Research Paper

Sustained Release of Ciprofloxacin Hydrochloride and Loteprednol Etabonate from Ophthalmic Ocuserts for Treatment of Bacterial Conjunctivitis

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Ciprofloxacin hydrochloride being a fluoroquinolone antibacterial drug is very frequently preferred in the treatment of bacterial conjunctivitis by the eye specialists. Addition of loteprednol etabonate only adds up to the anti-inflammatory activity of the developed formulation. The objective of the present work was to develop ocular inserts of ciprofloxacin hydrochloride with loteprednol etabonate and further evaluate its potential as a sustained novel ocular drug delivery system. Ophthalmic solutions, suspensions are known for its poor bioavailability and poor therapeutic responses due to many pre-corneal constraints. The researchers usually get triggered with these constrains and strive to formulate controlled and sustained drug delivery system. Ocular inserts based on solvent cast technique were formulated and characterized for *in vitro* drug release studies using a flow through apparatus that simulated the eye conditions. Compatibility of ciprofloxacin hydrochloride, loteprednol etabonate, polymer and excipients were checked as preliminary preformulation studies. Different combinations of ciprofloxacin hydrochloride, loteprednol etabonate, carbopol 974, 980, 981, polyethylene glycol 400 and glycerine were formulated by solvent cast method and optimized on was evaluated. Fabricated ocuserts were evaluated for its clarity, smoothness, surface pH, drug content and *in vitro* drug release study to find the optimized film. Formula ciprofloxacin hydrochloride with loteprednol etabonate and carbopol 980 was found to be the best formulation fulfilling the needs of all organoleptic parameters and also the *in vitro* release study. Based on *in vitro* correlation and stability studies, it was concluded that this ocular insert formulation could be a promising controlled release formulation for the researchers.

Key words: Ciprofloxacin hydrochloride, loteprednol etabonate, carbopol 974, 980, 981, ocular inserts and beta-cyclodextrin complex

Instilling medicaments in eye is a complex process and has emphasized scientists to work in multi-disciplinary areas related to the eye including chemical, biochemical, pharmaceutical, medical, clinical and toxicological sciences. In the recent years, attention has been increased on two main objectives. Aiming at finding an effective and a safe drug molecule for various ocular conditions and diseases that are poorly controlled and aiming at improving the existing ocular dosage forms and to develop newer delivery systems for improving the ocular bioavailability of existing molecules[1,2].

Ocular dosage forms are specialized dosage forms especially designed to be instilled onto the external surface of the eye (topical), administered inside (intraocular) or adjacent (periocular) to the eye or used in conjunction with an ophthalmic device.

In terms of sterility ocular preparations are equal with the parental dosage forms. Not only sterility but also in regards with osmotic pressure (tonicity), preservative quantity, tissue compatibility, pyrogen free intraocular dosage forms, particulate matter and suitable packaging[3]. Numerous physiological anatomical constraints are imposed by human

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eye and hence only a small fraction of the administered drug, effectively 1 % or even less of the instilled dose is ocularly absorbed. The above factors are the driving force for the clinician to recommend a frequent dosing at an extremely high concentration which may results in several side effects of ophthalmic products. Newer and novel ophthalmic delivery systems are being explored just to overcome the problems of conventional ocular therapy and to overall improve the ocular bioavailability of the drug.

Conventional ocular dosage forms are customarily been restricted to solutions, suspensions and ointments. With the recent advancements in material science, the range of ophthalmic dosage forms has expanded significantly which includes gels, either preformed or spontaneous gels responsive to the ocular environment and ocular inserts both forms reducing dosage frequency[4,5].

The aim of the present work was to formulate ocusert with a definite concentration of ciprofloxacin hydrochloride and loteprednol etabonate for the treatment of ocular conjunctivitis and compared for the sustained release of active based United States patents filed for ocular suspension of ciprofloxacin hydrochloride and loteprednol etabonate and methods developed for its analysis[6,7]. The dosage form was fabricated with the objective of increasing the residence time of the drug, reducing the dosing frequency by combining with carbopol 974, 980, 981, Polyethylene Glycol (PEG) 400, Polyvinyl Alcohol (PVA) and glycerine[8,9].

