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FORMULATION AND EVALUATION OF CIPROFLOXACIN LOADED NIOSOMAL OCUSERT

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ABSTRACT

The main aim of pharmacotherapeutics is the attainment of an effective drug concentration at the intended site of action for a sufficient period of time to elicit the response. To overcome the drawbacks of conventional ophthalmic dosage form, many progresses have been done to improve the pre-corneal drug absorption and minimize pre-corneal drug loss. Preparation of ocursert helps to retain the volume and increase contact time. Topical administration of drugs is the most favoured route for management of ocular inflammation as it provides higher ocular drug concentration keeping away the systemic side effects associated with other method of administration. Ciprofloxacin is a fluoroquinolone antibiotic used to treat different types of bacterial infections like conjuctivitis. The goal of the present study is to formulate and evaluate ciprofloxacin niosomal ocuserts for ophthalmic delivery. In this study Ciprofloxacin niosomes were prepared by using ether injection method using span 60 as surfactant. High entrapment efficiency and *invitro* drug release can be obtained by the preparation of niosomes. Niosomes are optimized by 3^2 Full factorial design using design expert software version 13 stat Ease. From the release kinetics it is evident that the drug ciprofloxacin is released in a sustained manner over a period of time and shows zero order model. 9 formulation were prepared and incorporate the best niosomes into ocusert. Preparation of ocusert by solvent casting method using hydroxy propyl methyl cellulose as polymer. For the prepared ocusert drug content was found to be 96% and *invitro* drug release at the end of 7 hours was found to be 77.2%. Solubility can be increased with preparation of this biocompatible ocusert. Controlled and prolonged drug delivery can be achieved by preparation of ocusert. Achieve increased ocular contact time and reduce precorneal losses. To increase ocular

bioavailability of the drug pH of the ocular formulation should be similar to pH of tear fluid, in this preparation it was found to be 6.9 and is satisfactory.

Keywords; ciprofloxacin, span 60, entrapment efficiency, hydroxy propyl Methyl cellulose, Ether injection, solvent casting

INTRODUCTION

Novel Drug delivery System (NDDS) refers to the approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects. NDDS is a combination of advance technique and new dosage forms which are far better than conventional dosage forms. Advantages of Novel Drug Delivery System are: Optimum dose at the right time and right location, Efficient use of expensive drugs, excipients and reduction in production cost, Beneficial to patients, better therapy, improved comfort and standard of living **[1]**.

Vesicular system such as liposomes, niosomes, transferosomes, pharmacosomes and ethosomes provide an alternative to improve the drug delivery. Niosomes play an important role owing to their nonionic properties, in such drug delivery system **[2]**. Eye is a unique organ, the complexity of which provides a unique challenge to drug delivery. 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. Ocular drug delivery is challenging due to the presence of anatomical and physiological barriers **[3]**. Major concerns with topical delivery include poor drug absorption and low bioavailability **[4]**. About 90% of dose applied topically from such solutions is lost due to precorneal losses (nasolacrimal drainage) and tearing results in poor availability as contact time is less between drug and ocular tissue. The conventional ocular preparations are eye drops and ophthalmic ointments. As soon as the eye drop solution is instilled into cul-de-sac, it is rapidly drained away from the precorneal cavity by constant tear flow and lachrymal-nasal drainage. Only about 1-2% of instilled dose is absorbed into the target tissues and relatively concentrated solution is required for installation to achieve an adequate level of therapeutic effect. The frequent periodic instillation of eye drops becomes necessary to maintain a continuous sustained level of medication **[5]**. 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. The viscosity enhancing agents such as methylcellulose are added to eye drop preparations or ophthalmic drug is formulated in water insoluble ointment

formulation to sustain the duration of intimate drug-eye contact **[6]**.

MATERIALS AND METHODS

Ciprofloxacin API was collected from Yarrowchem, Mumbai, Span60, Cholesterol, Hydroxy propyl methyl cellulose required for this study was supplied by Balaji drugs and chemicals. Potassium dihydrogen phosphate Disodium hydrogenphosphate and all other chemicals were provided by Nice Chemicals, Cochi.

