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Development of gel based ophthalmic preparation of solid lipid nanoparticles containing ofloxacin and prednisolone

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Abstract
The aim of the present study was focused on the development of solid lipid nanoparticles based gelling system of antibiotic drugs to be administered through ocular route. Five formulations (OF1, OF2, OF3, OF4 and OF5) of solid lipid nanoparticles were prepared containing ofloxacin and four formulations (PF1, PF2, PF3 & PF4) of solid lipid nanoparticles were prepared containing prednisolone. Solid lipid nanoparticles were prepared by emulsification followed by sonication method. Prepared ofloxacin and prednisolone containing solid lipid nanoparticles were evaluated for particle size, shape, surface morphology, drug content and in-vitro drug release studies. The average particle size was found to be in range 354.2 nm for ofloxacin & 349.2 nm for prednisolone formulations. The particles were uniform, spherical in shape and had 60 to 88.3%w/w of drug entrapped for ofloxacin formulation & 58 to 84.45%w/w for nanoparticles containing prednisolone. The drug release from solid lipid nanoparticles showed sustained release of drug. All the formulation showed better result in terms of stability. Among the five formulations of ofloxacin and four formulation of prednisolone the best result were found with OF4 formulation of ofloxacin & PF1 formulation of prednisolone. The solid lipid nanoparticles of ofloxacin & prednisolone were incorporated into gel so as to make it suitable to be administered by ocular route. Solid lipid nanoparticles containing gel showed drug delivery up to 88.7% to 92.7%. Ofloxacin & prednisolone containing nanoparticles loaded gel showed better result when compared with the ofloxacin nanoparticles; because the release rate revealed that the gel gave higher release of drug initially for quick onset of action.

Keywords: solid lipid nanoparticles (SLN), ofloxacin, prednisolone, ocular route, gelling system

1. Introduction
Solid lipid nanoparticles were firstly introduced in the beginning of 1991. These are submicron in size range (50-100nm) composed of physiological lipids [1, 2]. These nanoparticles posses a lipid core matrix in a nanometer range, stabilized by a surfactant layer [3, 4]. These are based on biocompatible lipids and provide sustained effect on the formulation either by diffusion or dissolution [5]. SLN have several advantages over other colloidal carriers, such as the possibility of controlling drug release, long term stability, drug targeting, and good drug loading of drugs may it be lipophilic or hydrophilic, free from biotoxicity due to the use of physiological lipids [6]. The solid lipid nanoparticles, due to their nano size range can be an effective ocular drug delivery system as they improve ocular bioavailability, enhance corneal absorption, prolong the ocular retention time and provide a sustained drug release profile [7]. The solid lipid nanoparticles were realized by exchanging the liquid lipid (oil) of the emulsion by a solid lipid meaning that lipid is solid at room temperature and at body temperature also [8]. The use of solid lipid instead of liquid lipid was much better idea to achieve controlled drug release, as the mobility of the drug in the solid is considerably lower as compared with liquid oils [9]. The smaller size of solid lipid nanoparticles offer several advantages like larger surface area, high drug loading capacity, interaction with target site up to molecular level and enhances the bioavailability of drug. The lipid core provides incorporation of wide variety of drugs, which get dissolved, dispersed and entrapped in it. Due to their biodegradable and biocompatible properties the solid lipid nanoparticles are used to deliver lipophilic drugs, macromolecules, proteins, peptides, genes, antigens, food molecules, hydrophilic drugs and diagnostic molecules [10].

1.1 Solid Lipid Nanoparticles for Ophthalmic Use
Ophthalmic drug delivery is one of the most interesting and challenging task which the pharmaceutical researcher encounter due to the unique anatomy and physiology of eye [11]. Eye is an unique and challenging organ for therapeutic drug delivery on to the surface as well as in the interior part of the ocular structure. Most of its anatomical and physiological makeup/architecture interferes with the fate of the administered drug and bioactive. Tears permanently wash the surface of eye [12]. Recently the use of nanotechnology in the ophthalmic field has gained much attention, because nanoparticulate drug delivery is considered to be one of the most promising technologies to overcome poor drug stability and difficulties in delivery of the drug across the biological membrane. Various types of ophthalmic conventional formulations like solution, suspension, ointment are available in the market, but all these formulations have some disadvantages like rapid precorneal elimination of drug, high variability in efficiency and blurred vision. The ophthalmic solutions lead to poor bioavailability of drug by dilution and drainage from the eyes and the therapeutic response of the drug is reduced as well and delayed [13, 14].

1.2 Solid Lipid Nanoparticles based gel for ocular use

Poor bioavailability and therapeutic response which is exhibited by the conventional ophthalmic preparations due to limited permeability and rapid elimination can be overcome by the use of gelling system. Solid lipid nanoparticles are incorporated into the in-situ gel for sustained release of the drug, to prolong the residence time and to increase the bioavailability of the drug [15]. Conventional dosage forms like eye drops have some major problems that they cannot provide the desired concentration of drug into the eye due to the loss of drug through nasolacrimal drainage. Gel formulations have found to be successful in achieving much better drug product effectiveness, safety and reliability. Ocular drug delivery system based on the concept of gelling system work by increasing precorneal residence time, thus improve the ocular bioavailability and improve patient acceptability [16, 17].

Solid lipid nanoparticles when incorporated into the gel made up of suitable polymers like HPMC (hydroxyl propyl methyl cellulose), CMC (carboxy methyl cellulose), Carbopol will improve the bioavailability of the drug in eye and resident time. It may prove to be more effective as compared to conventional dosage forms.

The advantages of these systems are as follows:

- Less blurred vision as compare to ointment
- More comfortable than soluble or insoluble insertion
- Decreased nasolacrimal drainage of the drug which may cause undesirable side effect due to systemic absorption
- Sustained and prolonged drug release, maintaining relatively constant plasma profile
- Reduced frequency of application hence improve patient compliance and comfort
- Increased bioavailability due to increased precorneal residence time and absorption [18, 19].

