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Original Article

DEVELOPMENT AND EVALUATION OF CIPROFLOXACIN HYDROCHLORIDE LOADED OCULAR INSERT BY USING "PLANTAGO OVATA" AS NATURAL POLYMER

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ABSTRACT

Objective: The present work focus in the direction of "Development and evaluation of Ciprofloxacin Hydrochloride loaded ocular insert by using *"plantago ovata" as natural polymer".* The current work was carried out to evaluate the control release profile of ocular insert. Natural polymer in ocular insert was used for studying the long acting property. Natural polymer is also used to enhance the bioavailability of drug and reduce toxicity. It is also used to increase the duration of action of drug for prolongs action and gives better *in vitro* performance as compare than to the conventional ocular formulation.

Methods: Solvent casting method was used in the formulation of Ciprofloxacin Hydrochloride loaded ocular inserts. Different ocular insert formulations of varying polymer concentration were prepared. Ocular insert formulation H-1 to H-3 was prepared by using different concentration of HPMC and formulation P-1 to P-4 was prepared by using different concentration of Plantago Ovata.

Results: The ocular inserts formulation was within the acceptable limits. All the pre formulation parameters of polymers such as derived properties, compressibility index, Hausner's ratio, viscosity, melting point, swelling ratio, loss on drying, PH of mucilage solution and pre formulation of active pharmaceutical ingredient such as estimation of drug by using UV spectroscopy, determination of melting point, solubility, partition coefficient and FTIR for compatibility study of drug and excipient were evaluation. FTIR analysis also confirmed no drug-excipient interaction.

Conclusion: Prepared inserts in the present study were semitransparent. The mixing of the drug in to the polymer is uniform, due to this; the drug content of all formulation is good. Formulation P4 was selected because it showed better release profile, drug content and other physicochemical properties than other formulated batch when compare. All the prepared inserts showed *in vitro* drug release for the period of 4 h as compare to the marketed formulation. An *in vitro* drug release study revealed that ocular formulation gives a prolong action. The formulation was found to be long acting.

Keywords: Ciprofloxacin Hydrochloride, HPMC, Plantago Ovata, Occular insert

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INTRODUCTION

The present work focus in the direction of "Development and evaluation of Ciprofloxacin hydrochloride loaded ocular insert by using "Plantago ovata" as natural polymer". Ocular insert were developed to enhance the activity and increase the availability of drug in ocular region for prolong duration of action and their long time release property. Solvent casting method was used in the fabrication of the formulation.

A basic concept in ophthalmic research and development is that the therapeutic efficacy of an ophthalmic drug can be greatly improved by prolonging its contact with the corneal surface. Ophthalmic inserts have many advantages over conventional dosage form like increased ocular residence time, possibility of releasing drugs at a slow and constant rate, accurate dosing, exclusion of preservatives and increased shelf-life. It also ensures better patient compliance due to lower frequency of administration and lower incidence of side effects [1].

Soluble ocular inserts are slowly soluble into the ocular region so that they do not require to be removed from their application site. The drug release from soluble ocular inserts promote continuous release rate. This is due to diffusion mechanism and gel layer formation outside the core of the insert [2-3].

Ciprofloxacin hydrochloride is the hydrochloride salt form of ciprofloxacin. It is second generation fluoroquinolone related to anti bacterial activities that usually result in the death of bacteria. This broad spectrum activity allow the use of Ciprofloxacin Hydrochloride in a variety of infections including those affecting the respiratory tract, urinary tract, skin, soft tissues and the eyes. Studies in literature showed that fluoroquinolones antibiotic group was more effective in the treatment of ocular infections than some other broad spectrum antibiotics [4].

The main aim of this study is to reducing the side effect which is produce by the conventional dosage form and the synthetic polymers used in the formulation by using Natural Polymer. Plantago ovata is a natural herb used as drug for the treatment of various diseases and it mostly used as pharmaceutical excipients like binder, gelling in nature and it, also used as enteric coated material, tablet disintegrator and sustain release drug formulation [5].

MATERIALS AND METHODS

Material

Ciprofloxacin hydrochloride was kindly gifted by Cipla pharmaceuticals (Pithampur). Seeds of plantago ovate was procured by local market (Indore), HPMC was purchased from Lobo Chemie private Ltd (Mumbai, India), Glycerin by Merck (Mumbai, India).

Methods

Isolation of mucilage

The dried seeds of *plantago ovate were* soaked in distilled water for 24 h. After this period the mixture of *plantago ovata* and water was boiled for 1 h and keep a side for 2 h. The viscous fluid was filtered through the muslin cloth, squeezed out and separating the mucilage from the seeds. The collected mucilage precipitated by the using of double amount of ethanol. After this the collected mucilage was

dried in the oven at 50-55 °c. Dried mucilage was scraped and powdered by the using pestle-mortar and Sieved by using mesh no.60 and store in desiccators [6-8].

Preformulation studies

Pre-formulation studies of polymer involves the application of physicochemical parameters like derived property, compressibility index, hausner's ratio, melting point, swelling ratio, loss on drying, PH of the mucilage solution [9-12]. Whereas preformulation of drug comprises of spectrophotometric estimation, solubility, melting point, partition coefficient and drug Excipient compatibility studies.

