

Sustained Release Bioadhesive Ocular Inserts of Olopatadine Hydrochloride: Formulation and Characterization

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ABSTRACT

Objective: To develop bioadhesive ocular inserts of Olopatadine hydrochloride for treating the allergic eye conditions with sustained ocular delivery which will reduce dosing frequency. **Methods:** Matrix type ocular inserts were prepared by the solvent casting technique using teflon coated petri plates and characterized *in vitro* for drug release studies. Nine formulations were prepared having different ratios of polymers such as carbopol 980P, HPMC K4M and NaCMC (90:10, 70:30 and 50:50) and optimized. All the formulations were evaluated for thickness, weight variation, folding endurance, drug content uniformity, *in vitro* release study, bio/mucoadhesion studies, surface pH, swelling index, % moisture absorption, % moisture loss, release kinetics, histological study and stability study. **Results:** The optimized formulation 'F5' containing polymers Carbopol 980P and HPMC K4M in the ratio of 70:30 was selected on the basis of drug release studies. The formulation F5 was found to act as bio/mucoadhesive insert with sustained drug release by increasing residence time in the eye. **Conclusion:** The prepared inserts showed sustained drug release by increased residence time achieved through bioadhesion and thus may overcome the drawbacks of eye drops.

Key words: Olopatadine hydrochloride, Ocular inserts, Solvent casting, Bioadhesive, Drug release.

INTRODUCTION

Many parts of the eye are relatively inaccessible to systemically administered drugs and as a result, topical drug delivery remains the preferred route in most cases. Drug may be delivered to treat the precorneal region for such infections as conjunctivitis and blepharitis or to provide intraocular treatment via cornea for diseases such as glaucoma and uveitis.¹

Ocular drug delivery systems are developed to treat eye conditions locally, whereas past formulations are targeted to reach systemic circulation and these are designed to overcome all the disadvantages of conventional dosage forms such as rapid and extensive

elimination of drugs from the precorneal lachrymal fluid.²

The frequent administration of eye drops is necessary to maintain an adequate level of ophthalmic drugs. The addition of suitable polymers to eye drops may result in increased bioavailability by prolonging the corneal contact time. The commonly available ophthalmic ointments, although better retained than eye drops, do not efficiently release all types of drugs and they are poorly tolerated by many patients. These factors have intensified the search for alternative ophthalmic dosage forms i.e. ocular inserts which aimed at ensuring a prolonged time

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of residence of the medication in the eye by increasing contact time with the conjunctival tissues.³

Ocular inserts are described as single, sterile, thin and multilayered, drug impregnated, solid or semisolid consistency devices, whose size and shape are especially designed for application in eye. Ocular inserts offer several advantages such as increased ocular residence time, drug release at a slow and constant rate, accurate dosing, reduction of systemic absorption, better patient compliance, possibility of targeting internal ocular tissues, increased shelf life with respect to aqueous solutions and absence of preservatives, thus reducing the risk of sensitivity reactions.^{4,5} Other advantages include prolonged drug activity and increased bioavailability.⁶ Olopatadine hydrochloride is an antiallergic agent with histamine H1 receptor antagonistic action that is indicated for the signs and symptoms of allergic rhinitis chronic urticaria, eczema dermatitis, prurigo, pruritis cutaneous, psoriasis vulgaris and erythema exsudativum multiforme. Olopatadine hydrochloride exhibits potent antihistamine activity *in-vivo* following its systemic administration.⁷

In the present study, an attempt was made to formulate bioadhesive ocular inserts of Olopatadine hydrochloride using polymers for overcoming the drawbacks of conventional ocular dosage form such as poor bioavailability, drug wastage due to spillage as well as naso-lachrymal drainage and frequent administration.

MATERIALS AND METHODS

Materials

Olopatadine hydrochloride was obtained as gift sample from Ami life Sciences, Vadodara, Gujarat. Hydroxy propyl methyl cellulose K4M (HPMC), Carbopol 934P, Carbopol 980P and Sodium Carboxy methyl cellulose (CMC) were obtained from Chemdyes corporation, Rajkot. All other reagents used were of analytical grade.

Methods

Characterization of Drug

The drug was characterized for solubility,⁸ melting point⁹ and identification test¹⁰ using UV spectrophotometer by preparing Simulated tear fluid (STF) and standard curve in STF pH 7.2.

