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Research Article

FORMULATION AND EVALUATION OF NOVEL ANTI-BACTERIAL CIPROFLOXACIN LOADED NIOSOMAL CREAM

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ABSTRACT

The development of Ciprofloxacin loaded niosomes using combination of Span-60 and Lipotin A, to increase the local effect of Ciprofloxacin on the bacterial infected skin. Ciprofloxacin encapsulated niosomes were formulated by thin film hydration technique using rotary vacuum evaporator and were incorporated into cream base. The formulation was optimized by changing the ratio of Span 60 and Lipotin A, based on maximum entrapment efficiency and drug retention using ex-vivo drug diffusion study. The selected optimized formulation was subjected to in-vitro study and antibacterial activity study which was compared with the conventional Ciprofloxacin cream. Ciprofloxacin loaded Niosomal cream with 70-90% entrapment efficiency was successfully developed using combination of span60 as non-ionic surfactant and Lipotin A as a dispersing agent. The optimized Ciprofloxacin loaded niosomal cream was found to show maximum drug retention with 71.49% within 12 hours, which has been require for local effect. It also provided more antibacterial activity and sustained release of drug by *in-vitro* study with 46.22% diffusion within 8 hours, as compared to conventional Ciprofloxacin cream. Thus, the developed Ciprofloxacin loaded niosomal cream was considered to be an enhanced topical delivery of ciprofloxacin through skin with sustained action, with maximum retention for prolong effect and thereby, providing successful local treatment of various bacterial skin infections.

Keywords: Niosomes, Ciprofloxacin, antibacterial activity, skin retention, sustained release, topical, improving local effect.

INTRODUCTION

Bacterial skin infections like cellulitis, folliculitis and impetigo are caused by susceptible *Staphylococcus aureus*. Cellulitis mainly affects the dermis and subcutaneous fat of skin and their symptoms include an area of redness and the skin may be swollen.[1] Folliculitis means an infection of the hair follicles of the skin. In folliculitis, many hair follicles in one area of the skin are affected. The affected hair follicles swell into small pus-filled pimples.[2] Impetigo may present in two forms: small vesicles with a honey-colored crust or discrete purulent lesion. Impetigo usually occurs on exposed areas of the body, most frequently the face and extremities. The lesions remain well-localized but which are frequently multiple and may be either bullous or non-bullous in appearance. Bullous lesions appear initially as superficial vesicles that rapidly enlarge to form flaccid bullae filled with clear yellow fluid, which later becomes darker, more turbid, and sometimes purulent. The non-bullous lesions begin as papules that rapidly evolve into vesicles surrounded by an area of erythema and then become pustules that become enlarge and break down over a period of 4–6 days which form characteristic thick crusts.[3]

Ciprofloxacin can use to treat the bacterial skin infections like folliculitis, cellulitis, impetigo affected by mainly *Staphylococcus aureus.* Also due it low molecular weight (331.4 Da) and its moderate lipophilicity (log p= 0.28), [6] Ciprofloxacin was selected as a good candidate for the study. But there are limitations to use this antibacterial drug for topical skin infection treatment. The main reasons behind this are the poor skin retention and low permeability of the stratum corneum layer in the skin.[7] In 1992 Vogt studied the antibacterial activity of the topical quinolones against bacteria commonly found in acne vulgaris in vitro.[8] Ciloxan ophthalmic solution is approved by FDA for the treatment of infections caused by specific microorganisms in the conditions of corneal ulcers and conjunctivitis.[9]