Spectrophotometric estimation of drug

For the estimation of drug, UV visible spectroscopic method was adopted [13]

Ciprofloxacin hydrochloride solution of about 200 ppm was accurately prepared in water. This solution was scanned in the 200-400 nm UV regions. The wavelength maximum was observed and wavelength maximum obtained was adopted for absorbance measurement.

For standard stock solution accurately weighed Ciprofloxacin hydrochloride (100 mg) was transferred to a volumetric flask and sufficient water was added to produce 100 ml (this is stock solution). From the above stock solution 10 ml was withdrawn and transferred to a volumetric flask and sufficient water was added to produce 100 ml (this is standard stock solution). From the above standard stock solution different aliquots were prepared in the concentration range from 1-10 ug/ml**.** Absorbance of aliquots were measure on UV-VIS spectrophotometer at **λ** max 318 nm using water as blank solution [14]. Graphical representation of standard curve of Ciprofloxacin Hydrochloride was shown in fig. 1.

Determination of melting point

Capillary method was used for the determination of melting point [15].

Solubility determination

Different solvents were used for the solubility determination of drug such as water, methanol, ethanol, simulated tear fluid pH 7.4 and acetone.

Partition co-efficient (shaking flask method)

Ten mg of drug was added in 100 ml of volumetric flask containing 50:50 ml ratio of n-octanol: water and the mixture was allow to be shaking by mechanical shaker for 24 h. After this allow the solution for separation of two phases for 1 hour. The mixture was divided in two immiscible phase, both phases were separated (by separating funnel) and the absorbance of both phases was taken and concentration was calculated of each phases.

$$\text{Partition Co efficient} = \frac{\text{Drug concentration in octanol}}{\text{Drug concentration in Water}}$$

Drug-excipients compatibility studies

Chemical interaction between the pure drug and the other excipients which were used in the formulation was detected by the use of Infrared spectroscopic method. In this the FTIR spectra of pure drug and physical mixture (drug and polymer mixture) were taken as in the ranging from 4000–650 cm–1. The drug, and 1:1 ratio of polymer and plasticizer (each 10 mg) was mixed in 400 mg of Kbr. Compressed this mixture about 100 mg by the using of a hydraulic press at 10 tones pressure to prepared a pellet. Pellets of the physical mixture were scanned in the ranging from of 4000-400 cm-1in IR spectrophotometer. Collecting the IR spectra of physical mixtures and compared with drug to detect any visible or invisible of peaks [16].

Formulation of ocular inserts

Preparation of ocular inserts was done by using solvent casting method-in this method accurately weighed the polymer (either plantago ovata mucilage or HPMC) and dissolved in distilled water and formulate a clear solution. In another beaker drug was dissolved in water (2 ml) under mild agitation. And then the drug solution was added to polymeric mixture with gentle agitation. Then glycerin was added to the above mixture. This mixture was transferred into a glass mould and dried in a room temperature for 3 d (72 h). After complete drying polymer films containing drug were formed. The dried films of drug were cut to circular discs (ocular inserts) of diameter 1.0 cm, and stored in the desiccators until further studies [17]. Optimization data was shown in table 1.

Table 1: Optimization data of ciprofloxacin hydrochloride ocular insert

Formulation	Ciprofloxacin hydrochloride	Mucilage plantago ovate (polymer)	HPMC (polymer)	Plasticizer (glycerin)	Solvent (distill. water)
P1	30 mg	50 mg	-	8 mg	10 ml
P2	30 mg	100 mg	-	8 mg	10 ml
P3	30 mg	200 mg	-	8 mg	10 ml
P4	30 mg	300 mg	-	8 mg	10 ml
H1	30 mg	-	200 mg	8 mg	10 ml
H2	30 mg	-	300 mg	8 mg	10 ml
H3	30 mg	-	400 mg	8 mg	10 ml

Evaluation of ophthalmic inserts

Physical appearance

It was done by visual inspection. In this following property was studied like the color, clarity, smoothness and nature of the drug [18].

Surface PH

Surface PH of the ocular insert was determined by the using of PH indicator paper after allowing the inserts to swell on 2% agar solution for 5 h. The surface PH was measured by means of a PH paper which was placed on the surface of swollen film of insert [18-20].

Swelling index

Swelling studies of prepare ocular insert was determined in the STF 7.4 PH. In this three inserts were taken and weighed accurately and place in the test tube individually containing 4 ml of STF 7.4 PH. At specific time intervals the inserts was removed and the excess water present on their surface was removed using a blotting paper and reweighed the ocular insert. The procedure was repeated till there was no increase in the weight of ocular inserts. Swelling index of ocular insert was then calculated.

Thickness

Thickness of the ocular insert was carried out by using vernier callipers. Thickness of insert was measured at the five different point such as centre and four corners and the average was determined by the using of vernier callipers [21-22].

Uniformity of weight

This was carried out by the using digital electronic balance. In this evaluation five insert were taken from each batch and weighted individually and variation of weight measured by digital electronic balance [23].

Folding endurance

The polymeric ocular films flexibility was determined in terms of folding endurance. A small strip of ocular film was cut evenly and folded separately at the same place until it broke. The film could be folded at the same place with access number of times without break give the folding endurance [24].

Moisture absorption

The percentage moisture absorption test was measured out to check the integrity and of the ocular film. Individually weighed the ocular films and was placed in a desiccator having 100 ml of saturated salt solution of sodium chloride (~75 % humidity). After three days ocular films was taken out and reweighed; the percentage moisture absorption was calculated by using following formula.

