830	430	3980	2010	1470	580

ACCELERATED STABILITY STUDIES

Optimized formulation was analyzed for visual appearance, clarity, pH and drug remaining for 6 weeks of stability studies reveal that there was no change in visual appearance and clarity. All the formulations showed slight changes in pH, but it were in acceptable limits (±0.5).Study of % drug remaining in all formulations reveals that there were no definite changes observed to justify for drug degradation.

Table 6. Accelerated stability studies

Number of weeks	Visual Appearance		Clarity		pH		% Drug remaining	content
	RT	40^0C	RT	40^0C	RT	40^0C	RT	40^0C
0	Transparent	Transparent	Clear	Clear	7.4	7.4	92.89	92.89
1	Transparent	Transparent	Clear	Clear	7.3	7.6	92.73	92.40
2	Transparent	Transparent	Clear	Clear	7.5	7.8	92.69	92.11
3	Transparent	Transparent	Clear	Clear	7.5	7.6	92.42	91.79
4	Transparent	Transparent	Clear	Clear	7.3	7.3	92.31	91.59
5	Transparent	Transparent	Clear	Clear	7.3	7.2	92.16	91.32
6	Transparent	Transparent	Clear	Clear	7.2	6.7	91.78	89.83

DISCUSSION

Most commonly available ophthalmic preparations, when instilled into eye are rapidly drained away from the ocular cavity due to the tear flow and naso-lachrymal drainage. Ophthalmic ointments give blurred vision, leading to poor patient acceptance. Formulation of in-situ gel with better residence time enhanced and reduces frequency of dose improved patient compliance. FTIR of Indomethacin with other excipients shows that there was no or less interaction of drug and good opportunity to formulate into in-situ gel.

In-situ gel was prepared by using poloxamer and methyl cellulose. Methyl cellulose improves its adhesion property.

The optimized formulation (PM-3) was transparent and clear in appearance with 92.89 % drug content. The sol gel transformation of in-situ gel was found 33.70±0.30 ^{o}C with immediate gelation property.

The in-vitro drug release of optimized formulation was found 84.63 % drug release in 5 hr. Optimized formulation follow the Higuchi model.

Viscosity of optimized formulation was measured by Brookfield viscometer. Viscosity of optimized formulation before gelation at 10, 20, 50, 100 rpm was found 1750, 1160,830,430 cps and after gelation 3980, 2010, 1470, 580 cps respectively.

Optimized formulation was analyzed for visual appearance, clarity, pH and drug remaining for 6 weeks of stability studies reveal that there was no change in visual appearance and clarity. All the formulations showed slight changes in pH, but it were in acceptable limits (±0.5).Study of % drug remaining in all formulations reveals that there were no definite changes observed to justify for drug degradation.

CONCLUSION

In the data obtained from experimental work, it can be concluded that polymeric in- situ gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Due to good stability and biocompatibility the in-situ gel dosage forms become very reliable. Use of in-situ gel for the delivery of medicaments will be the subject of research in future.

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REFERENCES:

1. Shulin D., Recent developments in ophthalmic drug delivery. PSTT, 1, 8,(1998), 328-335.

2. Gratieri T., Gelfuso G. M., Rocha E. M., Sarmento V. H., Freitas O. de, Lopez R. F. V. A poloxamer/chitosan in situ forming gel with prolonged retention time for ocular delivery. European Journal of Pharmaceutics and Biopharmaceutics. 75, (2010) 186–193.

3. Rathapon. A., Thanasanchokpibull, S., Fuongfuchat, A., Sukitaya, V. S., (2011). Optimization and evaluation of thermoresponsive diclofenac sodium ophthalmic in situ gels. International Journal of Pharmaceutics. 411, 128–135.

4. Rathore K. S., Nema R. K. and Sisodia S. S. An overview and advancement in ocular drug delivery systems. IJPSR, (2010); Vol. 1 (10): 11-23.

5. Jiawei Li, Hainan Zhaoa. Comparison of systemic absorption between ofloxacin ophthalmic in situ gels and ofloxacin conventional ophthalmic solutions administration to rabbit eyes by HPLC–MS/MS. International Journal of Pharmaceutics 450, (2013), 104– 113.

6. D.kute S, Somnath C. Sakore, Bhaswat S. Chakraborty Formulation approaches in ocular drug delivery system. International Journal Of Pharmacy&Technology.2010, 2, 2 , 118-145.

7. Hong-R. L., Sung K.C. Carbopol/ pluronic phase change solutions for ophthalmic drug. Journal of Controlled Release 69, (2000), 379–388.

8. El-Kamel A.H.. In vitro and in vivo evaluation of Pluronic F127-based ocular delivery system for timolol maleate. International Journal of Pharmaceutics 241 (2002) 47–55

9. Aparna V. Bhalerao, Singh Sitanshu S.. In situ gelling ophthalmic drug delivery system for glaucoma. International Journal Of Pharma And Bio Sciences.2,2, (2011),7-14.

10. Bhoyar B.S., Agnihotri VV. and Bodhankar M.M., 2011. New method for sustained ocular drug delivery: based on polymeric combination with thermo sensitive gelling agents. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2,3,1151-1160.

11. Katariya D. C., Poddar S.S.,2012. Current status of ophthalmic *in-situ* forming hydrogel. International journal of pharma and bio sciences. International journal Pharm Bio Science; 3,3, 372 – 388.

12. Asasutjarit.R., S. Thanasan., FuongfuchatA., VeeranS., 2011. Optimization and evaluation of thermoresponsive diclofenac sodium ophthalmic in situ gels. International Journal of Pharmaceutics. 411,128–135.

13. Jovita K., Sonker K, Pandey M, Kymonil K. M., Saraf S. A., 2012. Formulation and characterization of a novel pH-triggered in-situ gelling ocular system containing gatifloxacin. International Current Pharmaceutical Journal, 1,3, 43-49.

14. Peppas NA, Bures P., Leabandung W, Ichikawa H. Hydrogels in pharmaceutical formulations, Eur J Pharm and Biophar 2000;50:27-46.

15. Nagarwal R.C.,Kumar R.,Dhanawat M., Pandit J.K.,2011.Modified PLA nano in situ gel: A potential ophthalmic drug delivery system. Colloids and Surfaces B: Biointerfaces. 86, 28–34.

16. Suryawanshi Sarika S., Kunjwani H K, Kawade Jayashree V,Alkunte Mohita A, Yadav Dattatraya J. Novel Polymeric in Situ Gels for Ophthalmic Drug Delivery System. IJRPS 2012,2(1),67-83.