Drug-Excipients Compatibility Study

Spectra were obtained for physical mixtures of drug/excipients and either drug or excipient alone using a model Bruker Alpha T FTIR spectrophotometer (Bruker Optik GmbH, Germany).

Optimization of Plasticizer, Polymer and Formulation Batch

Inserts were prepared using Carbopol 934P and HPMC K4M at different concentrations. Glycerin (20 % w/w of polymer) was incorporated as plasticizer. Inserts were evaluated for physical characteristics with different concentrations such as 10, 15, 20 and 25% w/w of plasticizer. From the study it was found that Glycerin gave good flexibility with 20 % w/w, less with 10% w/w and 15% w/w and sticky with 25% w/w. And therefore Glycerin, 20% w/w was selected for further studies.

To check the physical stability of ocular inserts, the ocular inserts from each batch were kept in 50 ml beaker containing 30 ml of STF pH 7.2 with continuous stirring. Each ocular insert was found to be stable less than 24 h and also found that the film prepared from polymers HPMC E15LV and Na CMC with concentration of 0.5% were readily water soluble as compared to 0.3%. The optimized quantity of both polymers was selected as 0.3% w/v. Hence, the polymer HPMC E15LV was replaced with HPMC K4M and same procedure was repeated. To increase the physical stability of ocular inserts carbopol 934P was replaced by carbopol 980P. Total polymer concentration used was 0.7% w/v and the ratios for polymers i.e. carbopol 980P: HPMC K4M and carbopol 980P: NaCMC were 90:10, 70:30 and 50:50.

Formulation of Olopatadine Hydrochloride Ocular Inserts

The inserts were prepared in nine batches (F1 to F9) by solvent casting method.¹¹

Evaluation of Prepared Ocular Inserts

Thickness

The thickness of 5 inserts from each batch was measured using a micrometer screw gauge.¹²

Weight Variation Test

Five randomly selected ocular inserts were taken and weighed individually using calibrated digital balance.¹³

Folding Endurance

Folding endurance was calculated by folding the ocular inserts repeatedly in the same position till a crack appeared. Number of folds required to produce the crack were counted.¹³

Surface pH

Surface pH of the insert was determined by allowing it to swell in a closed petridish at room temperature for 30 min in 0.1 ml of double distilled water. The swollen

devices were removed and surface pH was determined using digital pH meter.¹⁴

Percentage Moisture absorption test

The films were weighed and placed in desiccator containing saturated solution of sodium chloride and 84% humidity was maintained. After three days, the films were taken out and reweighed. The % moisture absorption was calculated using the following formula.¹⁵

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial Weight}}{\text{Initial Weight}} \times 100$$

Percentage Moisture loss

The inserts were weighted and kept in desiccator containing anhydrous calcium chloride. After three days, the inserts were taken out and reweighed. The percentage moisture loss was calculated using the following formula.¹⁵

$$\% \text{ Moisture loss} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Final Weight}} \times 100$$

Swelling index

Swelling index was calculated with the help of following formula.¹⁶

$$\text{Swelling Index (SI) \%} = \left[\frac{wt - w_0}{w_0} \right] \times 100$$

Where wt: weight of swollen insert after time t; w₀: original weight of insert at zero time

Tensile strength and Elongation at Break

Tensile strength and elongation at break was determined by modified apparatus. The apparatus consisted of a base plate with a pulley aligned on it. The film was fixed in insert holder at one end of base plate and another end was fixed with help of forceps having triangular end to keep the film straight during stretching. A thread was tied to the triangular end and passed over the pulley, to which a small pan was attached to hold weights. A small pointer was attached to the thread that travels over the graph paper affixed on the base plate. The weights were gradually added to the pan till the film was broken. The weight necessary to break the film was noted as break force and the simultaneous distance travelled by the pointer on the graph paper indicated the elongation at break.¹⁶

$$\text{Tensile strength (g/mm}^2\text{)} = \frac{\text{break force (g)}}{\text{cross-sectional area of the sample (mm}^2\text{)}}$$

$$\text{Elongation at break (\%)} = \frac{\text{increase in length at break point (mm)}}{\text{Original length (mm)}} \times 100$$