2. Materials and Methods

Table 1: List of drug and chemicals

S. No.	Chemical	Source
1.	Ofloxacin	Mankind Pharma Ltd. Sirmour, H.P.
2.	Prednisolone	Yarrow Chem. Product Mumbai
3.	Glycerol monostearate	Central drug house Pvt. Ltd. Mumbai
4.	Soft paraffin, HPMC	SDFCL, Fine chemical Ltd. Mumbai
5.	Cholesterol, Methyl alcohol, Potassium di-hydrogen phosphate	Merck Specialities Pvt. Ltd. Mumbai
6.	Tween-80, Span-20	Thomas Baker chemical Ltd. Mumbai
7.	Polyvinylalcohol	Central drug house Pvt. Ltd. New Delhi
8.	Sodium hydroxide (N_aOH)	Qualigens Fine chemical Ltd. Mumbai

Method of preparation of SLN

Method of preparation of ofloxacin loaded solid lipid nanoparticles

The solid lipid nanoparticles containing the drug ofloxacin were prepared by the method of solvent emulsification and evaporation followed by sonication. In this method the lipids were melted on a hot plate. The drug ofloxacin was dissolved slowly in the melted lipids containing span-20 under magnetic stirring. Lipids solution containing the drug was added dropwise into aqueous solution under magnetic stirring. The emulsion was then added into 1% PVA solution. The system was maintained under stirring for 30 minutes, covered with aluminium foil to avoid contamination and final formulation was sonicated for 20 minutes. After sonication the lipid nanoparticles were lyophilized.

Table 2: Formulation design for preparation of Ofloxacin loaded SLN

Ingredients	OF1	OF2	OF3	OF4	OF5
Glycerol monostearate	0.5gm	1gm	1.5gm	2gm	1gm
Soft paraffin	0.5gm	0.5gm	0.5gm	0.5gm	0.5gm
Cholesterol	0.2gm	0.2gm	0.2gm	0.2gm	0.2gm
Tween-80	0.1%	0.1%	0.1%	0.1%	0.1%
Span-20	0.1%	0.1%	----	0.1%	----
Polyvinylalcohol	1.0%	1.0%	1.0%	1.0%	1.0%
Drug	0.5gm	0.5gm	0.5gm	0.5gm	0.5gm

Method of preparation of prednisolone loaded solid lipid nanoparticles

The solid lipid nanoparticles containing the drug prednisolone were prepared by the method of solvent emulsification and evaporation followed by sonication. In this method the lipids were melted on a hot plate. The drug prednisolone was dissolved slowly in the melted lipids containing span-20 under magnetic stirring. Lipids solution containing the drug was added drop wise into aqueous solution under magnetic stirring. The emulsion was then added into 1% PVA solution. The system was maintained under stirring for 30 minutes, covered with aluminium foil to avoid contamination and final formulation was sonicated for 20 minutes. After sonication the lipid nanoparticles were dried by lyophilization.

Table 3: Formulation design for preparation of Prednisolone loaded SLN

Ingredients	PF1	PF2	PF3	PF4
Glycerol Monostearate	2gm	1.5gm	0.5gm	1gm
Soft paraffin	0.5gm	0.5gm	0.5gm	0.5gm
Cholesterol	0.2gm	0.2gm	0.2gm	0.2gm
Tween-80	0.1%	0.1%	0.1%	0.1%
Span-20	0.1%	----	0.1%	----
Polyvinylalcohol	1.0%	1.0%	1.0%	1.0%
Drug	0.3gm	0.3gm	0.3gm	0.3gm

Preparation of Solid Lipid Nanoparticle Loaded Gel

From all the 9 formulations, optimized formulation of ofloxacin OF4 and PF1 of prednisolone formulation was selected on the basis of characteristics like particle size, drug content and *in-vitro* release profile. The formulations OF4 and PF1 showed supremacy among the other formulations in term of particle size; drug content and drug release profile. These formulations were further incorporated in ophthalmic gel. HPMC 4% w/v was used as a gel base and SLP of OF4 & PF1 were dispersed in gel base and stirred for 2 hours at 1200 rpm. The gel was allowed to stand overnight to remove entrapped air and ensure complete homogeneity and gelation.

3. Result & Discussion

3.1 Preformulation Studies

Preformulation studies commence when a newly synthesized drug show sufficient pharmacological promise in animal model to warrant evaluation in man. Preformulation data must be generating to serve as a basis for the design of a delivery system to achieve stability and maximum bioavailability [20, 21, 22].

The drugs ofloxacin and prednisolone were identified and evaluated as per the test for identification given in the official monograph. The physical appearance as observed was as following:

3.1.1 Physical Appearance of Drugs

For ofloxacin

- **Color:** pale yellow, white to light yellowish
- **Odor:** odorless
- **Texture:** crystalline powder
- **Taste:** bitter

For prednisolone

- **Color:** white
- **Odor:** odorless
- **Texture:** crystalline powder
- **Taste:** tasteless

3.1.2 Identification and Authentication of Drug

Melting point

Melting points of the drugs samples were determined by using capillary tube method.

Melting points of drugs were found to in range of: Ofloxacin (250-257ºC), Prednisolone (266-273ºC) which tallied with the reported values.

Solubility studies

Solubility may be defined as a spontaneous interaction of or more substances to form a homogeneous dispersion. The solubility of ofloxacin and prednisolone were studied in various aqueous and non aqueous solvents. Accurately weighed 10-10mg of drugs was taken in test tubes separately. Then 10-10 ml of solvent was added in both test tubes at room temperature and shaken for 24 hours in vortex mixture. After that the solubility was observed visually for clear fluid. The results are shown in table no. 4.

Table 4: Solubility of drugs in different solvents

S. No.	Solvents	Ofloxacin	Prednisolone
1	Alcohol	Soluble	Soluble
2	Chloroform	Sparingly soluble	Sparingly soluble
3	Water	Insoluble	Insoluble
4	Ether	Slightly soluble	Slightly soluble
5	0.1N HCl	Freely soluble	Soluble
6	Phosphate buffer (7.4 pH)	Soluble	Insoluble

Calibration Curve of Ofloxacin and Prednisolone in Methanol

U.V. estimation of the ofloxacin and prednisolone was done by U.V. Spectrophotometric method using U.V. and visible spectrophotometer-1601 (Shimazu Japan). The calibration curve was prepared in methanol. The data was regressed to obtain a straight line. The R^2 value of ofloxacin was found to be 0.998 and for prednisolone it was found to be 0.996 in methanol. This indicated good linearity. The calibration curve of both drugs obeyed Beer Lambert's law in the concentration range studied. The results are shown in figure no. 1 and figure no 2.