Topical formulation requires the novel vesicular carriers system to deliver the poorly permeable drug through the skin. Niosomes are one of the novel vesicular drug delivery system, a non-ionic surfactant based vesicles of the alkyl or dialkyl polyglycerol ether class with cholesterol,with subsequent hydration in aqueous media.[10] These niosomes can entrap both the hydrophilic as well as lipophilic drug[11].Usually niosomes are made up of non-ionic surfactant bilayer and liposomes are made up of phospholipid bilayer,[12-13] but here we developed niosomes which are made of both non-ionic surfactant as well as phospholipid bilayered by combination of Span 60 (Sorbitan monostearate) as a non-ionic surfactant and Lipotin A (a compound of Soya lecithin as a Phospholipid with ethoxylated coco fatty acid), to enhanced better entrapment, skin retention, sustained activity and permeation ability of drug on the upper stratum corneum layer of skin. Topical niosomal formulation is biocompatible, relatively non-toxic and readily permeable through the biomembrane. Also due to lower drug doses, it reduces systemic side effects of the drug as compared to oral route.[14-15] Ciprofloxacin (anti-bacterial drug) has ability to treat various bacterial skin infections caused by *Staphylococcus aureus* and *Pseudomonas aeruginos,* but the poor skin retention and the low local permeation rate due to stratum corneum barrier of the skin thereby resulting in poor local effect.Since the use of niosomes to enhance topical skin delivery of ciprofloxacin an antibiotic agent has not been investigated yet. Hence in order to achieve this goal, Ciprofloxacin loaded niosomal cream were prepared with combination of Span-60 and novel Lipotin A by using suitable thin film hydration technique. Thus, it enhance the local bioavailability, permeation ability, sustained release activity and increase residence time of drug on the skin, with complete eradication of bacterial pathogens of skin infection.

MATERIALS AND METHODS

Ciprofloxacin was received as gift sample from DR. Reddy's, Mumbai. Lipotin A (combination of soya lecithin and ethoxylated coco fatty acid) was received as gift sample from Evonik industries, Mumbai. Span 60 (Sorbitan monostearate) was received as gift sample from Mohini chemicals Pvt. Ltd, Mumbai. Cholesterol was purchased from Qualigen chemicals Pvt Ltd. All other ingredients like chloroform, sodium acetate, glacial acetic acid etc, were purchased from S.D. Fine chemicals, Mumbai.

Preparation of Niosomes

Niosomes were developed by using Thin film hydration technique by rotary vacuum evaporator. Surfactant (span 60) + lecithin + cholesterol (2:1:0.5 ratio) were weighed accurately and dissolved in round bottom flask containing chloroform-methanol mixture (2:1) together with glass beads. This round bottom flask (RBF) was connected to the rotary vacuum evaporator, and then vacuum was applied. The RBF was rotated at 150rpm and the bath temperature was maintained at 28˚C tocompletely evaporate chloroform until the dried solid thin lipid film was deposited on the wall of flask. This dried film was then hydrated by addition of acetate buffer pH 5.5 containing dissolved drug. This hydrated solution mixture was agitated at 60˚C for 1 hour, in order to ensure complete hydration of film. Then obtained niosomes dispersion was sonicated using bath sonication for 2 min to reduce the particle size.[16] Thus the niosome dispersion was formed and was stored at 4^0C overnight for further characterization. The niosome dispersion was centrifuged and the niosomes pellets were separated.[17]

Preparation of w/o Cream base: Accurately weighed quantity of ingredients in oil phase such as liquid paraffin, cetostearyl alcohol, white bees wax and propyl paraben were taken in one beaker and aqueous phase ingredient such as borax was taken in another beaker containing adequate water and both this beakers containing different phases were heated on water bath till 75 ^{0}C temp and at this temperature point, the oily phase was added to aqueous phase with constant stirring. Stirring was continued till room temperature is attained and cream base was formed.

Incorporation of Niosome in w/o cream base: Adequate quantities of cream base and Niosome were mixed on tile using geometric mixing pattern part by part.

Optimization of niosome formulation

The niosomal formulations prepared with combination of Span-60 and Lipotin A were subjected to optimization base on their entrapment efficiency as well as ex-vivo drug diffusion study and there ratios were varied to optimize the formulation so as to get maximum entrapment efficiency and skin retention. Some formulations prepared without Lipotin A were also subjected to optimization and compared with the formulations containing Lipotin A. So as to verify the best optimized niosomal formulation.

Characterization of ciprofloxacin niosomes

Particle size: Particle size of Ciprofloxacin niosomes was performed using Digital electronic microscope with Motic image analyser. Niosomes were spread on a glass slide and observed under the microscope for particle size and shape determination. Also the particle size distribution and polydispersity index were measured by Particle size analyser (Malvern instrument).