MATERIALS AND METHODS

Ciprofloxacin hydrochloride was obtained as a gift sample from Indoco Remedies, Verna Industrial Estate, Verna, Goa and loteprednol etabonate was from Ajanta Pharma Pvt. Ltd., carbopol 974, 980 and 981 were gifted by Lubrizol Pvt. Ltd., Mumbai. PVA, PEG 400, Beta-cyclodextrins (β-cyclodextrins) used were procured from Hi-Media. Analytical grade chemicals were used for the analytical purpose.

Preformulation studies:

Preformulation studies were performed on the procured drug samples and excipients with respect to description, melting point, solubility, Infrared (IR) spectra, Ultraviolet-Visible (UV-Vis) spectroscopic studies and Differential Scanning Calorimetry (DSC)[10].

UV spectroscopy study:

Determination of wavelength of maximum absorption: Pure drug sample of ciprofloxacin hydrochloride and loteprednol etabonate were weighed separately and diluted in distilled water. The prepared solutions were scanned in the wavelength region of 200-400 nm. UV-Vis spectrophotometer (UV-Vis Shimadzu) was used for the scanning purpose.

Determination of linearity and range: Ciprofloxacin hydrochloride (25 mg) and loteprednol etabonate (25 mg) were weighed separately and transferred in two separate (25 ml) volumetric flask. It was further dissolved and diluted up to mark with methanol and water to get a stock solution having strength of 1 mg/ml and further diluted to get 0.1 mg/ml[11,12].

Aliquots of 0.25 ml, 0.5 ml, 0.75 ml, 1.0 ml, 1.25 ml, 1.5 ml, 1.75 ml, 2.0 ml, 2.25 ml and 2.5 ml of working standard solution of individual drugs were transferred to a series of 10 ml standard volumetric flask and diluted with phosphate buffer pH 6.8 to get (2.5 µg/ml) till (15 µg/ml) of ciprofloxacin hydrochloride and (2.5 µg/ml) till (20 µg/ml) loteprednol etabonate respectively. The resulting solutions were estimated in a UV-Vis spectrophotometer at 274 nm and 245.8 nm respectively for ciprofloxacin hydrochloride and loteprednol etabonate. Beer-Lambert law was verified by plotting a graph of concentration against absorbance. The absorbances measured were tabulated in Table 1 and the standard curves were shown in fig. 1 and fig. 2.

DSC:

DSC-60 Shimadzu, TA-60 WS collection software was employed to study the thermal property of drug and excipients alone and in combination. Endothermic and exothermic parameters of the drug and polymer were subsequently obtained.

IR radiation:

Fourier transform infrared spectroscopy spectrums of the obtained sample were compared with the reference standard Fourier transform infrared spectroscopy spectrum of ciprofloxacin

TABLE 1: ABSORBANCE OF CIPROFLOXACIN HYDROCHLORIDE AND LOTEPREDNOL ETABONATE

Concentration (µg/ml)	Ciprofloxacin hydrochloride absorbance at 274 nm	Loteprednol etabonate absorbance at 245.8 nm
0	0	0
2.5	0.29±0.015	0.09±0.015
5	0.54±0.02	0.171±0.01
7.5	0.872±0.02	0.263±0.015
10	1.169±0.01	0.345±0.015
12.5	1.462±0.015	0.429±0.01
15	0.29±0.015	0.53±0.015
17.5	--	0.622±0.02
20	--	0.688±0.015

Note: Each value is the mean of three observations. Mean bearing at least one common superscript within a row do not differ significantly ($p<0.05$)