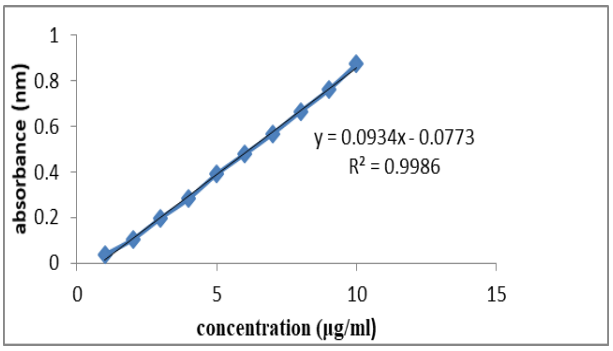

Fig 1: Calibration curve of ofloxacin in methanol at λ_{max} 298.6

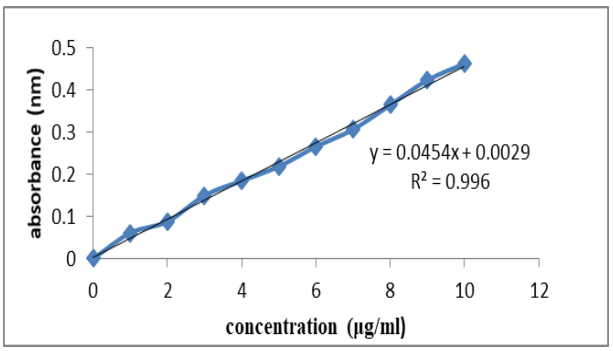

Fig 2: Calibration curve of prednisolone in methanol at λ_{max} 248.8

Simultaneous determination of ofloxacin and prednisolone in methanol

An accurately weighed quantity of prednisolone (10mg) and ofloxacin (10mg) were transferred to a separate 100ml volumetric flask and dissolved and diluted to the mark with methanol to obtain standard solution having concentration of prednisolone (100µg/ml) and ofloxacin (100µg/ml).

Accurately measured standard stock solutions of each prednisolone (0.1-1ml) and ofloxacin (9.9-9ml) were transferred in a series of 10ml volumetric flask separately and diluted up to the mark with methanol. The absorbance of the solution was then measured at 298.6 nm (ofloxacin) and 248.8nm (prednisolone) by the using U.V. and visible spectrophotometer-1601 (Shimazu Japan). The results are shown in figure no 3.

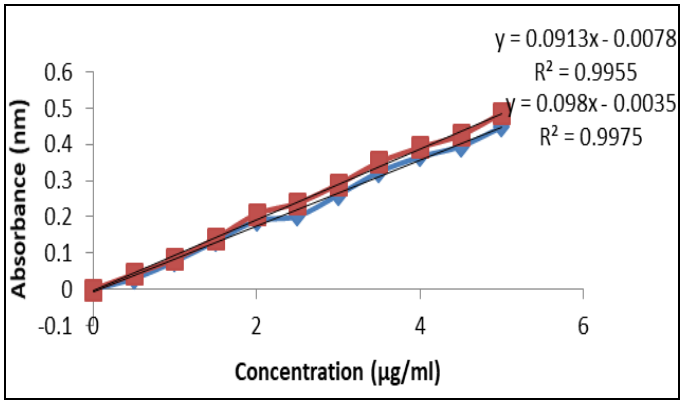

Fig 3: Simultaneous calibration curve of ofloxacin and prednisolone in methanol

Drug Polymer Compatibility Studies (Ft-Ir)

FT-IR studies were done to confirm the identity of the drug and to detect the interaction of the drug with carrier or excipients. FT-IR spectral measurement for pure ofloxacin drug, prednisolone drug, glycerol monostearate polymer and the formulations were taken at ambient temperature. The results depict that both drugs did not show any incompatibility.

The formulation containing ofloxacin showed peaks at 2918.42 cm^{-1}, 2850.91 cm^{-1}, 1734.08 cm^{-1}, 1623.17 cm^{-1}, 1527.69 cm^{-1}, 1468.86 cm^{-1}, 1287.54 cm^{-1}, 1145.77 cm^{-1}, 1056.07 cm^{-1}, 955.77 cm^{-1}, 851.61 cm^{-1}, and 804.35 cm^{-1}.

The formulation containing prednisolone showed peaks at 2921.32 cm^{-1}, 2852.84 cm^{-1}, 1736.01 cm^{-1}, 1664.64 cm^{-1}, 1465.96 cm^{-1}, 1383.98 cm^{-1}, 1180 cm^{-1}, 1108.15 cm^{-1}, 1057.04 cm^{-1}, 721.41 cm^{-1}.

The results are shown in figure no. 4, 5, 6, 7 and 8 comparisons of FTIR spectra of pure ofloxacin and prednisolone drugs and glycerol monostearate it was clear that there was no significant interaction of the encapsulated drugs with the excipients within various formulations.