Zeta potential: The zeta potential of Ciprofloxacin niosomes was measured by using a Zetasizer, (Malvern Instrument). The samples were placed in electrophoretic cell and measured in the automatic mode.

Surface morphology by Scanning Electron Microscopy (SEM)

The morphological observation of Ciprofloxacin loaded niosomes was performed to analyze the size, size distribution and shape of the Niosomes vesicles by Scanning Electron Microscopy (SEM) after sufficient dilution with distilled water.[18]

Differential Scanning electron Microscopy (DSC)

Ciprofloxacin loaded niosomal formulation was analyzed by Differential scanning calorimeter [Heat flux-SII Nanotechnology]. The sample (10mg) was placed in aluminium pans and sealed. Heat runs were set from 172-725^{0}C using nitrogen as a blanket gas. The thermogram of niosomal formulation containing Ciprofloxacin was obtained at scanning rate of 10^0C/min and compare with the thermogram of pure Ciprofloxacin drug.

In-vitro drug diffusion study

In-vitro drug release of ciprofloxacin niosomal cream was determined by using Franz diffusion apparatus. Acetate buffer pH 5.5 was used as diffusion medium. Dialysis membrane was mounted on Franz diffusion cell in between the donar and the receptor compartment. The antibacterial niosome cream and conventional cream were separately placed over the dialysis membrane on two separate diffusion cell. The temperature of the diffusion medium was maintained at 37±1ºC by a thermostatic arrangement. Sink conditions were maintained by magnetic stirring at 600-800rpm. Aliquots of 2ml were withdrawn at predetermined time intervals and replenished by equal volumes of fresh diffusion medium. Withdrawal of sample aliquots was carried out for a period of 8hrs. The drug concentration in the withdrawn aliquots was determined by UV spectrophotometric at λmax 274 nm and was calculated using standard calibration curve.[19]

Ex-vivo drug diffusion study

Ex-vivo skin diffusion study of ciprofloxacin niosomal cream was performed on porcine ear skin. The excised skin membrane was mounted on Franz diffusion cell after thorough washing with hot distilled water and removal of subcutaneous fats. Acetate buffer pH 5.5 was used as diffusion medium. The niosomal cream and conventional cream were applied over the two separate skin membrane. The temperature of the diffusion medium was maintained at 37±1ºC by a thermostatic arrangement. Sink conditions were maintained by magnetic stirring at 600-800rpm. Aliquots of 2ml were withdrawn at predetermined time intervals and replenished by equal volumes of fresh diffusion medium. Withdrawal of sample aliquots was carried out for a period of 8hrs. The drug concentration in the withdrawn aliquots was determined UV spectrophotometrically λmax 274 nm and was calculated using standard calibration curve. At the end of 24 h, the skin was cut, homogenized and extracted with acetate buffer pH 5.5 which was suitably diluted and was analyzed spectrophotometrically to evaluate retention of drug in skin. Ciprofloxacin flux through the skin was calculated by plotting the cumulative amounts of drug penetrating the skin against time and determining the slope of the linear portion of the curve and the χ-intercept values (lag time) by linear regression analysis. Drug fluxes ($\mu g/cm^2\ h^{-1}$), at steady state, were calculated by dividing the slope of the linear portion of the curve by the area of the skin surface through which diffusion took place. At the end of 24 h, the skin was cut, homogenized and extracted with methanol and suitably diluted and analyzed spectrophotometrically to evaluate retention of drug in skin.[20]

Entrapment efficiency: Ciprofloxacin niosomes dispersion was centrifuged and the niosomes pellet was separated. The 50mg niosomes pellet was weighed and added to 10ml volumetric flask containing acetate buffer pH 5.5 and sonicated for 1hour. Then appropriate dilution was made to get absorbance below 1 according to Bear's lamberts law. The absorbance was recorded at 274 nm using UV spectroscopy and content of entrapped drug as well as percentage of entrapment efficiency was calculated using following formula given below:

% Entrapment Efficiency of Ciprofloxacin Niosomes = Weight of entrapped drug × 100 / Weight of total amount of drug

Drug content determination: Ciprofloxacin in Niosome based cream was measured by dissolving known quantity of cream in 50% ethanol with acetate buffer pH5.5 and recording the absorbance at 270nm using UV-visible spectrophotometer.