Drug content and content uniformity

One insert from each batch was grounded in a glass pestle mortar and to it 100 ml of STF was added to make suspension. The suspension so obtained was filtered and filtrate was assayed spectrophotometrically at 220

nm. Uniformity of the drug contents was determined by assaying the individual inserts.¹⁶

Ex vivo Bioadhesive Strength

Freshly excised conjunctival membrane of an adult goat was used as model membrane for the measurement of bioadhesive strength which was obtained from a local slaughter house. The underlying skin was removed and placed in aerated saline solution at 4°C until used. Preparation was placed in an aerated saline at 4°C, which was later washed with distilled water and STF phosphate buffer (pH 7.2, 37°C) before use. Bioadhesive strength of the insert ($n = 3$) was measured on a modified physical balance.¹⁷

In vitro drug permeation and release

The *in vitro* drug permeation studies through the goat conjunctival membrane were done by using modified Franz diffusion cell at 37°C ± 0.5°C (diameter of 1.5 cm with a diffusional area of 1.76 cm²). Fresh goat conjunctival membrane was mounted between the donor and receptor compartments. The ocular insert was placed in donor compartment with the core facing the membrane and the compartments clamped together. The receptor compartment (15 ml capacity) was filled with STF pH 7.2. The temperature of media was maintained at 37 ± 0.5°C with the help of temperature-controlled water jacket and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm. A 2 ml sample was withdrawn at predetermined time intervals and analyzed for drug content at 220 nm using a UV spectrophotometer. The volume of release media was maintained by adding equal volume of the fresh media after every sampling.¹⁶

Drug Release Kinetics

To analyze the mechanism of drug release from ocular inserts, the *in vitro* release data were fitted to various mathematical models like zero-order, first-order, Higuchi and Korsmeyer-Peppas models.^{17,18}

Sterilization and test for sterility for ophthalmic films

In the present study, all films were sterilized separately by exposing them to UV radiation for 30 min. The irradiated ophthalmic films were tested for their sterility as per the Indian Pharmacopoeia to detect the presence of viable forms of bacteria, fungi and yeast in or on sterilized preparations. The tests were carried out under aseptic conditions to avoid accidental contamination of the product during the test.¹⁹ Direct inoculation method (method B) was adopted for performing test for sterility.²⁰

Histological study

Histological study was performed to evaluate the irritation and toxicity of formulation using isolated goat eye conjunctiva which was obtained from a local slaughter house within 2 h of killing. In this method three samples of isolated conjunctiva were taken and first was treated with STF pH 7.2, which acted as a positive control, second was treated with Isopropyl alcohol (IPA) which acted as a negative control and third was exposed to optimised formulation which acted as a test. All the samples were sent to the pathological laboratory for evaluating tissue damage to conjunctiva.^{21,22}

Stability studies

The optimized ocular inserts were subjected to the stability studies. The accelerated stability studies were carried out according to ICH guidelines by storing the samples at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for 6 months.²³

RESULTS AND DISCUSSION

Characterization of Drug

The drug Olopatadine hydrochloride was found to be freely soluble in water and also soluble in 0.1N HCl,

0.1N NaOH, ethanol, methanol, Phosphate buffer pH 7.4 and STF pH 7.2.

The melting point range of the drug was found consistent with melting range given in literature.²⁴

Drug-Excipients Compatibility Study

FTIR spectra of Olopatadine hydrochloride in combination with polymers and in formulation are shown in Figure 1. Spectroscopic studies (FTIR) showed that there was no chemical interaction between the drug and excipients.

Evaluation of Prepared Ocular Inserts

The results for thickness, weight variation, folding endurance, surface pH, swelling index, percentage moisture absorption, percentage moisture loss, tensile strength with elongation at break, drug content and bioadhesive strength are shown in Table 1 and Table 2.

The prepared inserts were observed translucent, colourless, smooth, uniform in appearance and did not show visible crack or imperfection. All the formulations passed test for thickness, weight variation, folding endurance, surface pH, percentage moisture absorption, percentage moisture loss, swelling index, tensile

Table 1: Evaluation of Ocular Inserts.