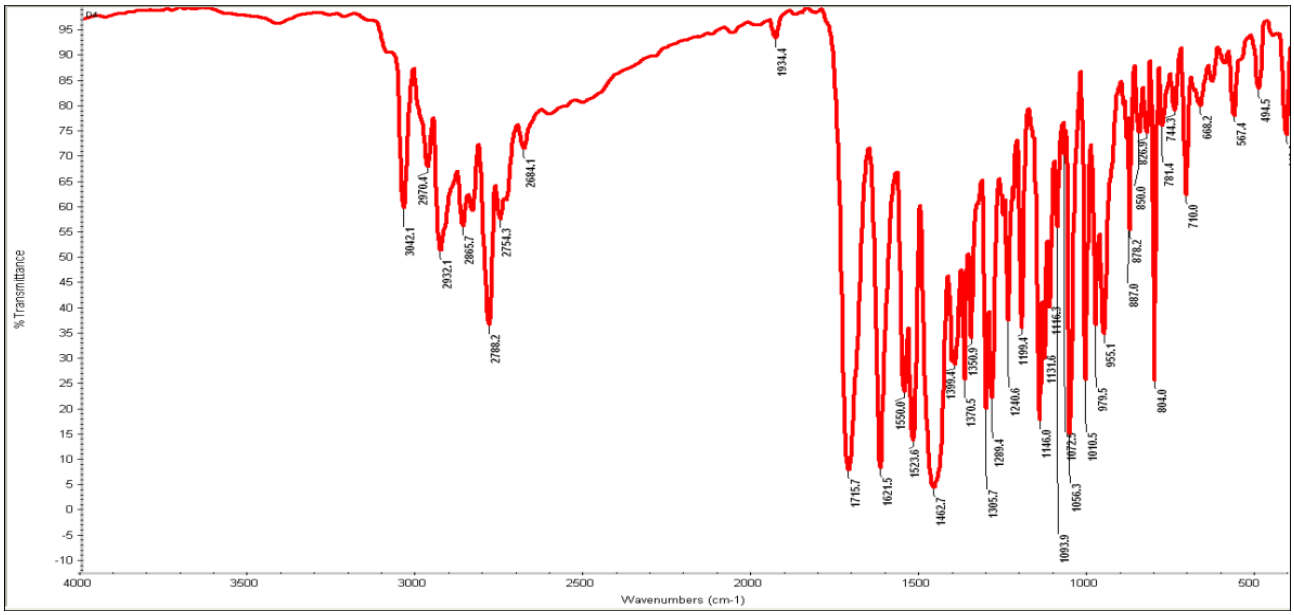

Fig 4: FT-IR spectrum of pure drug ofloxacin

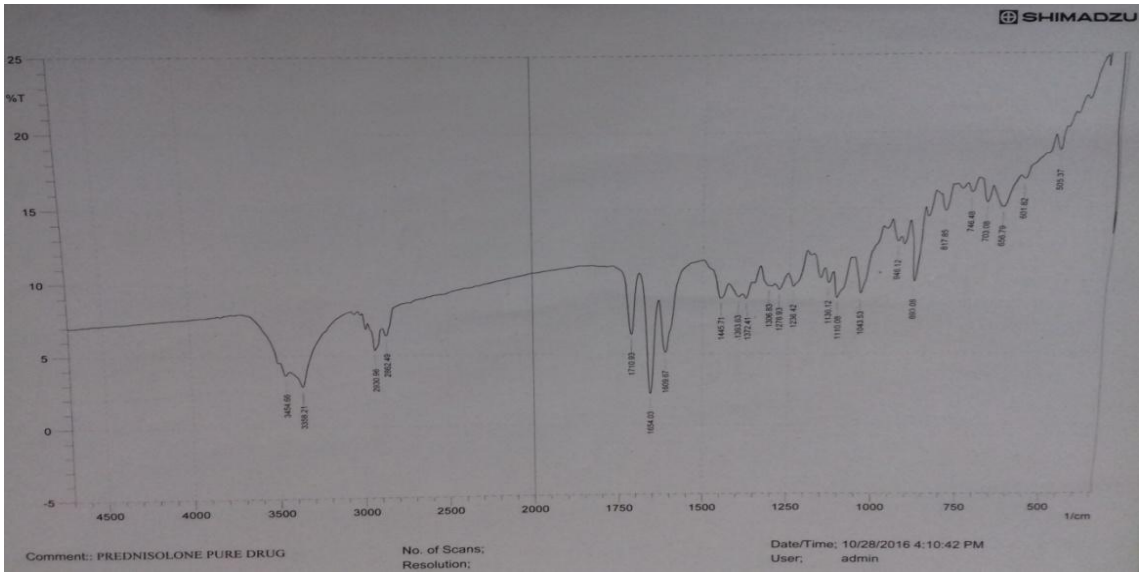

Fig 5: FT-IR spectrum of pure drug Prednisolone

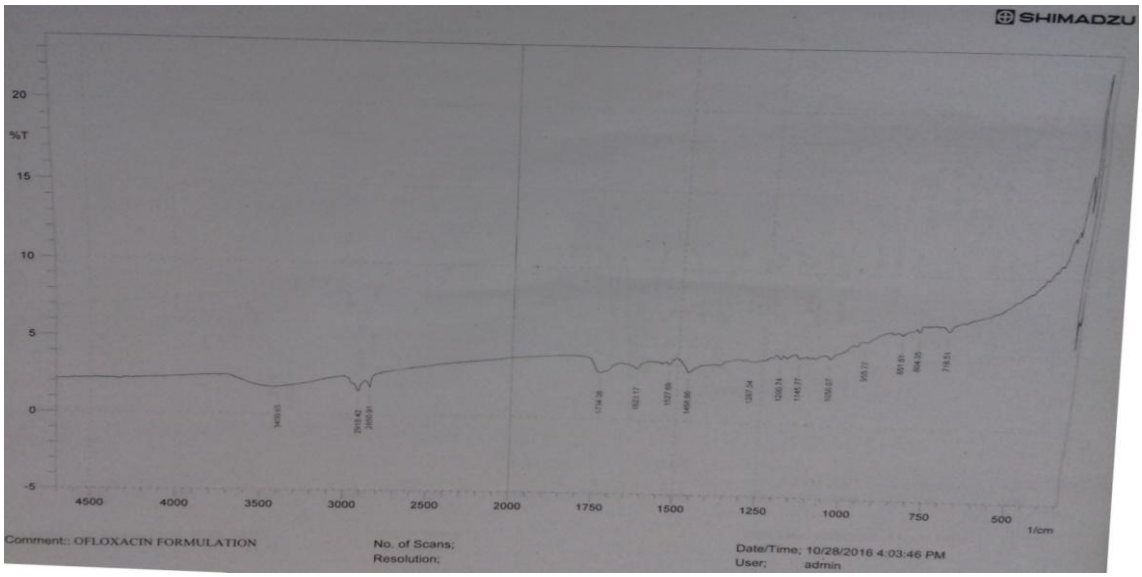

Fig 7: FT-IR spectrum of ofloxacin formulation

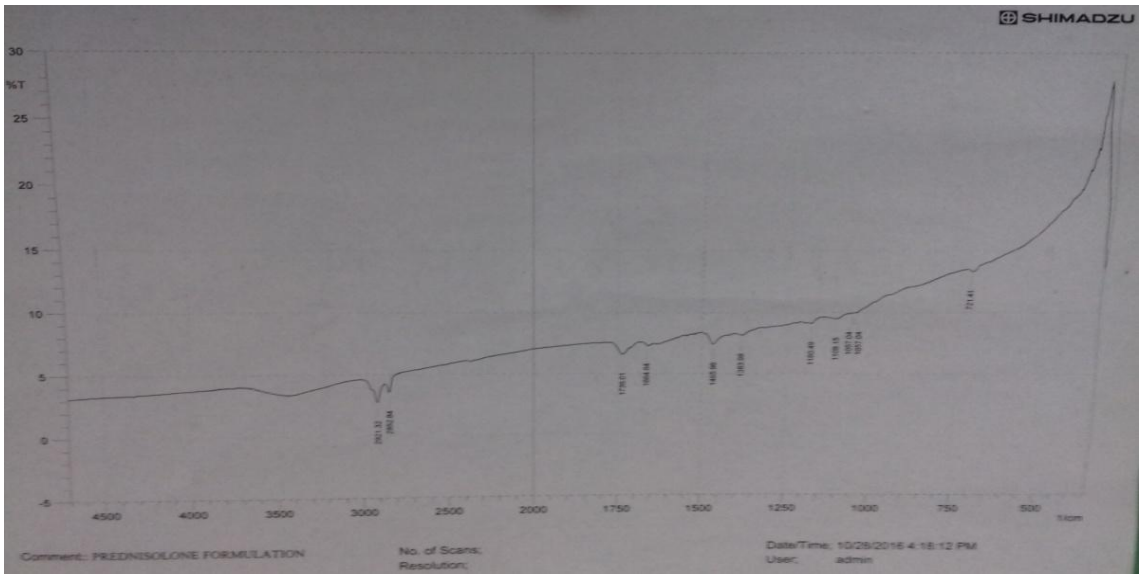

Fig 8: FT-IR spectrum of Prednisolone formulation

Evaluation of solid lipid nanoparticles

Shape and surface morphology

Shape and surface morphology of the optimized solid lipid nanoparticles of ofloxacin and prednisolone was visualized by scanning electron microscopy (SEM). The samples were coated with gold before the examination. All the particles displayed smooth surface and spherical surface. The SEM images of all the formulations are shown in figure. 9 & 10

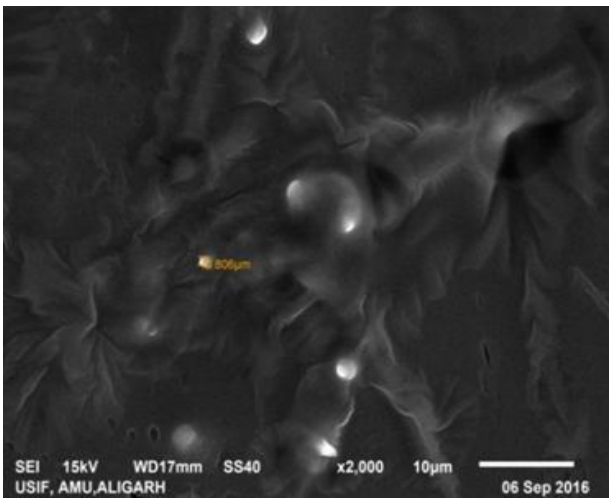

Fig 9: SEM image of ofloxacin loaded solid lipid nanoparticles

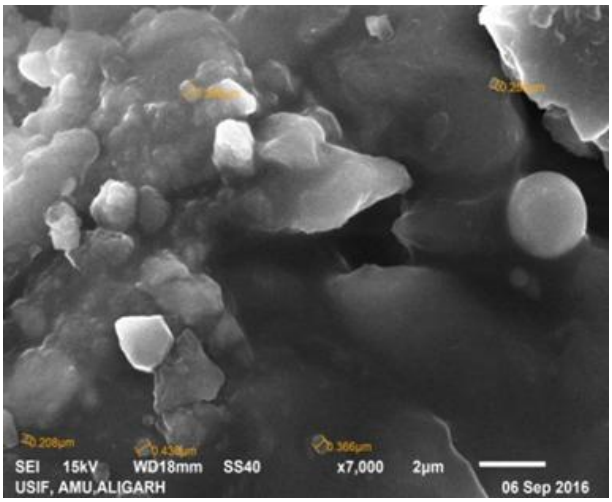

Fig 10: SEM image of prednisolone loaded solid lipid nanoparticles

Particle size and size distribution