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{ X } 100$$

Percentage moisture loss

The percentage moisture loss test was measured out to check the integrity of the ocular film at the dry condition. Individually weighed the ocular films and placed in desiccators having 100 ml of anhydrous calcium chloride. After three ocular films was taken out and reweighed; the percentage moisture loss was calculated by using following formula.

$$\text{Moisture loss (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{ X } 100$$

Drug content uniformity

Ocular inserts from each batch were dissolved in the 100 ml volumetric flasks containing simulated tear fluid PH 7.4 and solution was filtered. Then, mishearing the absorbance in a UV spectrophotometer at 278 nm after suitable dilution with STF PH 7.4 against a blank insert prepared using a free drug.

***In vitro* drug release study**

In vitro drug release studies were performed in vertical Franz diffusion cell. STF pH 7.4 was placed in the receiver compartment. An ocular insert of Ciprofloxacin Hydrochloride was placed in the donor compartment. Egg membrane was used to separate the donor and receiver compartments. The diffusion cells were maintained at (37±0.5 °C) with stirring at 600rpm throughout the experiment. At fixed time intervals, 5 ml of the sample was withdrawn from receiver compartment though side tube and analyzed by UV-Visible spectrophotometer at 278 nm [25].

Sterility testing

Sterility testing for the ophthalmic preparation is one of the most important requirements. The sterility testing for ocular insert intended for detecting the presence of viable microorganisms. According to this study if the microorganisms are placed in the culture media and providing nutritive material, water, kept at a favorable temperature, the microorganisms will grow up, and turbidity will form because of the presence of microorganism in a clear medium. In this study, two media were used namely, alternate thioglycolate medium (FTGM) and soya bean-casein digest medium (SCDM) to identify the presence/absence bacteria and fungi, in the prepared sterilized ocular inserts [26-27].

RESULTS AND DISCUSSION

Characterization of mucilage of plantgo *ovate*

The physiochemical properties of dried powder of mucilage of *plantago ovata* were given in table 2. According to IP, angle of repose shows excellent flow of powder which can be concluded that the mucilage having a good flow properties which is suitable for a formulation.

Table 2: Characterization table of mucilage of *plantago ovata*

S. No.	Properties	Mean
1	Angle of repose (g/ml)	26.27
2	Bulk density(g/ml)	0.32
3	Tapped density	0.51
4	Carr's index	37.52
5	Hausner's ratio	1.59

Melting point

Melting point *plantago Ovata* mucilage is found to be 72-80 ℃ which is suitable for the formulation.

Swelling ratio

The swelling ratio of mucilage, determined in distilled water, is found to be 3.0. There is a significant change in swelling by the end of the study, which indicated that the mucilage had excellent swelling properties.

Loss on drying

The weight loss on heating justified that the amount of moisture is available in the material to interact with the other material. For dried mucilage, the loss on drying was found to be 20.33%.

PH of the mucilage solution

PH of the 1 % solution of the mucilage of *plantago ovata* was detected by the digital PH meter and the sample PH was found to be 6.9.

Viscosity

The viscosity of the mucilage solutions was done by the Brookfield viscometer, the result shown in table 3 which indicate that the mucilage viscosity is suitable for the formulations.

Estimation of drug

Identification of drug

The identification of drug is done by UV Spectrophotometric method using distilled water. Fig. 1 show the standard curve of Ciprofloxacin Hydrochloride in distilled water.

Determination of melting point

The melting point of the ciprofloxacin hydrochloride was found to be 310-320 °c which was according to the standards.

Solubility determination

Solubility of ciprofloxacin hydrochloride in various solvents were given in table 4, which shows that the drug is soluble in STF PH 7.4 which is good for ophthalmic preparation.

Table 3: Viscosity of mucilage solution

S. No.	Solutions	Obtaining viscosity
1	0.1%	1.48 cps
2	0.2%	2.98 cps
3	0.3%	5.74 cps
4	0.4%	8.25 cps
5	0.5%	9.30 cps

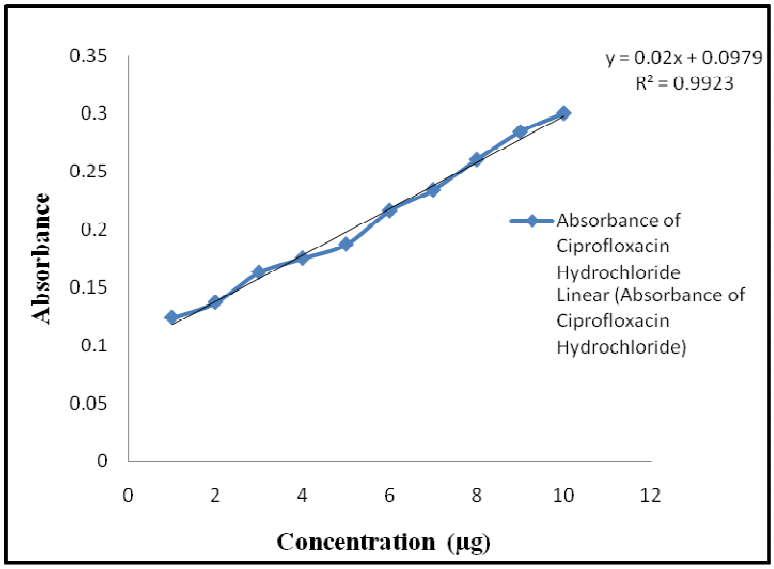

Fig. 1: UV estimation of ciprofloxacin hydrochloride in distilled water (λmax = 318 nm)