Batch code	Weight variation (mg) [*]	Thickness (mm) [*]	Folding endurance [*]	Surface pH [*]	% Swelling index [*]	Drug content (%) [*]
F1	8.587 ± 0.41	0.115 ± 0.005	457.0 ± 7.5	6.8 ± 0.115	50.18 ± 0.235	98.0 ± 0.122
F2	7.937 ± 0.57	0.100 ± 0.010	425.6 ± 10	7.1 ± 0.115	45.17 ± 0.152	99.3 ± 0.233
F3	6.907 ± 0.39	0.113 ± 0.006	389.6 ± 6.0	7.3 ± 0.115	55.34 ± 0.245	98.7 ± 0.261
F4	4.920 ± 0.27	0.087 ± 0.006	411.0 ± 8.5	7.2 ± 0.200	64.95 ± 0.164	98.7 ± 0.312
F5	6.433 ± 0.52	0.117 ± 0.006	404.3 ± 5.9	6.8 ± 0.000	41.85 ± 0.179	99.3 ± 0.289
F6	5.440 ± 0.54	0.110 ± 0.010	372.7 ± 5.1	7.1 ± 0.115	52.99 ± 0.212	98.7 ± 0.286
F8	7.230 ± 0.31	0.131 ± 0.003	278.3 ± 12	6.6 ± 0.346	20.81 ± 0.231	99.3 ± 0.313
F9	6.473 ± 0.09	0.125 ± 0.005	310.3 ± 4.5	6.8 ± 0.473	22.58 ± 0.146	98.7 ± 0.412

Mean±SD; *n=3

Table 2: Evaluation of Ocular Inserts.

Batch code	Tensile strength (g/mm ²) [*]	%Elongation at break [*]	% Moisture absorption [*]	% Moisture loss [*]	Bioadhesive strength (g) [*]
F1	0.281 ± 0.0032	32.4	10.19 ± 0.31	33.88 ± 2.7	10.8 ± 0.23
F2	0.252 ± 0.0029	30.3	11.26 ± 0.89	29.19 ± 5.9	9.90 ± 0.25
F3	0.210 ± 0.0036	28.9	23.50 ± 0.75	26.22 ± 4.7	8.20 ± 0.15
F4	0.291 ± 0.0028	36.9	12.71 ± 0.39	35.21 ± 4.2	10.2 ± 0.28
F5	0.272 ± 0.0037	32.6	23.29 ± 0.45	21.26 ± 5.5	8.90 ± 0.31
F6	0.241 ± 0.0026	30.8	11.70 ± 0.33	25.09 ± 6.2	8.10 v 0.19
F8	0.221 ± 0.0019	28.2	39.07 ± 0.13	12.81 ± 3.5	7.90 v 0.32
F9	0.232 ± 0.0041	33.5	35.27 ± 0.35	10.12 ± 2.5	7.80 ± 0.16

Mean±SD; *n=3

Table 3: Curve fitting of the <i>in vitro</i> Drug Release Data from Ocular Inserts F3 and F5.					
Formulation Code	Correlation coefficient (R^2)				
	Zero order	First order	Korsmeyer-peppas model	Higuchi model	Hixson-crowell model
F3	0.9784	0.9549	0.9429	0.7325	0.9295
F5	0.9864	0.9549	0.9835	0.5381	0.9653

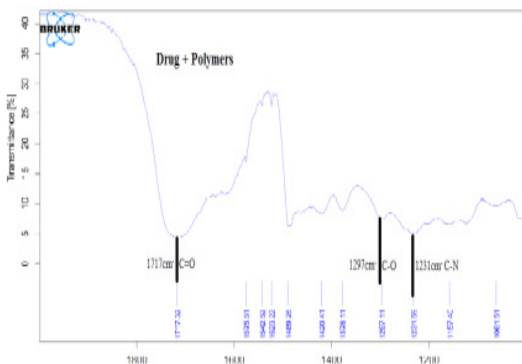


Figure 1: IR Spectrum of Drug and all Polymers.

strength and showed acceptable results with respect to drug content ($99.3 \pm 0.313\%$) and bioadhesive strength (7.80 ± 0.16 to 10.8 ± 0.23 g).

The thickness of the inserts was observed in the range of 0.087 ± 0.006 to 0.131 ± 0.003 mm and weight was observed 4.92 ± 0.27 to 8.59 ± 0.41 mg. The formulations were observed thin enough to prevent any irritation while placing and being in cul-de-sac.