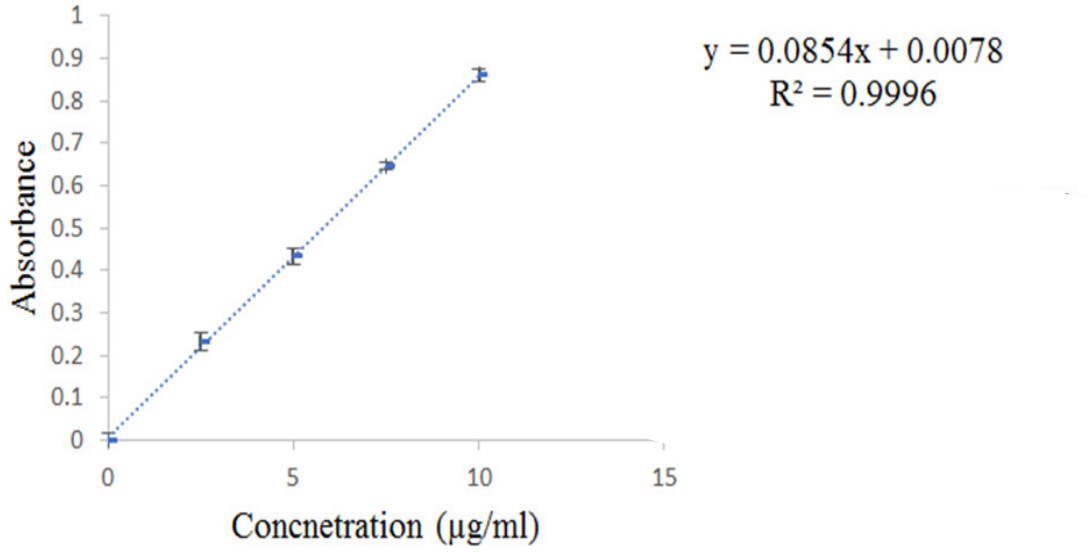

Fig. 1: Standard calibration curve of ciprofloxacin hydrochloride
Note: (▬) Ciprofloxacin hydrochloride absorbance (274 nm) and (• • •) Linear (ciprofloxacin hydrochloride absorbance)

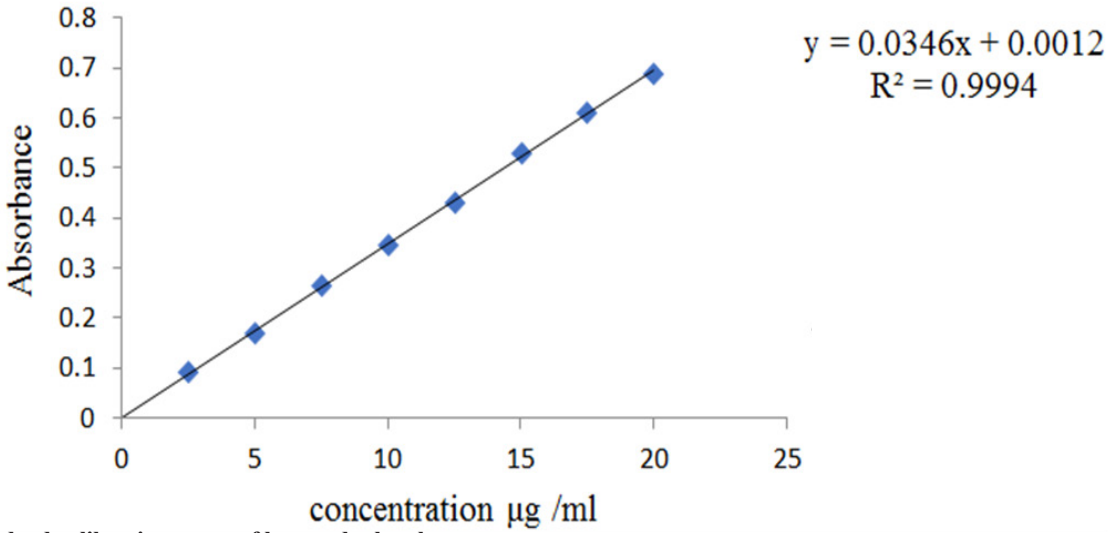

Fig. 2: Standard calibration curve of loteprednol etabonate
Note: (◆) Absorbance (245.8 nm) and (—) linear (absorbance (245.8 nm))

hydrochloride and loteprednol etabonate by potassium bromide method.

Preparation of ocusert:

Preparation of β-cyclodextrin and loteprednol etabonate complex: Poorly water-soluble drug like loteprednol etabonate needs to be complexed with β-cyclodextrin to enhance its solubility. Six different molar ratios (1:0.5 to 1:3) were prepared and evaluated. The solubility profile of the drug was checked and the ratio of 1:0.5 to be used (drug: β-cyclodextrin) was finalized based on percentage cumulative drug release[13].