Antibacterial activity

Protocol: The Nutrient agar media was used. *Staphylococcus aureus* micro-organism culture was used. Incubation time was setup for 24 hours. Method: Agar bore well diffusion / cup-plate method. Procedure: *Staphylococcus aureus* suspension (100µl) was introduced in each plates and 40ml of sterile nutrient agar media was poured into each sterilized plates.The plates were agitated carefully to allow for even distribution of the agar in the plates and a homogenous mixing of the agar with the test organism.The plates were left on a flat solid surface and allowed to harden.In each plate 1 cup, 10mm in diameter was bored in the medium with cork borer. The disks of agar were removed by sterilized dissecting needle while being careful not to damage the cups.In each plate, equal amount of prepared niosomal cream formulation and conventional cream formulation, having same strength was placed in the cup and the plates were incubated at$37^0C\pm2^0C$ for initially 8hoursthen after 24 hours in B.O.D. incubator.The entire operation was carried out under aseptic conditions and mean zone of inhibition was calculated from 4 plates. The zone of inhibition obtained for the prepared formulation was compared with that of the conventional formulation to assess the efficacy of the prepared formulation.[21-22]

Skin-irritation study

Skin irritation study of niosomal cream was carried out on male Albino Wistar rats using Draize's patch test method as per OECD guidelines. [Institutional Animal Ethics Committee (IAEC) approval no.CPCSEA/IAEC/BNCP/P-40/2015].The animals were housed in propylene cages, with free access to standard laboratory diet and water.Animals were acclimatized for 7 days before experimentation. Hair was removed from dorsal side of rats, 24 hrs prior to the application of the formulation.Formulation containing 5-10mg of drug was applied on the shaved skin of rats by uniform spreading within area of $4cm^2$ and the site of application was occluded with cotton bandage.The applied formulation was removed and the skin was observed visually for changes such as erythema (redness). [22-23]

RESULTS AND DISCUSSION

Particle size and zeta potential

Thin film Hydration method gives large, heterogenous multilamellar vesicles. Initially vesicles size analysis was revealed Z-average (d-nm) size of 4000nm with high Polydispersity Index (PDI) of 0.92 but good entrapment efficiency was achieved. Techniques such as Ultra Turrax and high pressure homogenization (HPH) were carried out to obtain size reduction and narrow size distribution i.e. lower PDI. The results indicated satisfactory size reduction and low PDI Fig. 16 but affected the entrapment efficiency adversely which could be due to vesicle rupturing at high pressure and speed. Hence, Bath sonication was used for further batches which gave vesicles in the size range of 200 to 300 nm. The particle size and polydispersity index of optimized formulation were found to be 217.6 nm and 0.285 respectively. The zeta potential of optimized F4 formulation was found to be -53.5 mV.