Solid lipid nanoparticle (1ml) were diluted up to 10ml with distilled waterand average particle size and polydispersity index measured by zeta sizer. The results of ofloxacin nanoparticles are shown in table no 5 and figure no. 11.

Table 5: Partical size and size distribution of ofloxacin loaded solid lipid nanoparticles

Formulation code	Particle size (nm)	Polydispersity index (PDI)
OF1	501.7	0.258
OF2	1143	0.402
OF3	676.4	0.146
OF4	354.2	0.309
OF5	2000	-

The particle size of the formulation OF4 was found to be 354.2 nm which was least among other formulations.

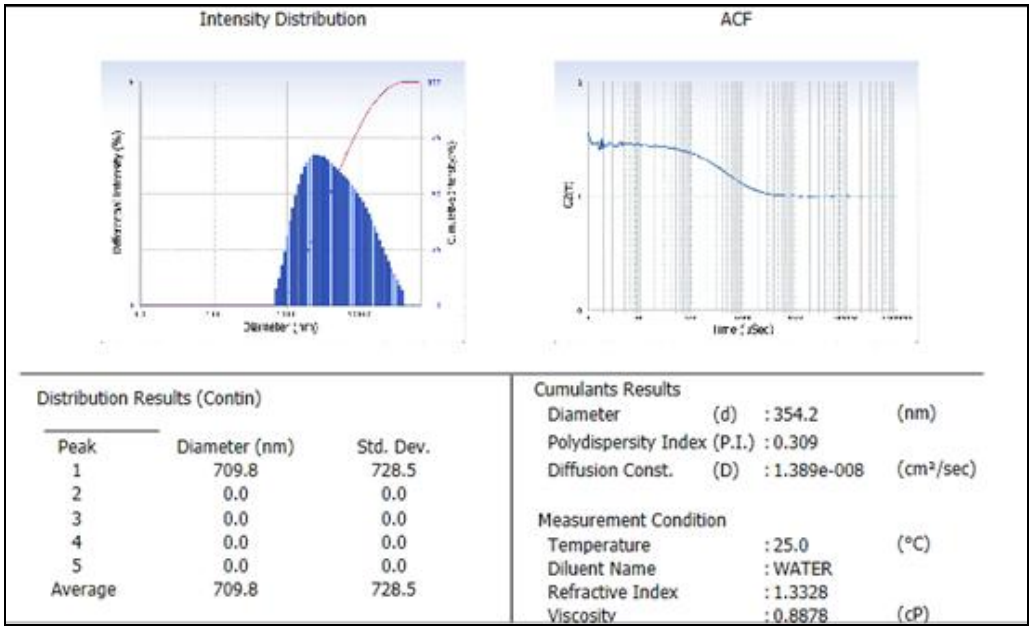

Fig 11: Graph showing particle size of OF4 formulation of ofloxacin

Zeta potential

Zeta potential is a key indicator of the stability of colloidal dispersions. The zeta potential measures the surface charge of particles. As the zeta potential increases, the particle surface charge also will be increase. Zeta potential can greatly influence particle stability in the suspension through