Preparation of ocusert of ciprofloxacin hydrochloride and loteprednol etabonate: Area of the chosen (9 cm) petri dish was calculated. Depending on the area of the petri dish the required drug quantity was calculated. Proportion of 1: 9 (carbopol: PVA cold water soluble) was kept for soaking in 20 ml of distilled water the previous night, followed by incorporation of drug dissolved in 2 ml of phosphate buffer pH 6.8 and PEG 400 and glycerin with stirring on magnetic stirrer for 6 h. At the end of 6 h, the preparation was poured in the mentioned perti dishes and was dried at 50° in a hot air oven for 4 h. 1 cm^2×1 cm^2 areas of the prepared films were used for the evaluation purpose. CLE 74 represents ciprofloxacin hydrochloride and loteprednol etabonate in carbopol 974, CLE 80 represents ciprofloxacin hydrochloride and loteprednol etabonate in carbopol 980 and CLE 81 represents ciprofloxacin hydrochloride and loteprednol etabonate in carbopol 981[14,15]. Composition of each ocusert is shown in Table 2.

Surface pH:

Ocular insert should be non-irritating to eye and should be compatible with lachrymal fluid. 0.1 ml double distilled water was taken and the prepared films were allowed to swell in it at room temperature for 30 min. The swollen films were placed under a digital pH meter and the surface pH was determined[16,17].

Drug content:

Fabricated film was cut in dimensions of 1 cm^2×1 cm^2 and dissolved in 10 ml phosphate buffer pH 6.8. 1 ml was further diluted to 10 ml and analyzed using UV-Vis spectrophotometer at the absorbance value of 274 nm and 245.8 nm respectively[18,19].

***In vitro* drug release study:**

In vitro studies were performed using Franz diffusion. The set up was placed on the magnetic stirrer with a minimum stirring rpm closely relating to eye blinking movement. Room temperature was maintained during the experiment. Semi-permeable membrane (dialysis membrane 50, Hi-Media) was used at the receptor site. 1 ml sample was withdrawn at periodic intervals and subsequently replaced with 1 ml phosphate buffer. Cumulative drug release was calculated from the withdrawn sample[20,21].

Antimicrobial activity:

The cup-plate technique with agar diffusion medium was used. The cup was bored at the center of the plate. The developed film and standard solution of pure drug were taken separately into soyabean casein digest medium earlier seeded with *Staphylococcus aureus* (*S. aureus*) organism. On placing the film and standard solution in the plate, they were incubated for a day at 37°. Compared

TABLE 2: MASTER FORMULA FOR CIPROFLOXACIN LOTEPREDNOL ETABONATE OCUSERT

Ingredients	Quantity		
	CLE 74	CLE 80	CLE 81
Ciprofloxacin	11.5 mg equivalent to 0.18 mg ciprofloxacin		
Loteprednol etabonate: 1:0.5 ß CD	40 mg equivalent to 0.3 mg loteprednol etabonate		
Carbopol 974	60 mg	--	--
Carbopol 980	--	60 mg	--
Carbopol 981	--	--	60 mg
Poly vinyl alcohol	540 mg	540 mg	540 mg
PEG 400	0.5 ml	0.5 ml	0.5 ml
Glycerin	25 mg	25 mg	25 mg
Distilled water	20 ml	20 ml	20 ml

with the standard the Zone of Inhibition (ZOI) was calculated[22].

Sterility testing:

Indian Pharmacopoeia 1996 standard procedure was employed to perform this test. Two media employed were fluid thioglycolate and soyabean casein digest media. The formulated films were cut into two equal halves under laminar air flow and dropped in the two test tubes simultaneously. Both the media were checked for microbial growth by incubating at 37° for 7 d. Positive and negative control samples were used for the comparison studies[23,24].

Antibacterial activity:

Serial dilution method was employed to carry out microbiological assay. *S. aureus* test organism was employed for the study. Two samples for testing were coded as A (film) and B (pure sample) for Minimum Inhibitory Concentration (MIC). The concentration of pure drug taken was 5 mg/ml. Drug solution of 51 µl contains 256 µg of the drug. Series of 14 test tubes were taken and numbered as 1-14. To the 1st test tube, 2000 µl of broth was added while 1000 µl broth was added to the rest of the test tubes numbered as 2nd till 14th. 51 µl of broth from the 1st test tube were withdrawn and discarded and replaced with drug solution corresponding to 128 µg of drug. 1 ml of the content from 1st test tube was transferred to 2nd and so on. This procedure is repeated till second last test tube corresponding to 128, 64, 32, 16, 8, 4, 2, 1, 0.5 and 0.25 µg/ml. The last test tube serves as negative control. 10 µl of *S. aureus* broth was added in each tube except negative and kept for incubation at 37° for 24 h. Further MIC was calculated[25].