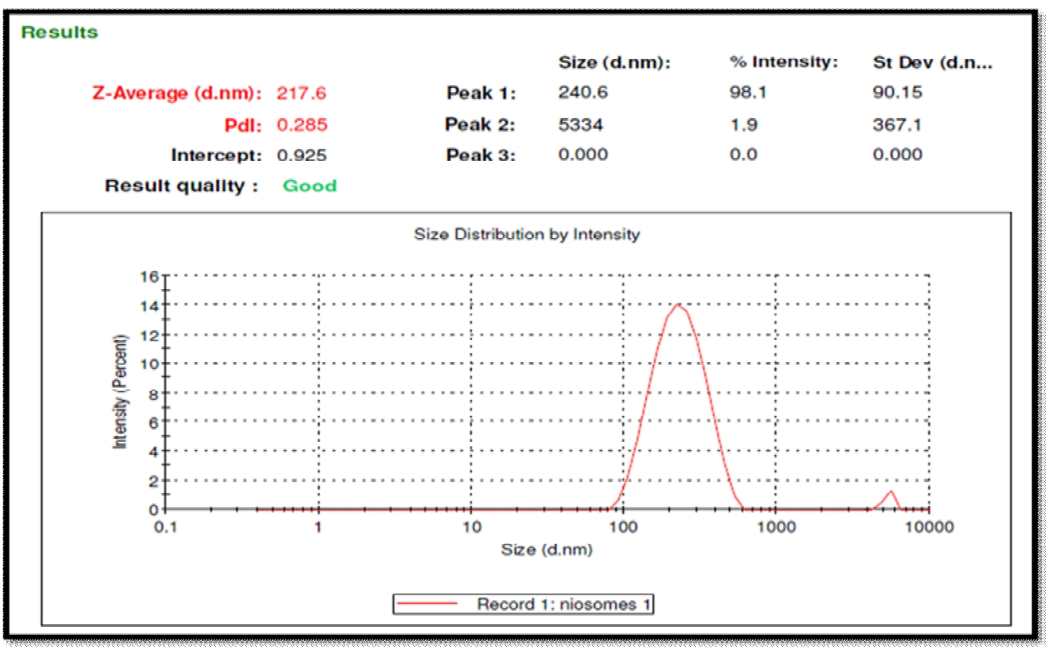


Figure 1: Graphical representation of Particle size of optimized Ciprofloxacin niosomal dispersion

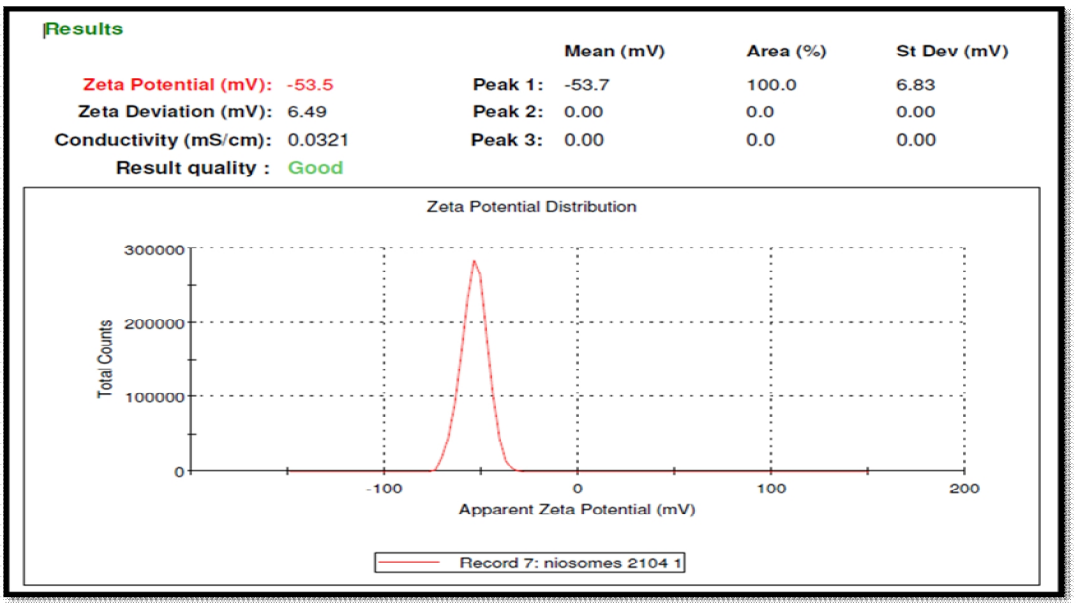
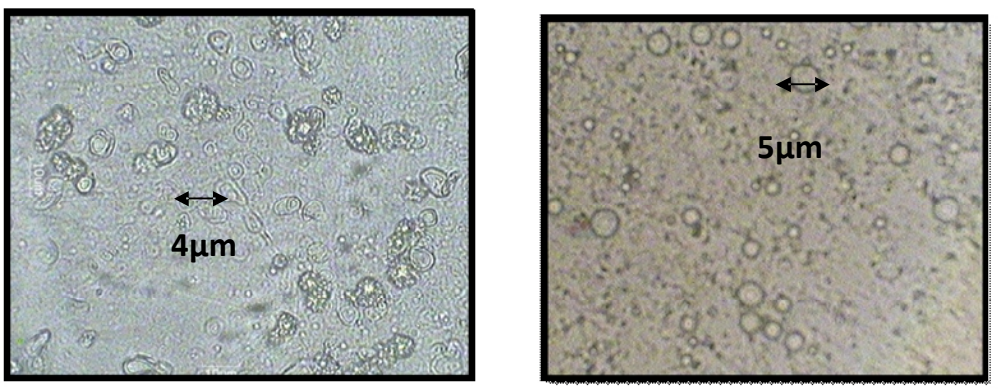