The recorded folding endurance for all batches was greater than 300, which was considered satisfactory and revealed good film properties.

Surface pH was found within the range of 6.6 ± 0.35 to 7.2 ± 0.2 . Tensile strength and elongation at break was found in the range of 0.21 ± 0.0036 to 0.29 ± 0.0032 g/mm² and 28.2 to 36.9 % respectively.

The drug content was found to be consistent in all the batches and was in the range of 98.0 ± 0.122 % to 99.3 ± 0.313 %.

The bioadhesive strength was found 7.80 ± 0.16 to 10.8 ± 0.23 g which increased upon the increased concentration of carbopol 980P. The swelling index was obtained in the range of 20.81 ± 0.231 to 64.95 ± 0.164 . The % moisture absorption and % moisture loss were found to be 10.19 ± 0.31 to 39.07 ± 0.13 and 10.12 ± 2.5 to 35.21 ± 4.2 respectively.

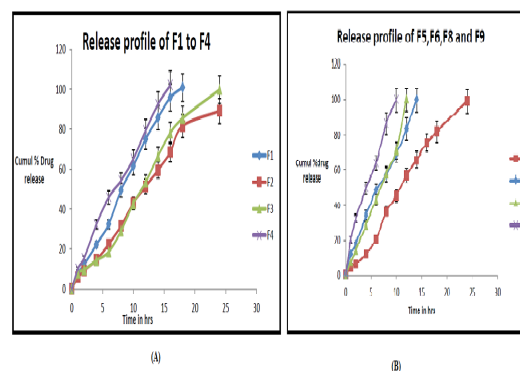


Figure 2: *In vitro* Drug Release from Bioadhesive Ocular Inserts : (A) F1 to F4 and (B) F5 to F9 Excluding F7.

It was observed that, as the hydrophilic polymer ratio increases, % moisture absorption increases and % moisture loss decreases.

***In vitro* drug permeation and release**

The results are shown in Figure 2.

The results of *in vitro* release study showed retardation in drug release in all the eight batches. The release of drug from the formulation F1 and F4 were found to be 100.95% and 102.19% at the end of 18 h and 16 h respectively. The release of drug from the formulation F6, F8 and F9 were found to be 99.97%, 100.23% and 99.86% at the end of 14 h, 12 h and 10 h respectively. The release of drug from the formulation F2, F3 and F5 were found to be 89.17%, 99.87% and 99.07% at the end of 24 h respectively. Hence, formulations F3 and F5 were selected for further investigation.

Drug Release Kinetics

Data of drug release of batch F3 and F5 were fitted to zero order, first order, Higuchi, Hixson crowell and Krosmeier-Peppas kinetic models. The results are shown in Table 3.

The mathematical kinetic study revealed that the formulation F3 and F5 both followed the zero order release pattern with R^2 value 0.9784 and 0.9864 respectively. So, from the results of *in vitro* drug release and kinetic models, the formulation F5 was selected as optimised for-

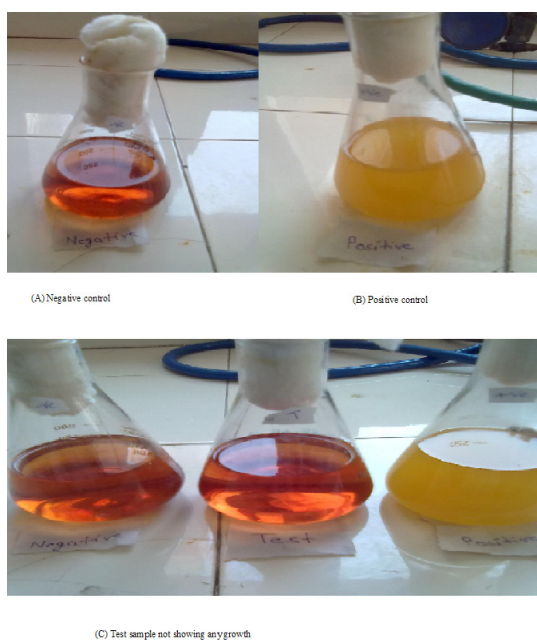


Figure 3: Test for Sterility; (A) Negative Control, (B) Positive Control and (C) Test Sample not Showing any Growth.