Table 4: Solubility of drug in various solvents

S. No.	Solubility	Solvent
1	Distilled water	*****
2	STF 7.4 PH	****
3	Methanol	***
4	Ethanol	**
5	Acetone	*

*insoluble, **very slightly soluble, ***slightly soluble, ****soluble, *****freely soluble,(*) sign indicates the solubility

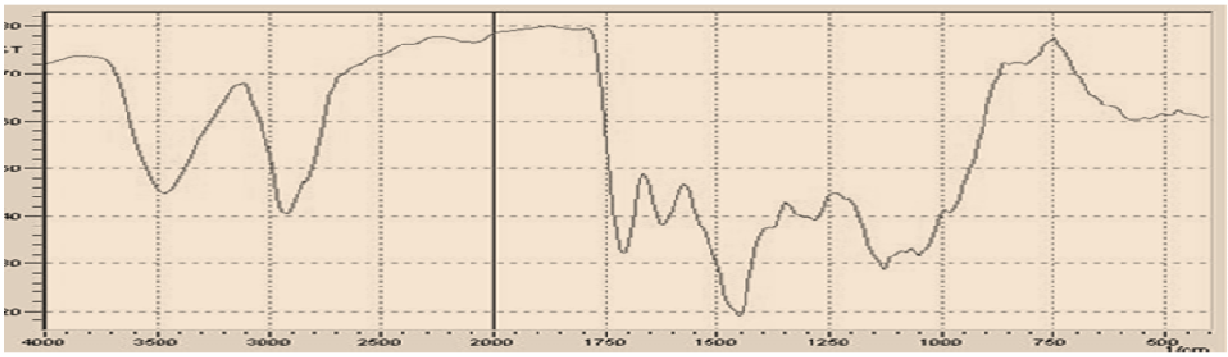

Fig. 2: FTIR of ciprofloxacin hydrochloride

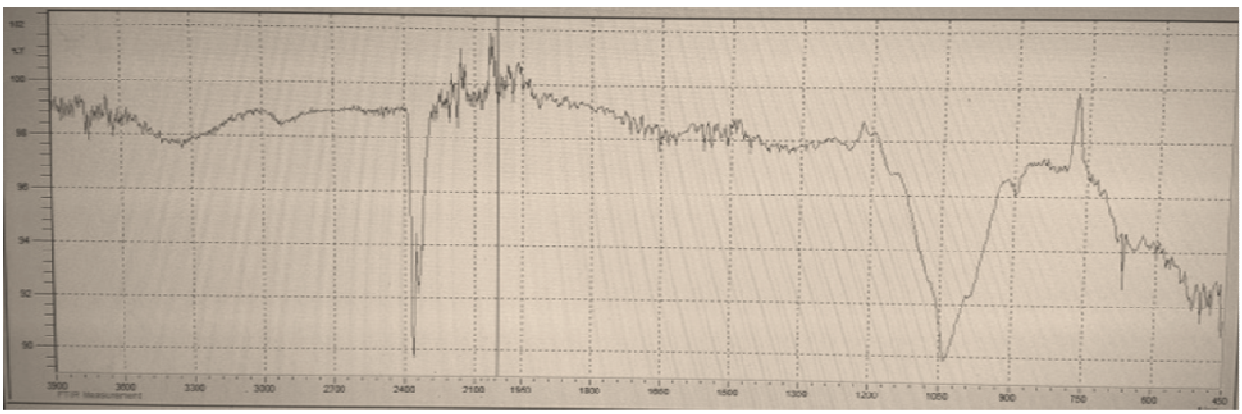

Fig. 3: FTIR of plantago ovate

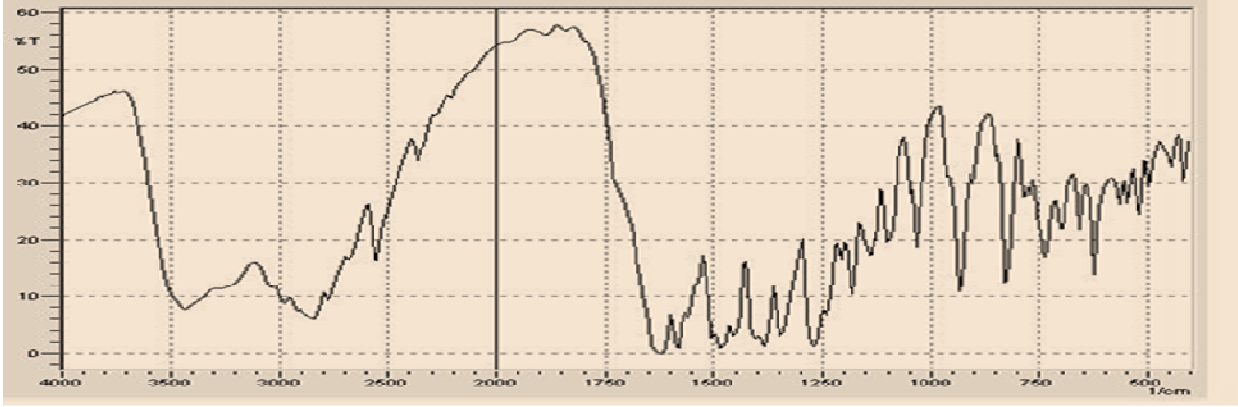

Fig. 4: FTIR of drug and polymer (plantago ovate) mixture)

Drug-excipients compatibility studies by FTIR method

In the FTIR spectra of the drug and polymer, the peak from 3500 to 3400 $cm^{-1}$was assigned to polymeric and hydrogen bonding while the band between 3000 and 2600 cm^{-1}represented the stretching vibration i.e., strong intermolecular hydrogen bonding. The band from 1650 to 1600 $cm^{-1}$was assigned to carbonyl stretching vibration. The band from 1400-1350 cm^{-1}represents esters and symmetric bending of methoxy groups. The peak between 1100 and 1000 cm^{-1}represented drug and polymer shows no major interactions.