Figure 2: Graphical representation of zeta potential of optimized ciprofloxacin loaded niosomes

Motic Microscopy

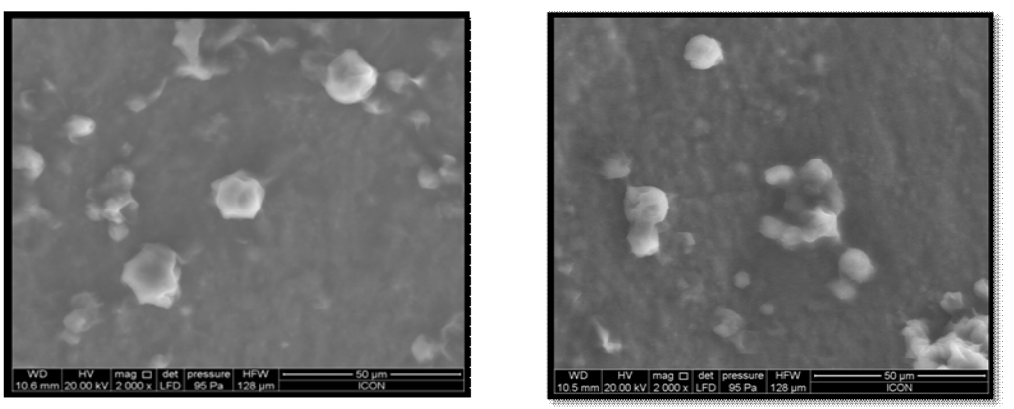
The motic microscopic images of Ciprofloxacin loaded niosomal dispersion was found to shows multilamellar spherical vesicles in the size range of 2 µm to 5 µm. The sample 1 showed the multilamellar irregular niosomes vesicles and sample 2 showed the unilamellar spherical niosomes vesicles.



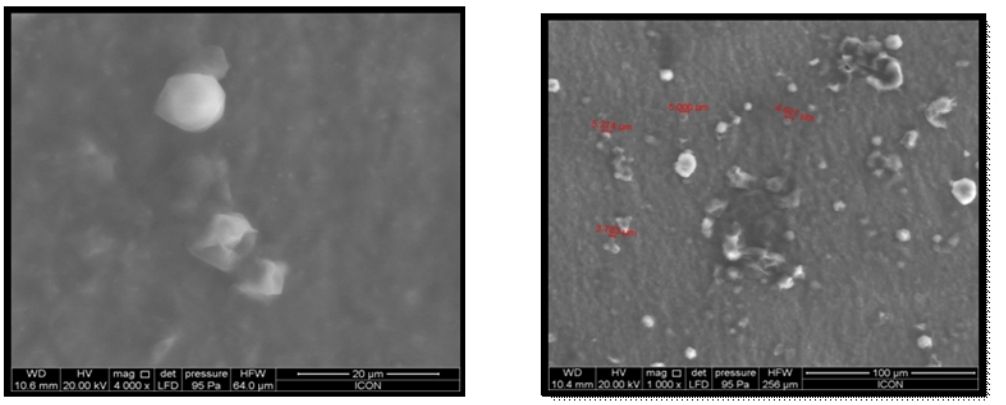
a) Sample 1 b) sample 2

Figure 3: Motic microscopy images of optimized Ciprofloxacin loaded niosomal dispersion