RESULTS AND DISCUSSION

Results of preformulation studies which confirm compatibility between active and excipients are represented in Table 3. IR spectra of pure drugs and excipients were plotted and compared with standard samples and it was confirmed that actives used were compatible with the excipients.

DSC was employed to understand thermal properties of loteprednol etabonate complexed with β-cyclodextrins. Endothermic peaks were observed due to glass transition for loteprednol etabonate at 240°, β-cyclodextrins at 121.1° and complex of loteprednol etabonate with β-cyclodextrins at 232°, 108° respectively (fig. 3-fig. 5) which indicates the drug profile of loteprednol etabonate is intact.

TABLE 3: PREFORMULATION STUDY ON DRUG AND EXCIPIENTS

Observed parameters	Ciprofloxacin hydrochloride	Loteprednol etabonate
Description	Ciprofloxacin is white in color, powder form	It is white to off white amorphous powder
Melting point	254.5°	221°
Solubility	Sparingly soluble in distilled water, freely soluble in DMSO, DMF, ethanol and methanol	Insoluble in water, freely soluble in DMSO, DMF, methanol and sparingly soluble in ethanol

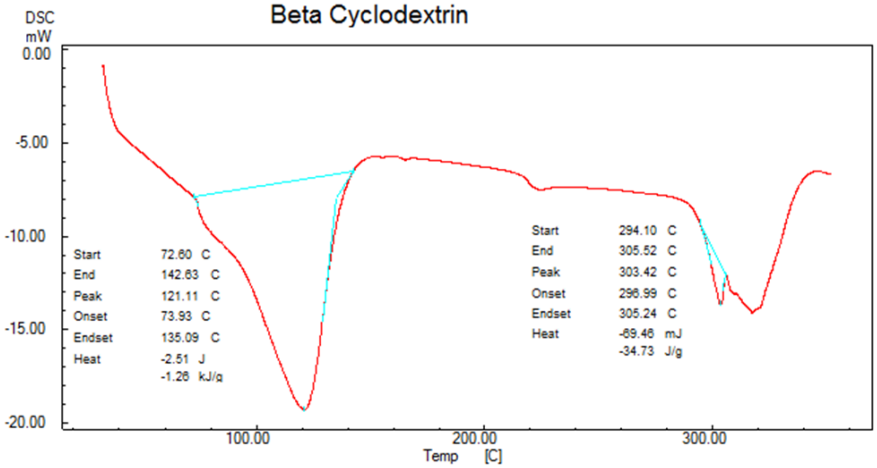

Fig. 3: Thermal analysis of β-cyclodextrin

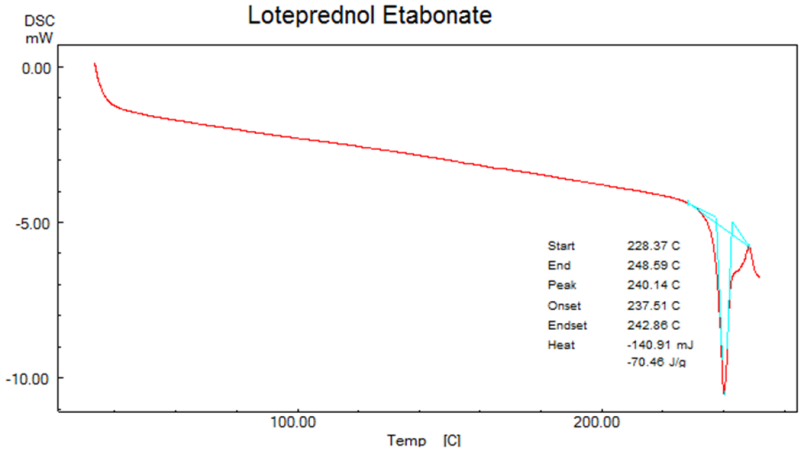

Fig. 4: Thermal analysis of loteprednol etabonate

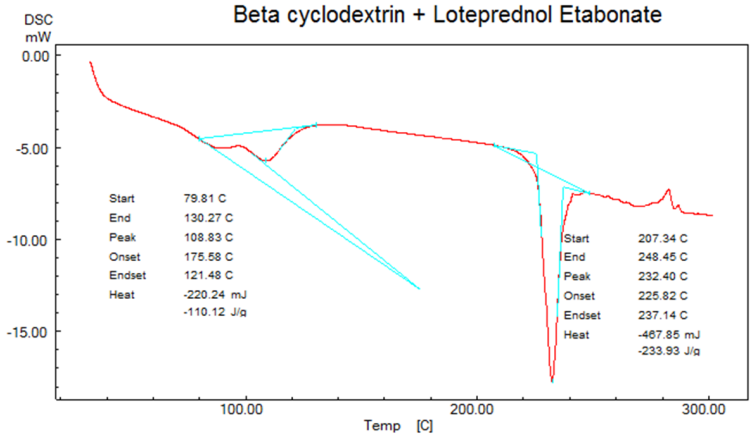

Fig. 5: Thermal analysis of β-cyclodextrin and loteprednol etabonate

Linear calibration curve was obtained in the concentration range of 3-15 µg/ml at λ_{max} 274 nm for ciprofloxacin hydrochloride and (2-25 µg/ml) at λ_{max} 245.8 nm for loteprednol etabonate. It followed Beer lamberts law with Regression coefficient (R^2) value of 0.999 for both ciprofloxacin hydrochloride and loteprednol etabonate. Due to poor water solubility, loteprednol etabonate was complexed with β-cyclodextrins in six different molar ratios ranging from 1:0.5-1:0.3 (drug: β-cyclodextrin) before incorporating in the ocusert. The solubility profile of the drug was checked in terms of high absorbance value and the ratio 1:0.5 (drug: β-cyclodextrin) was finalized based on percentage cumulative drug release as depicted in Table 4 and fig. 6.