FTIR spectrophotometer and UV-Visible spectrophotometer, Digital ph meter were manufactured by Shimadzua213748, Japan, Melting point apparatus by Raasa, Mumbai and Magnetic stirrer from Remi equipments, Mumbai

preparation of niosomes:

Ether injection method

The surfactant and lipid were first dissolved in suitable organic solvent. The prepared organic phase was then added drop wise into aqueous phase containing drug. Thus the dissolved organic solution containing surfactant were injected drop wise through 17 gauge needle into preheated 15 ml distilled water containing drug, which is magnetically stirred and maintained at 65°C for 45 min. Stirring was continued until all ether evaporating to get drug loaded niosome. Vaporization of ether leads to formation of vesicles **[7]**.

Table 1: Formulation code

formulation code (x1, x2)	cholesterol (mg)	surfactant (mg) span 60	drug (mg)-ciprofloxacin
F1(-1,-1)	20	25	5
F2(-1,0)	20	30	5
F3(-1,+1)	20	35	5
F4(0,-1)	25	25	5
F5(0,0)	25	30	5
F6(0+1)	25	35	5
F7(+1,-1)	30	25	5
F8(+1,0)	30	30	5
F9(+1,+1)	30	35	5

Preparation of ocusert

The method used here was solvent casting method. HPMC is dissolved in distilled water separately in a beaker. Then niosomal suspenion was poured into polymer solution withconstant stirring to get a homogenous solution. Required amount of glycerine was added as plasticizer and mixed well. The resulting solution was casted over the petridish **[8]**.

Optimization studies

Response surface methodology using two factorial three level full factorial design was chosen for the optimization of the prepared ciprofloxacin loaded niosomes. The responses obtained from the design matrix were statistically evaluated using design expert 13, statistical software trial package.

Entrapment efficiency

1ml of cooled niosomal formulation will be

centrifuged at 1300 rpm at 40ºC for 30 minutes. Clear supernatant after centrifugation will be filtered and recentrifuged Resulting sample after lysis with isopropyl alcohol will be analysed on UV-VIS spectrophotometer at 276nm **[9]**.

***Invitro* performance**

The niosomal preparation was taken in a dialysis tube, which acts as a donor compartment. Dialysis tube was placed in a beaker containing 250 ml of phosphate buffer saline of pH 7.4, which acts as a receptor compartment. The temperature of receptor medium maintained at 37 ºC and medium agitated using magnetic stirrer. 1 ml aliquots of sample was taken and made up to 10 ml with PBS. 1 ml of diffusion medium was replaced after every withdrawal so that the volume of the diffusion medium was maintained. The collected samples were analysed at 276 nm **[10]**.

kinetics of *in-vitro* drug release

In-vitro release data of ciprofloxacin loaded niosomes were plotted into different kinetic models such as Zero order (% CDR Vs time), First order (log % drug retained Vstime), Higuchi model (% CDR Vs root time), Korsmeyer-Peppas model (log % CDR Vslog time).

Evaluation

1.Drug content of ocusert

ocuserts were taken and dissolved or crushed in 10 ml of PBS Ph7.4 in a beaker and were filtered into 25 ml volumetric flask and the volume was made up to the mark withbuffer. 1 ml of the above sample was withdrawn and the absorbance was measured using UV spectrophotometer at 276nm after suitable dilutions **[11]**.

2.*Invitro* of ocusert

Two side open-ended glass tube was taken and to one side, semipermeable membrane was tied up. The ocusert was placed over this and the tear volume was maintained withthe help of PBS ph7.4. This set up is called as donar compartment. The beaker was placed over the magnetic stirrer and the temperature was adjusted to 28-30° C. thus therelease pattern was studied by withdrawing the samples at regular intervals of time (for every1 hour) and estimated in an UV-spectrophotometer at 276nm **[12]**.

3. pH

The ocuserts were allowed to swell in distilled water at room temperature for 30 minutes and placed under digital pH meter to determine the surface pH **[13]**.

4.Uniformity of Thickness

The thickness of the insert was determined using a screw guage at five separate points of each insert **[14]**.

5.Weight of ocusert

Weight of 3 ocuserts was found out individually and reported. Average weight is takenas weight of ocusert **[14]**.

6.% Moisture Absorption

It was carried out to check the physical stability or integrity at wet condition. The

prepared ocusert was accurately weighed and placed in a dessicator containing aluminium chloride with 79.5% moisture and it was kept for 3 days. The ocusert was taken out and reweighed after 3 days. The amount of moisture absorbed by the ocusert was calculated **[15]**.