Scanning Electron Microscopy



a) Sample 1 b) Sample 2



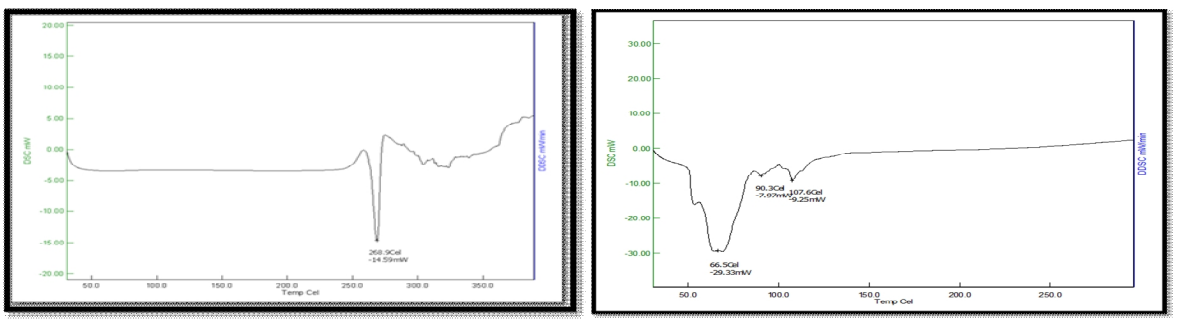
c) Sample 3 d) Sample 4

Figure 4: Scanning Electron Microscopy of Ciprofloxacin loaded niosomal dispersion

The SEM images of sample 1 showed homogenous Spherical bulb shape niosomes vesicles with magnification of 2000 x, sample 2 showed heterogenous as well as homogenous irregular spherical bulb shape vesicles with magnification of 2000 x, sample 3 showed clear spherical bulb shape niosomal vesicle with magnification of 4000 x, and sample 4 showed small spherical as well as irregular niosomal vesicles with magnification of 1000 x.

Differential scanning colorimetry (DSC)

The DSC thermogram endothermic peak of ciprofloxacin drug was disappeared in Ciprofloxacin loaded niosomal dispersion which ensures the drug is completely encapsulated and homogenously dispersed in the niosomes.



(a) (b)

Figure 5: (a) DSC spectrum of pure ciprofloxacin drug and (b) DSC spectrum of Ciprofloxacin loaded loaded niosomal dispersion

Optimization of Ciprofloxacin loaded niosomal cream

Table 1: Optimization of Ciprofloxacin loaded niosomal formulation

Batch No.	Drug (mg)	Surfactant (span 60) : Cholesterol	Soya Lecithin with ethoxylated coco fatty acid	Batch size (ml)	% Entrapment efficiency for sediment	% Drug diffused within 12 hours	% Drug Retained
F1	20	1:1	----	50	52	32.86	49.37
F2	20	2:1	----	50	63	45.21	51.46
F3	20	1:0.5	2	50	72	19.44	64.8
F4	20	2:0.5	1	50	86	12.62	71.49

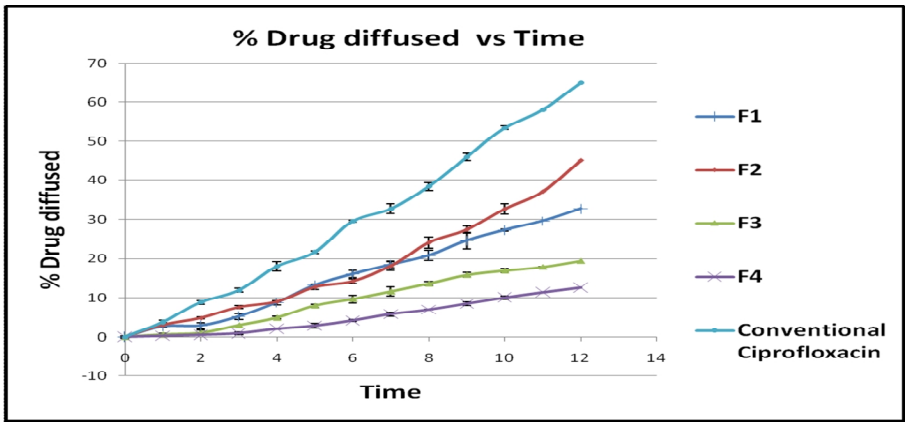


Figure 6: Comparative ex-vivo drug diffusion profile of different Ciprofloxacin loaded niosomal cream compared with conventional Ciprofloxacin cream within 12 hours

All formulation batches of Ciprofloxacin loaded niosomal cream i.e. F1, F2, F3 and F4 showed sustained release activity as compared to conventional Ciprofloxacin cream by ex-vivo drug diffusion study.