UV-Vis simultaneous estimation method was employed for evaluating the drug content from the combined dosage form. Other evaluated parameters of the prepared ocuserts with respect to surface pH, tensile strength, thickness are recorded in tabular column (Table 5).

Franz diffusion cell was used to study the cumulative drug release and it was found that formulation CLE 80 gave best results compared to other two formulations. The values are shown in Table 6 and graphical representation in fig. 7 and fig. 8.

ZOI of the formulated films were compared with that of pure drug against a positive and negative control by using ZOI measurement by cup plate method. Readings of this study is tabulated and images on ZOI's are depicted in Table 7.

MIC concentration was found to be 0.5 µg/ml for the film and 4 µg/ml for the pure drug. Turbidity below the mentioned concentration indicates growth of organism. The formulated ocular films prove to be a novel drug delivery system with a promising approach in achieving greater drug absorption in comparison to the conventional ocular drops. The fabricated film CLE 80 proved to be

the best amongst the three formulations in terms of drug content, and sustained release of medicament across 12 h obtained through *in vitro* drug release activity. The optimized film shows anti-microbial activity with high ZOI. No interactions between drug and excipients and also β-cyclodextrins were found when characterized with IR and DSC studies. Hence ocular film with ciprofloxacin hydrochloride and loteprednol etabonate serves as a boost for the researchers and boon to the patients in the future over the conventional ocular dosage forms with 12 h release profile.

TABLE 4: ABSORBANCE *Vs.* CONCENTRATION PLOT FOR LOTEPREDNOL ETABONATE β-CYCLODEXTRIN COMPLEX

Ratio	Absorbance	Concentration
Pure drug	0.034	0.01
1:0.5 ratio	0.093	0.027
1:1 ratio	0.078	0.022
1:1.5 ratio	0.053	0.015
1:2 ratio	0.05	0.014
1:2.5 ratio	0.045	0.013
1:3 ratio	0.038	0.011