7. % Moisture Loss

The prepared ocusert was initially weighed and kept in a dessicator containing fused anhydrous calcium chloride and it was kept for 3 days. The ocusert was taken out and reweighed after 3 days. The % of moisture loss was calculated **[15]**.

8. Stability studies

Procedure: The stability studies were carried out on the prepared ocusert at room temperature and refrigerator temperature (2-8) over a period of 45 days. The physical appearance, pH, viscosity and percentage drug content were evaluated before and after the stability study **[16]**.

RESULTS AND DISCUSSION

Table 2: Organoleptic properties

Parameters	Ciprofloxacin
Physical appearance	Crystalline
Colour	Yellowish-white

Determination of solubility

Table 3: Determination of solubility

✓ Solvent	✓ Solubility
✓ Water	✓ Sparingly soluble
✓ Ethanol	✓ Insoluble
✓ Dil HCL	✓ Soluble
✓ 0.02orthophosphoric acid	✓ Soluble
✓ Acetone	✓ Insoluble

Characterization by FT-IR spectroscopy

FT-IR Spectral analysis of pure drug was carried out.

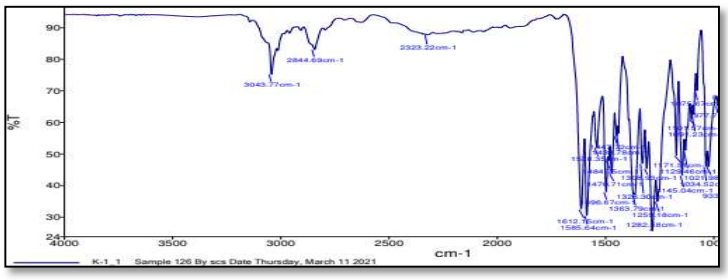


Figure 2: FTIR Spectrum of pure drug of ciprofloxacin

Table 4: Different peaks present in ciprofloxacin

Sl. No	Functional groups	Characteristic peaks (cm^{-1})	Observed peaks (cm^{-1})
1	N-H Stretching	3700 - 2500	2844.69
2	C-F Stretching	1400 - 1000	1328.30
3	CH Stretching	3000 - 2840	2844.69
4	O-H Bending	1300 - 1250	1282.58

Drug –Excipient compatibility study

This shows characteristic peaks are present in the standard reference spectrumof respective drug IR Spectral analysis was carried out to determine drug-excipient interaction.

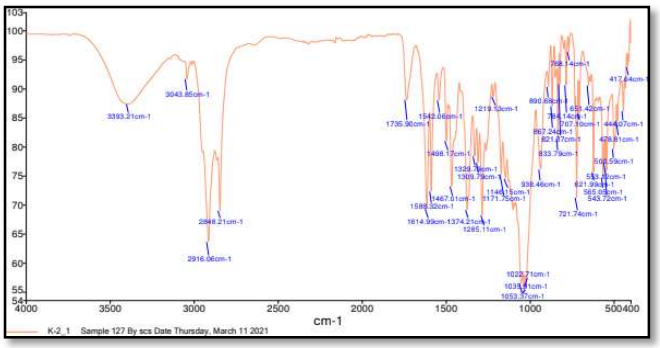


Figure 3: FT-IR spectrum of ciprofloxacin, span 60, cholesterol and HPMC

Determination of λmax

The maximum absorption of ciprofloxacin was found to be at wavelength of 276 nm.