Partition co-efficient

The partition coefficient value of ciprofloxacin hydrochloride is found to be 0.99. The log k values of ciprofloxacin hydrochloride show that the drug should Processes sufficient lipophilicity, which requirements is essential for the formulating it into an ocular insert

Physical properties

The result of physical properties like thickness, uniformity of weight and folding endurance were given in table 5.

Surface PH

The surface PH of the formulated ciprofloxacin hydrochloride ocular inserts by natural polymer is found between 6.0 to7.5 indicated the good for ocular formulation

Swelling study

Swelling percentage of the prepared ciprofloxacin hydrochloride ocular insert by natural polymer is found between 11.1to 86.6 **%** and by HPMC polymer is found to be 3.12 to 60 **%.** All the design batches of ocular inserts have a high swelling index Graphical representation of swelling profile is given in fig. 5 and 6.

Table 5: Physical properties of prepared ocular film of ciprofloxacin hydrochloride

S. No.	Batch	Thickness (mm)	Uniformity of weight (gms)	Folding endurance (no. of flods)
1	P1	0.38	0.0148	50.66
2	P2	0.49	0.018	57.63
3	P3	0.57	0.0174	60.23
4	P4	0.65	0.021	65.32
5	H1	0.14	0.0164	56.63
6	H2	0.10	0.0112	51.63
7	H3	0.20	0.0114	63.06

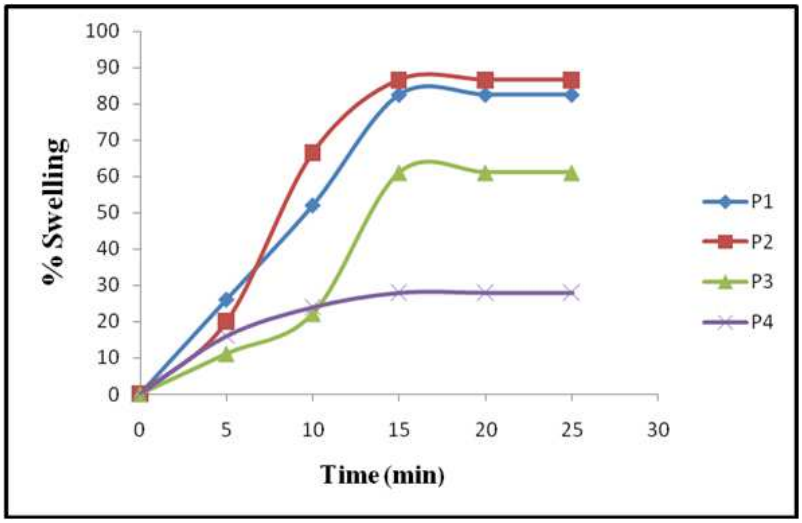

Fig. 5: Swelling profile of ciprofloxacin hydrochloride ocular insert containing natural polymer

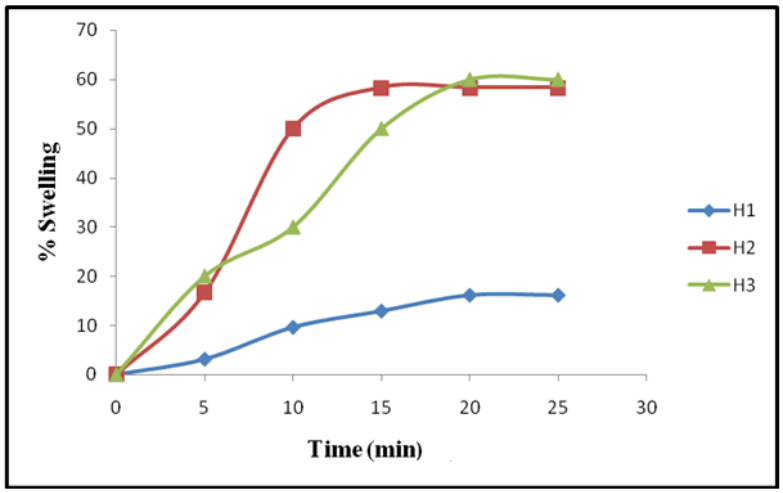

Fig. 6: Swelling profile of ciprofloxacin hydrochloride ocular insert containing HPMC

Moisture absorption/loss

The study found that prepared ocular insert shows high moisture absorption and insert absorbs large amount of moisture thus formulation were not stored for long time. The percent moisture absorbed and loss result is given in table 6 and graphically presented in fig. 7.