the electrostatic repulsion between particles. It can also determine the in vivo interaction of nanoparticles [23]. The zeta potential of OF4 formulation was found to be 13.86. The results are shown in figure no 12

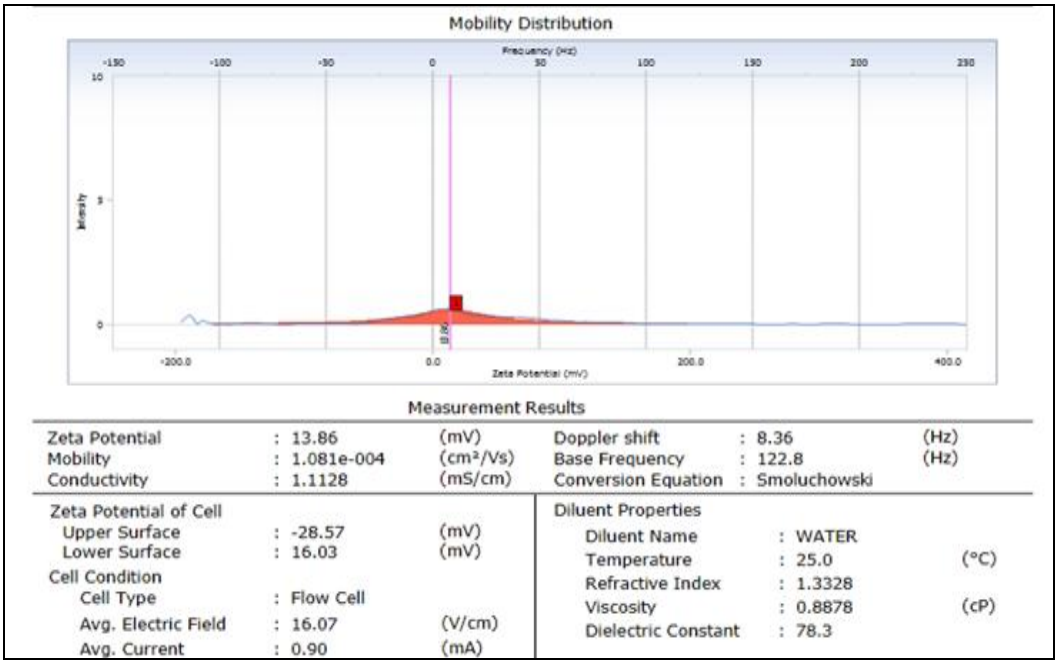

Fig 12: Graph showing zeta potential of OF4 formulation of ofloxacin

Prednisolone nanoparticles are evaluated for particle size and poly dispersity index. The results are shown in table no 6 and figure no 13.

Table 6: Particle size and size distribution of prednisolone loaded solid lipid nanoparticles

Formulation code	Particle size (nm)	Polydispersity index (PDI)
PF1	349.2	0.273
PF2	689.8	0.385
PF3	546.7	0.373
PF4	743.8	0.419

The particle size and polydispersity index of the formulation PF1 was found to be 349.2 nm and 0.273 respectively, which had least particle size and PDI.