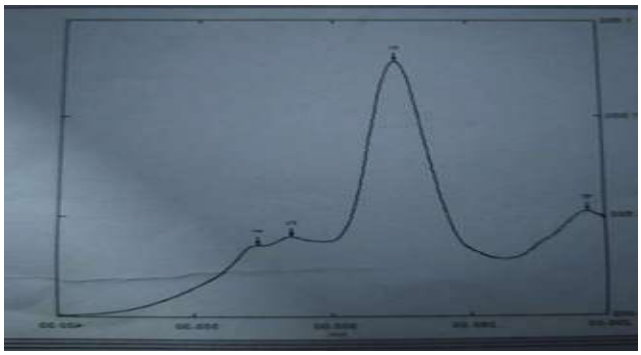


Figure 4: Determination of λmax of ciprofloxacin

Preparation of nine formulations of niosomes by etherinjection method

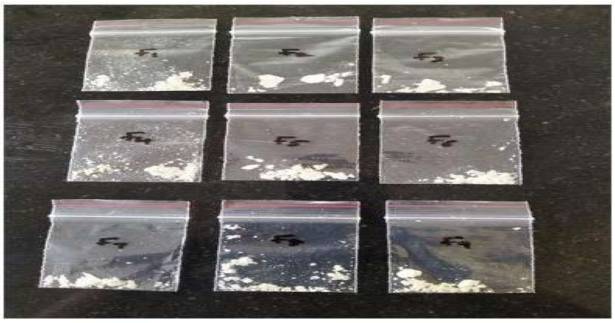


Figure 5: Nine formulations of niosomes

Performance of *invitro* test

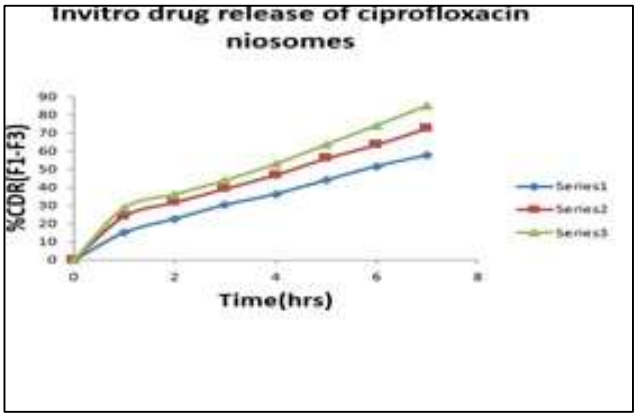


Figure 6: *Invitro* drug release of ciprofloxacin niosomes (F1-F3)

Table 5: *In vitro* drug release and entrapment efficiency

Run	Factor 1 A:cholesterol mg	Factor 2 B:surfactant mg	Response 1 entrapment efficiency (%)	Response 2 *invitro* drug release (%)
1	20	25	72.72	57.5
2	30	35	76.1	66.6
3	20	30	95.43	85.1
4	25	25	69.86	54.5
5	25	30	74.68	64.2
6	30	30	68.32	56
7	25	35	88.35	76.6
8	30	25	65.86	59
9	20	35	76.1	72.1

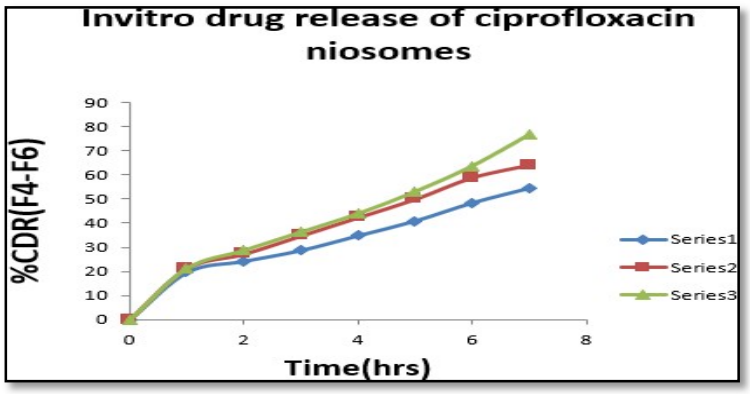


Figure 7: *Invitro* drug release of ciprofloxacin niosomes (F4-F6)

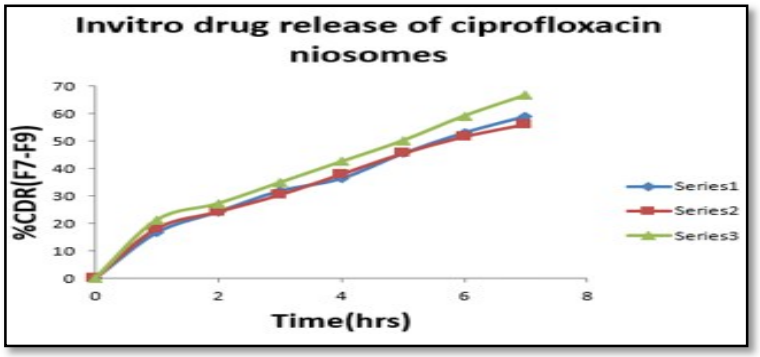
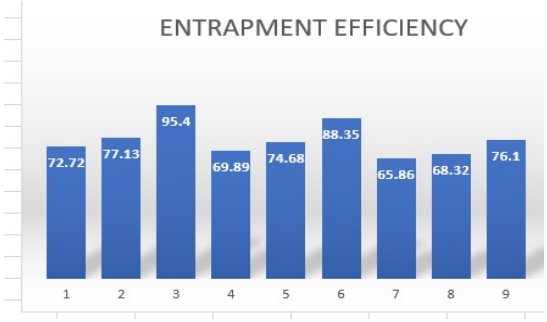