Table 6: % moisture absorption and loss

Batch	% moisture absorption	% moisture loss
P1	25	10
P2	21.73	14.28
P3	6.6	6.25
P4	12.90	4.5
H1	63.63	16.66
H2	12.5	12.5
H3	21.42	14.28

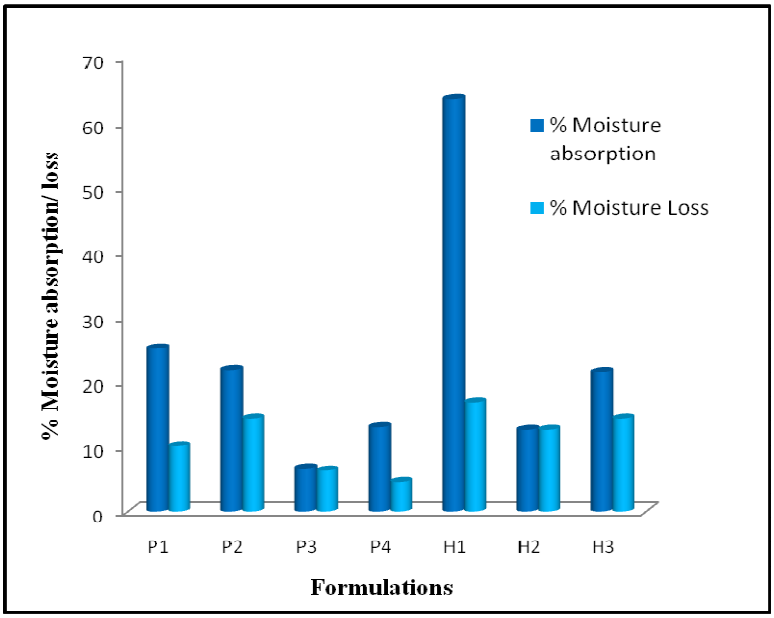

Fig. 7: Graphical representation of % moisture contain and loss of ciprofloxacin hydrochloride ocular insert contain natural polymer (P1-P4) and HPMC (H1-H3)

Drug contents

The test for content uniformity of drug in all batches of ocular insert contain natural polymer and HPMC is carried out to ascertain that the drug is uniformly distributed in the formulation. The amount of drug present in the prepare formulation containing natural polymer is found to be 91.38 to 98.19 and HPMC is found to be 92 to 94.19 which is presented in table 7 and graphically shown in fig. 8 and 9. This study shows the good uniformity in drug content in ocular insert.

Table 7: % drug content

S. No.	Batch	% drug content
1	P1	91.21
2	P2	90.18
3	P3	91.38
4	P4	98.19
5	H1	92
6	H2	94.19
7	H3	93.37

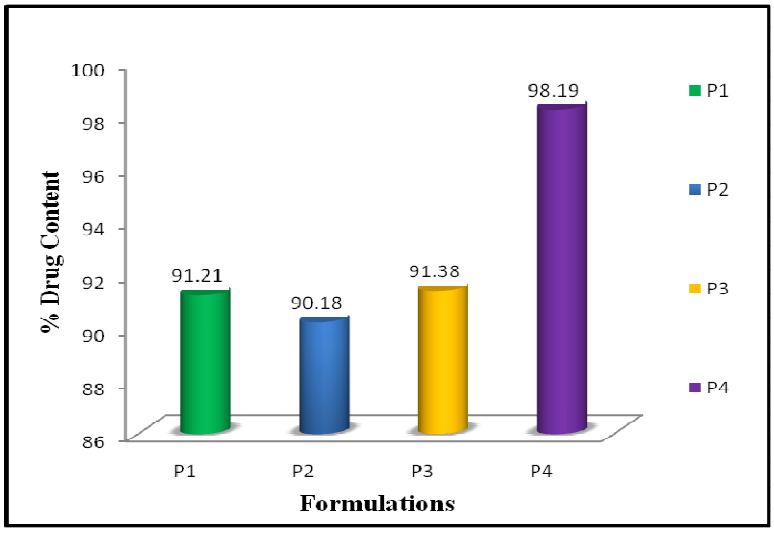

Fig. 8: % Drug content of ocular insert contain drug with natural polymer

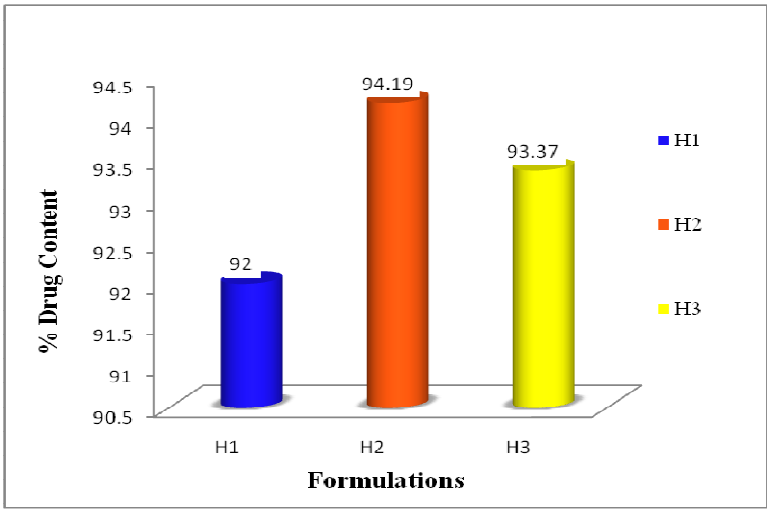

Fig. 9: % drug content of ciprofloxacin hydrochloride ocular insert containing HPMC

In vitro studies

In vitro studies were performed to compare the release rate of the drug from ocular insert containing HPMC and natural polymer (Plantago ovata) which is coded as H1 to H3 and P1 to P4. Cumulative percent drug release of ciprofloxacin hydrochloride loaded ocular insert is investigated for 4 hr. As results indicated that the % drug release for ocular insert P4 and H2 is 99.48 and 98.25 at the end of 4 h which was shown in table 8 and graphically presented in fig. 10 and 11.