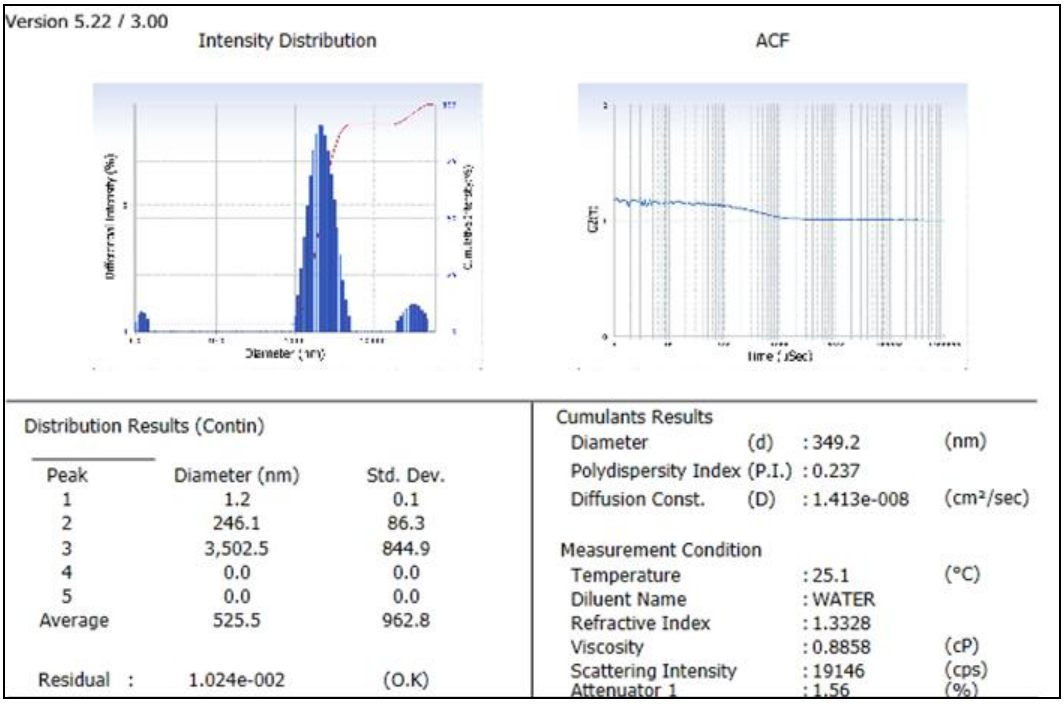

Fig 13: Graph showing particle size of PF1 formulation of prednisolone

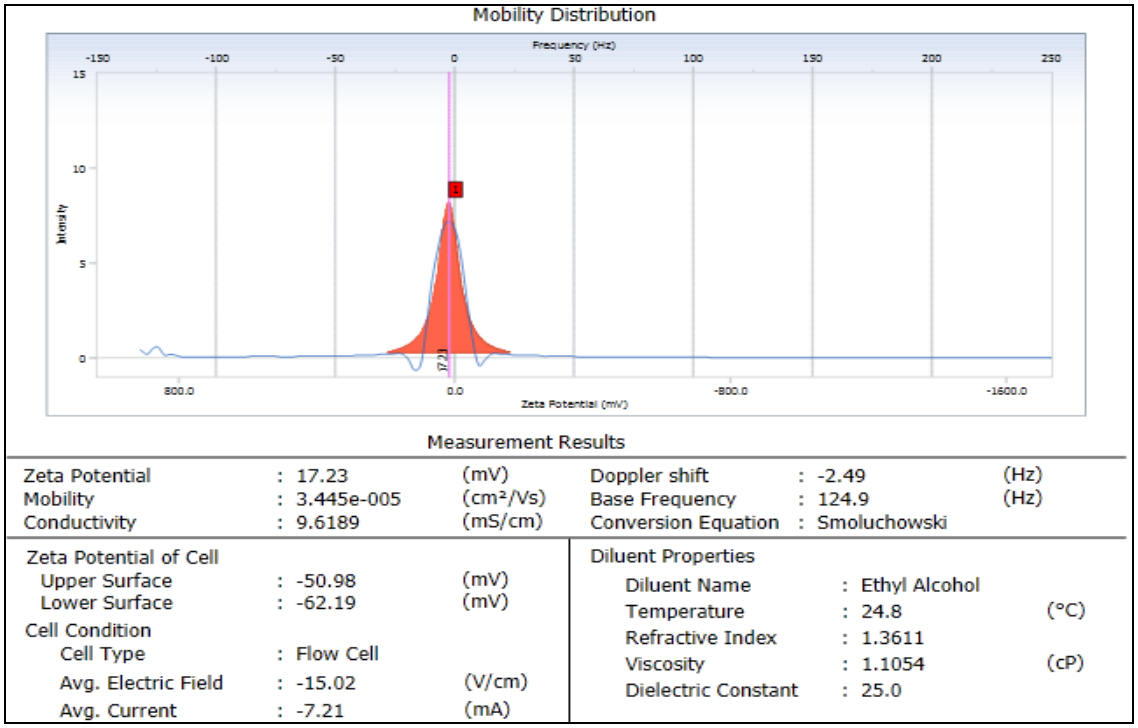

Fig 14: Graph showing zeta potential of PF1 formulation of Prednisolone

Drug content of solid lipid nanoparticles

The drug content of all formulations for ofloxacin and prednisolone showed good amount in them ranging 70-88%. The formulations had good entrapment capacity. The results are shown in table no. 7 and 3.5.

Table 7: Drug content of ofloxacin loaded solid lipid nanoparticles

Formulation	Drug content (%), mean±SD
OF1	81.28±0.212%
OF2	76.67±0.255%
OF3	81.27±0.99%
OF4	88.30±2.150%
OF5	74.87±0.537%

Value represent mean ± S.E. (n=3 in all formulations)

The drug content of the OF4 formulation of ofloxacin was found to be **88.30±2.150%.** It had maximum drug amount in it.

Table 8: Drug content of prednisolone loaded solid lipid nanoparticles

Formulation	Drug content (%), mean ± SD
PF1	84.45±0.495%
PF2	72.9 ±3.429%
PF3	71.3 ±1.131%
PF4	82.23 ±1.69%

Value represent mean ± S.E. (n=3 in all formulations)

The drug content of PF1 formulation of prednisolone was found to be 84.45±0.495% having maximum amount of drug in it.

Drug release of solid lipid nanoparticles

The drug release from formulation of ofloxacin and prednisolone were studied up to 240 minutes (4 hours), about 50% of drug released in 45 minutes by ofloxacin (OF4 formulation). The results of release of ofloxacin from formulations are shown in table no. 9 and figure no. 15.

Table 9: Drug release of ofloxacin

Time (minute)	OF1 (%release) mean±SD	OF2 (% release) mean±SD	OF3 (% release) mean±SD	OF4 (% release) mean±SD	OF5 (% release) mean±SD
0	0	0	0	0	0
10	6.43±0.643	6.3±0.424	8.12±1.054	13.1±4.101	1.8±0.071
20	10.8±1.549	14.7±1.287	16.02±0.049	28.5±1.131	7.8±0.000
30	14.4±0.424	23.6±0.361	26.4±0.495	38.2±1.626	12.8±0.354
45	23.6±1.160	34.3±1.442	43.08±0.099	50.5±0.849	24.03±1.987
60	27.9±0.877	39.5±0.750	55.2±1.061	60.11±1.485	35.2±0.071
90	36.3±0.262	43.4±1.138	59.0±0.707	71.9±1.838	62.7±0.849
120	43.6±1.146	50.0±1.860	67.5±0.990	76.7±0.141	73.4±0.212
180	53.5±0.000	53.9±0.424	71.2±4.455	82.07±2.185	79.1±1.980
240	57.8±0.813	59.7±1.492	80.4±0.778	88.5±0.071	84.7±0.212

n=3, values represent mean ±S.E.

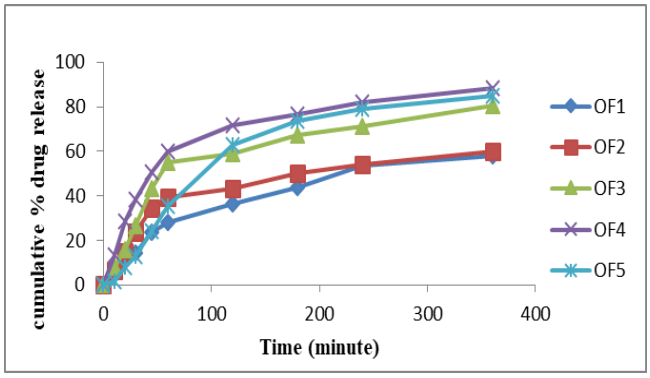

Fig 15: *In-vitro* release of ofloxacin from solid lipid nanoparticles

Prednisolone nanoparticles were assayed for drug release studies up to 240 minutes (4 hours). Drug showed sustained effect as per release rate results. The results are shown in table no. 10 and figure no. 16.