Figure 8: *Invitro* drug release of ciprofloxacin niosomes (F7-F9)

Entrapment efficiency



Optimization of niosomes

✓ Best formulation was found to be F3 with 20mg cholesterol and30mg surfactant.

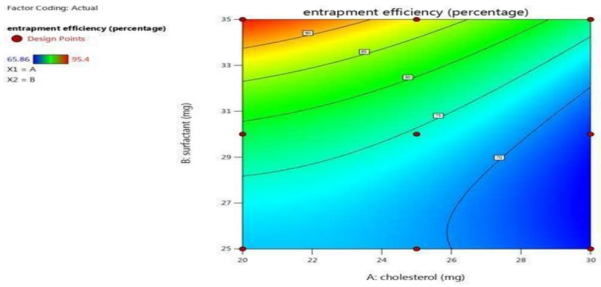


Figure 10: Contour plot for response Y1, entrapment efficiency

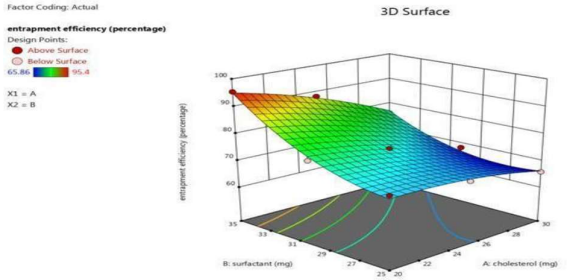


Figure 11: Response surface plot for response Y1, entrapment efficiency

The Model F-value of 58.50 implies the model is significant.

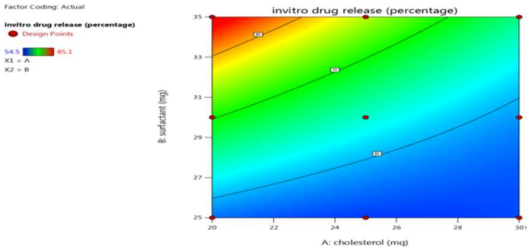


Figure 12; contour plot for response Y2, *invitro* drug release

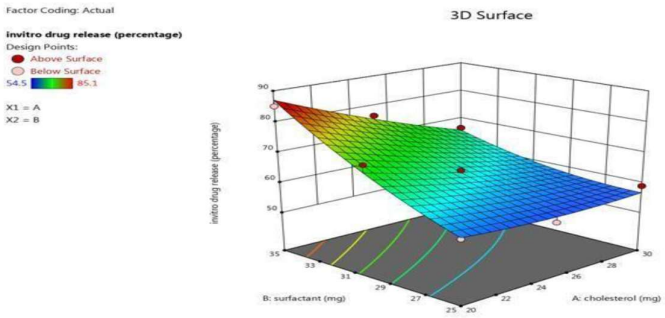


Figure 13: Response surface plot for response Y2, *invitro* drug release

The Model F-value of 16.99 implies the model is significant.