Comparative studies

Compared the selected batches of the formulation containing HPMC and Natural polymer plantago ovata according to their following evaluation studies such as folding endurance, % drug content, %swelling profile and *In vitro* release studies. The result is shown in table 9-10 and in fig. 12-13.

In vitro release studies

Comparison study of *In vitro* release shows that formulation batch P4 (of natural polymer) showed good release profile as compare to the formulation batch containing HPMC.

Sterility testing

The sterility testing of prepared ocular insert P4 is performed for bacteria and fungi by using FTGM (fluid thioglycolate medium) and SCDM (Soyabean casin digest medium)

Test for bacteria

In this study there was no sign of growth found in the 'test' and 'negative control' tubes containing ocular insert and there was macroscopic evidence of microbial growth in 'positive control' tube. The results found that the prepared ocular insert P4 tested for bacterial growths were passed the test for sterility.

Table 8: % drug release (*in vitro* studies) of ocular inserts

S. No.	Time (h)	% drug release of formulations						
		P1	P2	P3	P4	H1	H2	H3
1	0	0.45	0.21	0.17	0.11	0.89	1.56	1.71
2	½	2.11	1.41	8.46	7.52	2.46	10.72	9.73
3	1	14.56	7.69	20.02	25.68	15.45	28.96	20.90
4	1 ½	35.65	19.87	32.94	38.82	27.09	50.49	47.65
5	2	51.42	26.67	46.85	52.03	31.91	62.92	55.98
6	2 ½	78.90	38.27	72.44	69.55	49.07	74.48	62.80
7	3	-	49.89	85.01	83.66	68.77	80.22	70.37
8	3 ½	-	-	92.56	90.01	82.90	90.46	80.03
9	4	-	-	-	99.48	91.66	98.25	92.89

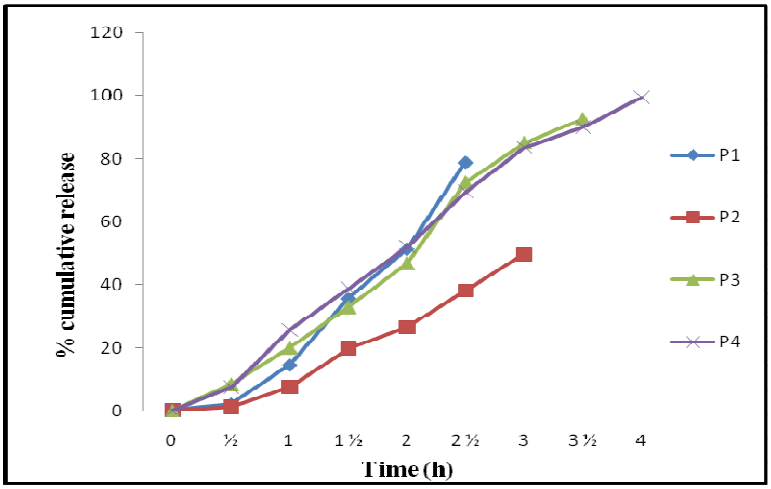

Fig. 10: Cumulative release of ciprofloxacin hydrochloride ocular insert containing natural polymer

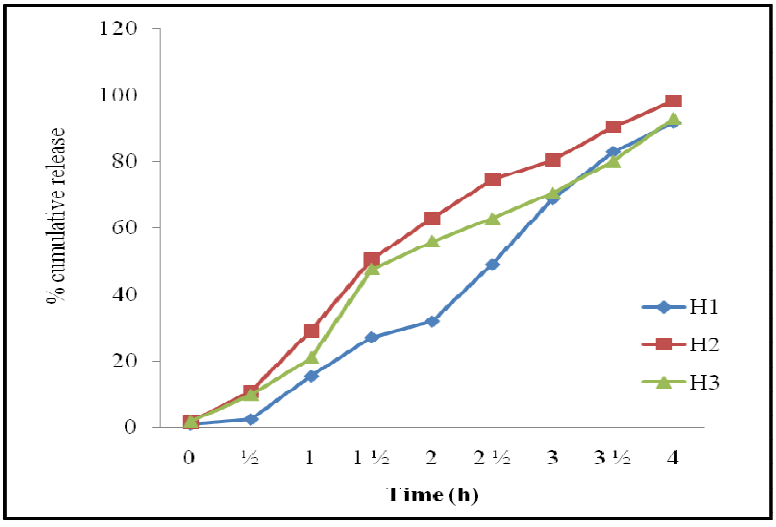

Fig. 11: Cumulative release of ciprofloxacin hydrochloride ocular insert containing HPMC

Table 9: Folding endurance and % drug content of selected batches of ciprofloxacin hydrochloride ocular inserts