Table 10: Drug release of prednisolone

Time (minute)	PF1 (% release) mean±SD	PF2 (% release) mean±SD	PF3 (% release) mean±SD	PF4 (% release) mean±SD
0	0	0	0	0
10	11.1±2.121	13.04±0.120	10.8±0.778	9.17±0.141
20	16.1±0.000	16.2±0.424	14.9±0.212	16.03±0.007
30	30.3±2.475	19.9±1.980	18.8±0.424	25.6±0.141
45	46.9±0.000	34.1±0.926	34.5±0.849	34.3±1.273
60	55.7±1.697	41.2±0.283	44.8±1.980	36.9±0.212
90	63.6±0.849	53.15±0.382	57.5±0.078	52.08±4.426
120	76.4±0.071	68.4±0.778	67.1±1.061	59.9±1.556
180	83.3±0.071	75.9±0.707	74.8±0.354	75.0±0.636
240	85.1±0.212	83.2±2.192	80.6±1.273	84.7±0.636

n=3, values represent mean ±S.E.

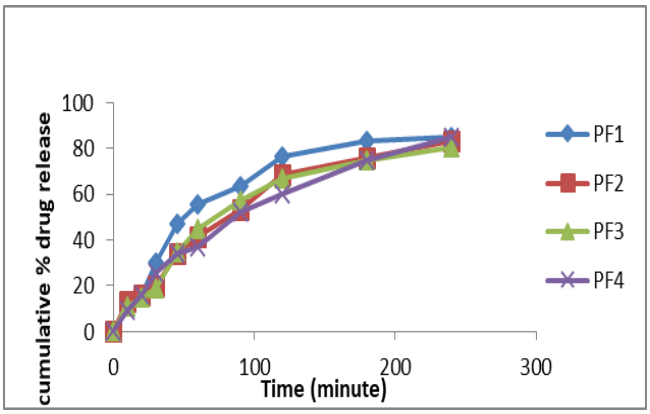

Fig 16: *In-vitro* release of prednisolone from solid lipid nanoparticles

Evaluation of gel

Ophthalmic gel containing ofloxacin and prednisolone nanoparticles was developed using HPMC as polymer. The gel was evaluated for various parameters. The results are as following:

Texture analysis

Colour: Creamy

Homogeneous: Homogenous

Spread ability: 9.56 ±0.014gm/sec

As per the result the gel was homogenous and spread easily.

pH

The pH of solid lipid nanoparticle based gel was found to be 7±0.495.

Viscosity

The two main prerequisites of a gelling system are viscosity and homogeneity. So the formulation should have an optimum viscosity that will allow easy release of drug.

The viscosity of gel was found to be 1390±4.950cps at 60 rpm at room temperature.

Drug content

The drug content of optimized solid lipid nanoparticle based gel was found to be 91.73%±0.014 (for ofloxacin) and 88.36%±0.113 (for prednisolone) respectively.

Drug release

The release studies were performed in phosphate buffer using corneal membrane of goat eye up to 240 minutes (4 hours). The drug release of optimized solid lipid nanoparticle based gel was found to be **92.73%±0.078** (for ofloxacin) and 88.7%±0.566 (for prednisolone) respectively.

Table 11: Drug release of ofloxacin and prednisolone nanoparticles loaded gel

Time (minute)	OF*(% release) Mean ±SD	PF*(% release) Mean ±SD
10	7.8±0.354	10.7±0.495
20	13.7±0.354	28.5±0.495
30	24.03±0.035	38.2±1.061
45	35.2±0.778	50.5±0.636
60	62.7±0.141	63.11±1.259
90	73.4±0.707	71.9±0.071
120	81.67±0.064	76.7±0.283
180	88.34±0.085	87.2±0.495
240	92.73±0.078	88.7±0.566

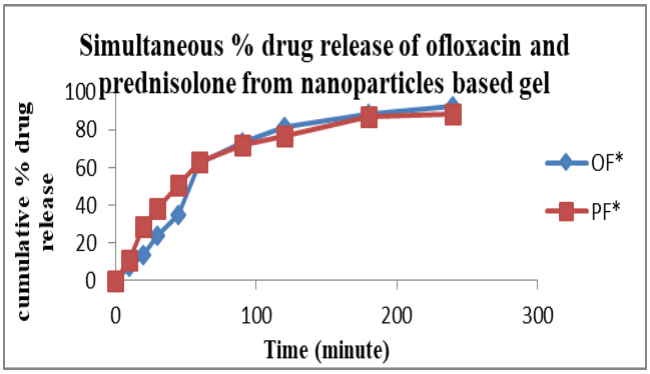

Fig 17: *In vitro* release of ofloxacin and prednisolone from ophthalmic gel

4. Conclusion

Both of the drugs ofloxacin and prednisolone are used to treat corneal infection like conjunctivitis. Ofloxacin is a fluroquinolone and widely used to treat the eye infections. Prednisolone is a corticosteroidal drug and can be used to treat various corneal diseases and inflammation either alone or in combination with antibiotics. Both the drugs could be successfully formulated as solid lipid nanoparticles. Formulation containing surfactant span 20 was in nano range. Formulation without span 20 had higher particle size. Formulation OF4 & PF1 were smallest in particle size. All the formulation was stable and redispersible as PDI was less than 1 with all formulation of ofloxacin and prednisolone. Zeta potential when assessed showed that formulation were stable. In terms of drug content of OF4 contained 88.30 ±2.150% of drug while that of prednisolone formulation PF1 was found to be 84.45±0.495% of drug which were highest in comparison to other formulations. In terms of release formulations OF4 & PF1 showed highest drug release for drugs ofloxacin and prednisolone respectively It can be concluded that solid lipid nanoparticles loaded gel formulation has potential for corneal diseases and can be further used for the development as marketed formulation.

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6. Conflict of Interest

The authors have no any kind of conflict of interest.

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