Kinetics of *invitro* drug release

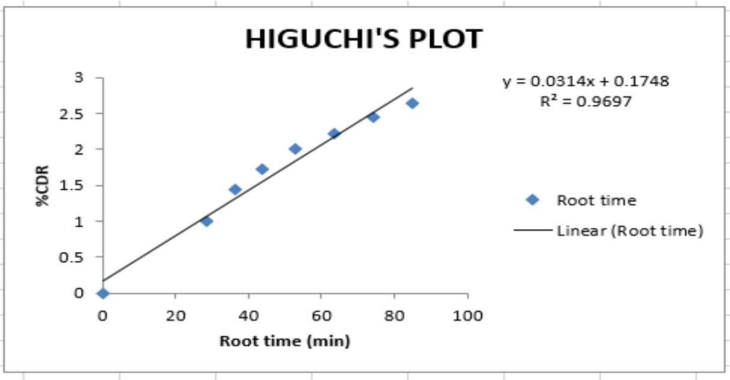


Figure 14: Plot of % Cumulative drug release Vs Root Time

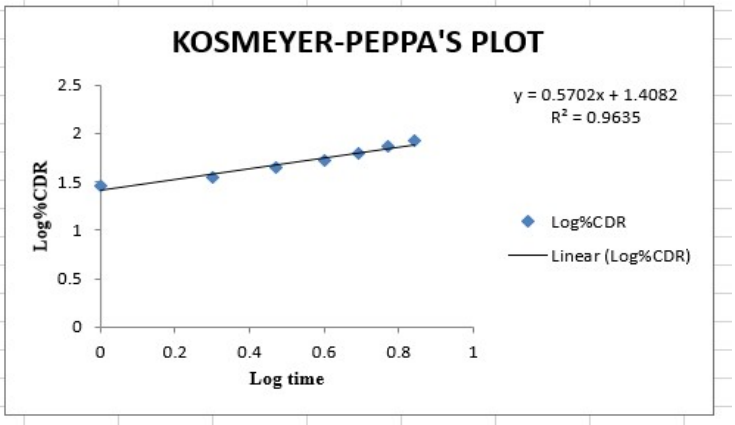


Figure 15: Plot of log % Cumulative drug release Vs log Time

SEM analysis

Showed spherical niosomes with magnification of 3000x

Ocusert is prepared using solvent casting method.

Evaluation of ocusert

1.Drug Content

For the prepared formulation drug content was found to be 96%

2. *Invitro* drug release

Table 6: *Invitro* drug release of ciprofloxacin niosomal ocusert

Time (min)	Absorbance(nm)	Conc(µg/ml)	Amount of drug in 200ml medium	%CDR
1	0.023	0.174	0.348	34.8
2	0.028	0.151	0.424	42.4
3	0.033	0.250	0.500	50.0
4	0.037	0.280	0.560	56.0
5	0.042	0.318	0.636	63.6
6	0.047	0.356	0.712	71.2
7	0.051	0.286	0.772	77.2

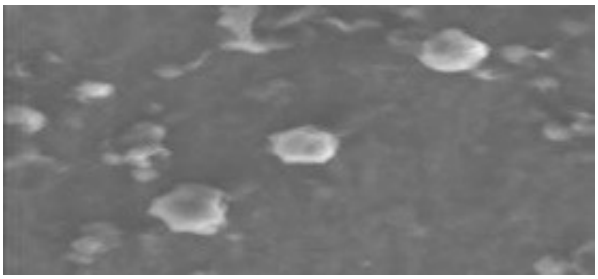


Figure 16; spherical niosomes with magnification of 3000x

Figure 17: Preparation of niosomal ocusert

Figure 18: Prepared ocusert

3. pH;

The ph of the formulations was found to be 6.9 and is satisfactory.

4.Uniformity of thickness

The thickness of ocuserts was found to be 0.5mm at different regions of ocusert.

5.Uniformity of weight

The average weight of ocular inserts were found to be in the range of 3 mg.

6.Percentage Moisture Absorption

For the various formulations, % Moisture absorption was found to vary between 31.33 to 32.21.

7. percentage Moisture Loss

For the formulation % Moisture loss was found to vary between 29.18 to 31.23.

8.stability studies

Niosomal ocuserts are stable since they kept at normal temperature and refrigerated temperature.

CONCLUSION

Identification and Characterization of the given drug sample Ciprofloxacin by Melting point and FTIR. Other preformulation

studies like organoleptic properties, solubility and analytical methods were performed. FTIR spectrum of pure drug with the excipients confirmed that there was no interaction between them, hence they are compatible. Ciprofloxacin niosomes prepared by ether injection method. Based on entrapment efficiency and *invitro* drug release, niosomes are optimised. Best formulation was found to be F3 with 20mg cholesterol and 30mg surfactant.

Entrapment efficiency of best formulation was found to be 95.43% and*invitro* drug release was found to be 85.1%. Incorporated best niosomes into ocusert and Different Evaluations of the ocusert performed. Entrapment efficiency and *invitro* drug release can be increased by niosomal preparation. Contact time can be increased by the formulation of ocusert. controlled and prolonged drug delivery can be achieved by formulaionof ocusert. Less amount is only required for this ocusert preparation so dose is reduced and cost can be reduced and less side effects. Frequent instillation of medication is not required

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