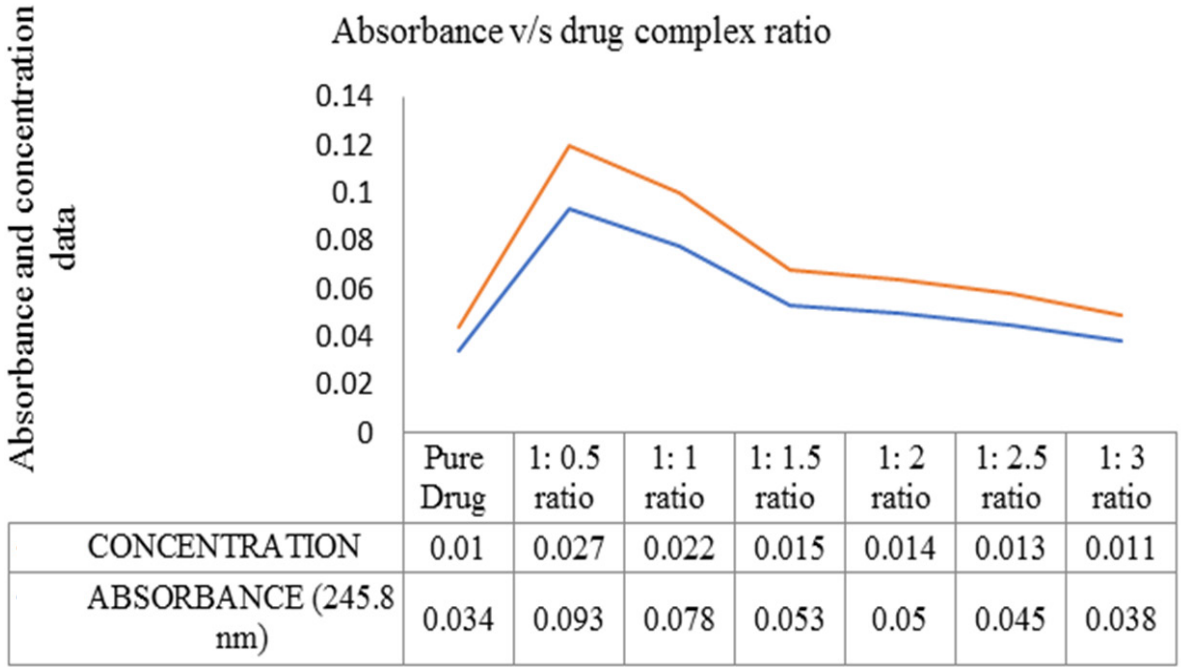

Fig. 6: Graph of absorbance v/s concentration of the complex
Note: ( ) Concentration and ( ) absorbance (245.8 nm)

TABLE 5: EVALUATED PARAMETERS WITH DRUG CONTENT

Formulation code		CLE 74	CLE 80	CLE 81
Surface texture		Smooth	Smooth	Smooth
Thickness (mm)		0.112±0.04	0.109±0.02	0.117±0.01
Weight (mg)		198±0.05	185±0.03	192±0.08
Tensile strength (g/cm^2)		415±0.05	425±0.08	430±0.03
% Drug content (±SD*)	Drug A	70	73.33	76.66
	Drug B	83.33	77.78	66.67

TABLE 6: PERCENTAGE CUMULATIVE DRUG DIFFUSION PROFILE OF CIPROFLOXACIN HYDROCHLORIDE AND LOTEPREDNOL ETABONATE

Time (h)	Percentage cumulative drug release					
	CLE 74		CLE 80		CLE 81	
	245.8 nm	274 nm	245.8 nm	274 nm	245.8 nm	274 nm
1	15.16±0.02	22.35±0.02	8.88±0.02	14.16±0.015	16.85±0.015	23.18±0.01
2	15.19±0.01	40.89±0.015	18.21±0.015	29.02±0.015	12.60±0.02	47.00±0.01
3	18.54±0.02	40.35±0.02	18.87±0.02	36.24±0.02	21.72±0.01	66.18±0.01
4	20.59±0.01	43.85±0.01	19.27±0.01	49.56±0.01	21.70±0.02	72.79±0.02
5	21.14±0.02	46.84±0.015	28.79±0.02	56.47±0.02	29.94±0.015	68.83±0.01
6	27.05±0.015	49.58±0.02	40.23±0.01	64.22±0.01	36.80±0.02	87.33±0.01
7	33.58±0.02	51.33±0.01	46.88±0.015	67.75±0.02	42.10±0.015	90.07±0.01
8	39.65±0.01	55.14±0.02	51.22±0.01	73.84±0.015	47.93±0.02	91.60±0.02
9	45.60±0.02	60.08±0.01	52.57±0.015	74.14±0.015	51.54±0.015	101.13±0.015
10	64.18±0.015	69.95±0.01	70.50±0.015	85.64±0.015	54.30±0.015	102.68±0.015
11	88.62±0.02	80.94±0.01	78.71±0.02	93.40±0.015	61.95±0.015	104.95±0.02
12	92.52±0.015	104.1±0.015	101.74±0.015	103.66±0.015	62.49±0.02	109.12±0.015