S. No.	Batch	Folding endurance	% drug content
1	H2	51.63	94.19
2	P3	60.23	91.38
3	P4	65.32	98.19

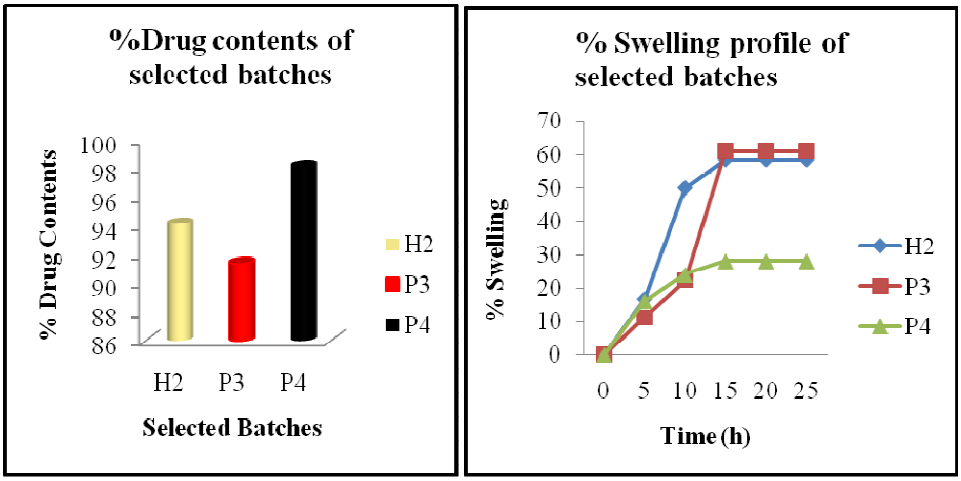

Fig. 12: Graphical representation of % drug content and %swelling profile of selected batches of ciprofloxacin hydrochloride ocular insert

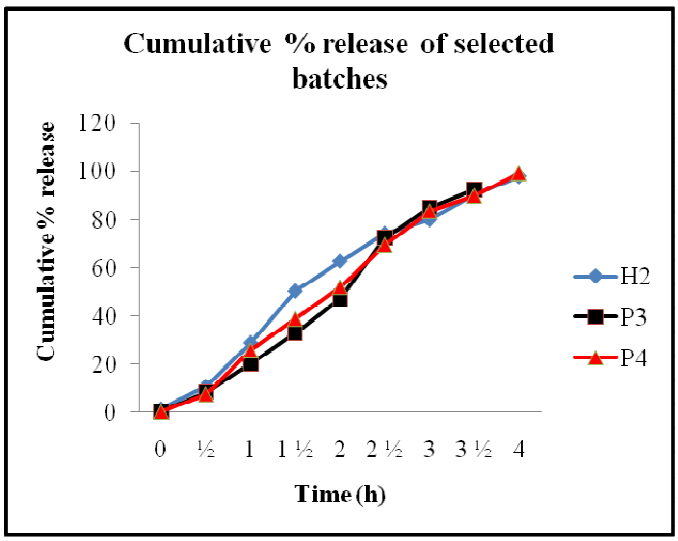

Fig. 13: Cumulative % release of selected batches of ciprofloxacin hydrochloride ocular insert

Table 10: % drug release of selected batch

S. No.	Time (h)	% drug release of selected formulation		
		H2	P3	P4
1	0	1.56	0.17	0.11
2	½	10.72	8.46	7.52
3	1	28.96	20.02	25.68
4	1 ½	50.49	32.94	38.82
5	2	62.92	46.85	52.03
6	2 ½	74.48	72.44	69.55
7	3	80.22	85.01	83.66
8	3 ½	90.46	92.56	90.01
9	4	98.25		99.48

On the basis of the above comparison studies formulation of P4 perform better as compare to all the selected formulation batches. The formulation p4 showing better release profile, drug content uniformity and acceptable swelling index high folding endurance batch P4 shows high folding endurance.

Table 11: Sterility test observation for bacteria

S. No.	Sample	Time (h)		
		12	24	36
1	Positive Control	+	+	+
2	Negative Control	-	-	-
3	Test	-	-	+

Test for fungi

In this study there was no sign of growth found in the 'test' Containing prepared ocular insert but 'negative control' tubes contain only SCDM, also shows some turbidity and minor growth of fungi and there was macroscopic evidence of microbial growth in 'positive control' tube. The results found that the prepared ocular insert P4 tested for fungal growths pass the test for sterility.

Table 12: Sterility test observation for fungi

S. No.	Sample	Time (h)		
		12	24	36
1	Positive Control	+	+	+
2	Negative Control	-	+	+
3	Test	-	-	+

CONCLUSION

The ocular inserts of ciprofloxacin hydrochloride were prepared using polymer Plantago ovata and HPMC by solvent casting method. Prepared inserts in the present study were semitransparent and the physicochemical properties of the insert are good. The mixing of the drug in to the polymer is uniform, Due to this uniformity; the drug content of all formulation is excellent. Formulation P4 was selected because it shows better release profile, drug content and other physicochemical properties than other prepared batches. All the prepared inserts showed drug *in vitro* drug release for the period of 4 h. An *in vitro* drug release study revealed that ocular formulation formulations give a prolong action. It can be concluded that the formulations prepared by the natural polymer (Plantago *ovata*) containing ciprofloxacin hydrochloride was used as anti bacterial. The formulation is long acting,

Thus the data collectively support the hypothesis that ciprofloxacin hydrochloride ocular insert formulation is promising delivery systems to enhance the drug release of ciprofloxacin hydrochloride

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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