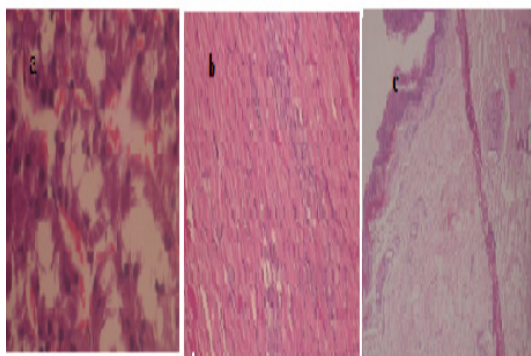


Figure 4: Histological Study; (a) Positive Control, (b) Negative Control and (c) Test Sample.

mulation and was evaluated for sterilisation, histological study and stability.

Sterilization and test for sterility for ophthalmic inserts

The results are shown in Figure 3.

The sterile inserts complied with the test for sterility as per the pharmacopoeial procedure. The positive control test showed the growth of micro organisms, which confirmed the suitability of media for test conditions. The negative control test did not show any growth of micro organisms, which affirmed the sterility apparatus used for the test and maintenance of aseptic conditions. Also, the test sample did not show any growth

of microorganisms which confirmed the insert's sterility and utility for further studies.

Histological study

The results are shown in Figure 4.

Regarding the irritancy of inserts, the positive control (applied with IPA) showed the maximum necrosis of conjunctival tissues. The negative control (applied with STF pH 7.2) as well as test sample did not show any damage to the tissue indicating non irritant nature of the inserts.

Stability Study

Stability study indicated the stability of the formulation.

CONCLUSION

The formulated optimized ocular insert (F5) containing Olopatadine hydrochloride had a potential for sustained action of drug release. Thus, the ocular inserts were successfully formulated as an alternative to eye drops which showed bioadhesive effect and increased residence time along with the sustained drug release.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

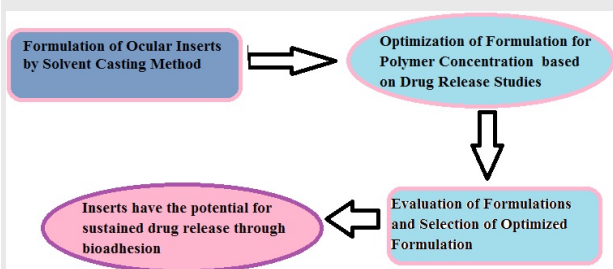
%: Percentage; **HPMC:** Hydroxy propyl methyl cellulose; **CMC:** Carboxy methyl cellulose; **STF:** Simulated tear fluid; **h:** Hour; **Min:** Minute; **SI:** Swelling Index; **g:** Gram; **nm:** Nanometer; **cm:** Centimeter; **rpm:** Revolutions Per Minute; **ICH:** International Conference on Harmonisation; **HCl:** Hydrochloric acid; **NaOH:** Sodium Chloride; **R²:** Regression Coefficient; **IPA:** Iso-propyl Alcohol.

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PICTORIAL ABSTRACT



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SUMMARY

- This study was undertaken to formulate and evaluate ocular inserts with an objective to minimize the disadvantages of eye drops. The drug candidate selected was Olopatadine hydrochloride which was characterized for various physicochemical parameters. FTIR studies showed that there is no incompatibility between the drug and excipients. The polymers were optimized based on their physical stability and accordingly carbopol 980P, NaCMC and HPMC K4M were selected. The ocular inserts were formulated using polymers and plasticizer and optimized by evaluating for various physicochemical parameters and also for the drug release studies which were found to be satisfactory. Based on the release kinetics, optimized formulation F5 was selected and evaluated for drug release, stability study and histological study. The results of these studies were found satisfactory giving the prolonged drug release more than 24 h. Thus, the ocular inserts were successfully formulated.



Dr. Prafulla M. Sabale: is working as Professor at Department of Pharmaceutical Sciences, RTM Nagpur University, Nagpur and he is having 21 years of teaching and research experience. He has completed his M. Pharm and Ph.D. From Pharmacy Department, The M. S. University of Baroda, Vadodara. He received grants from AICTE, UGC, GUJCOST and URPS. He was recipient of Young Gandhian Technological Award in the year 2011. He is life member of APTI, IPA, ISTE, ISCA etc.

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