Note: Each value is the mean of three observations. Mean bearing at least one common superscript within a row do not differ significantly ($p<0.05$)

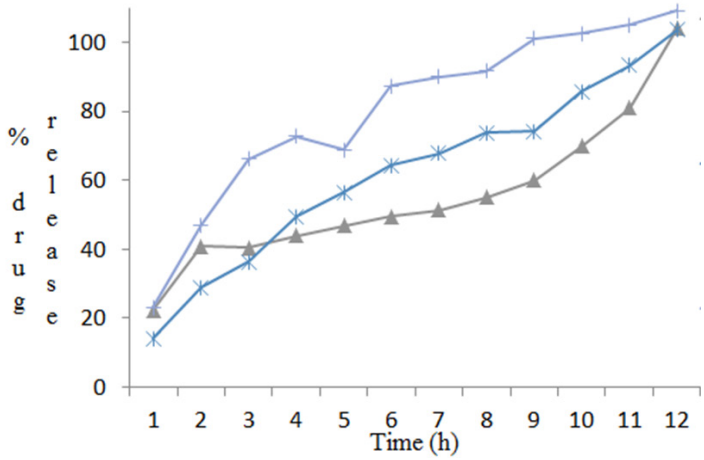

Fig. 7: Percentage cumulative release of ciprofloxacin hydrochloride
Note: ( ) % cumulative drug diffusion profile CLE 74 at 274 nm; ( ) % cumulative drug diffusion profile CLE 80 at 274 nm and ( ) % cumulative drug diffusion profile CLE 81 at 274 nm

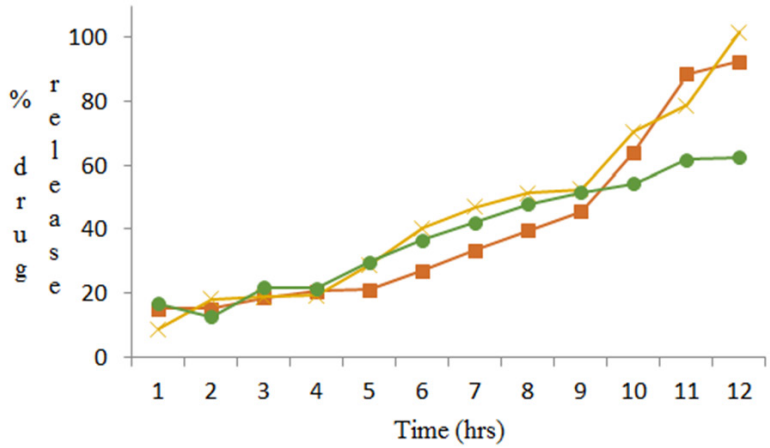

Fig. 8: Percentage cumulative release of loteprednol etabonate
Note: ( ) % cumulative drug diffusion profile CLE 74 at 245.8 nm; ( ) % cumulative drug diffusion profile CLE 80 at 245.8 nm and ( ) % cumulative drug diffusion profile CLE 81 at 245.8 nm

TABLE 7: ZONE OF INHIBITION VALUES

Formula	Zone of inhibition	
Negative control	--	--
Positive control	--	--
Ciprofloxacin	Present	3.2 cm
Loteprednol etabonate	Absent	0 cm
CLE 74	Present	3.9 cm
CLE 80	Present	4.1 cm
CLE 81	Present	3.6 cm

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Conflict of interests:

The authors declared no conflict of interests.

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