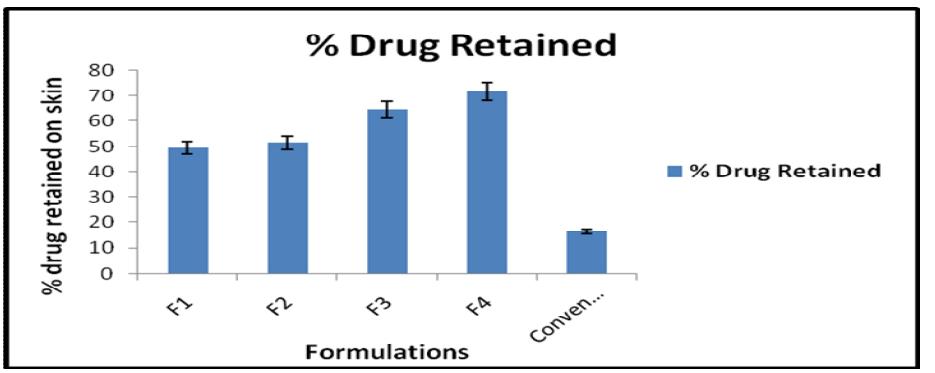


Figure 7: Bar interpretation of comparative % Drug retention study of different Ciprofloxacin loaded niosomal cream with conventional cream

From the above graphs, it was observed that the formulation F4 containing Span-60, Lipotin A and cholesterol combination (2:1:0.5 ratio), showed maximum entrapment efficiency and drug retention as compared to other formulations. The formulation F3 containing Span-60, Lipotin A and cholesterol combination (1:1:0.5 ratio), showed lesser entrapment efficiency and drug retention as compared to F4. The formulation F1 and F2 which made up of Span-60 and cholesterol combination without Lipotin A, showed least entrapment and drug retention. Therefore F4 was selected as the optimum formulation as it showed maximum entrapment of drug and drug retention for local effect on skin infection site.

The flux and permeability coefficient of optimized formulation F4 were found to be 556 µg cm^{-2} cm^{-1} and 0.216 cm hrs^{-1} respectively.

***In-vitro* drug diffusion study**

Table 2: In-vitro study of niosomal Ciprofloxacin cream compared with conventional Ciprofloxacin cream

Time	Niosomal ciprofloxacin cream		Conventional ciprofloxacin cream	
	Mean	Standard deviation	Mean	Standard deviation
0	0	0	0	0
1	5.508	0.383	7.517	0.316
2	9.499	0.239	11.15	0.853
3	17.14	0.770	24.97	0.518
4	21.32	1.04	36.92	0.349
5	23.94	0.74	45.42	1.011
6	27.63	0.33	53.11	0.682
7	38.50	1.647	56.58	0.567
8	46.22	1.282	65.81	0.438

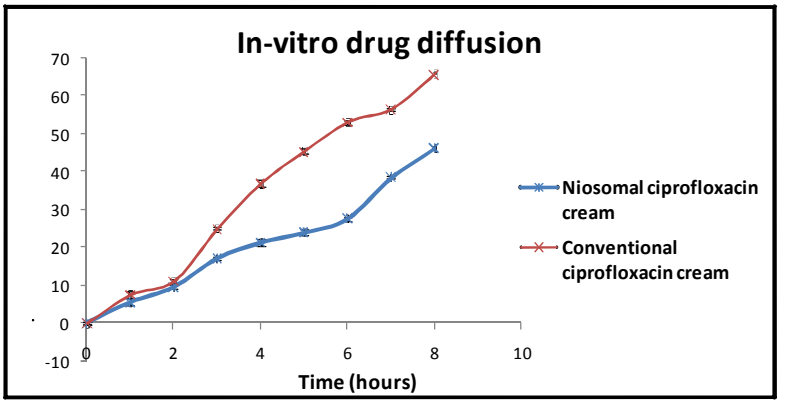
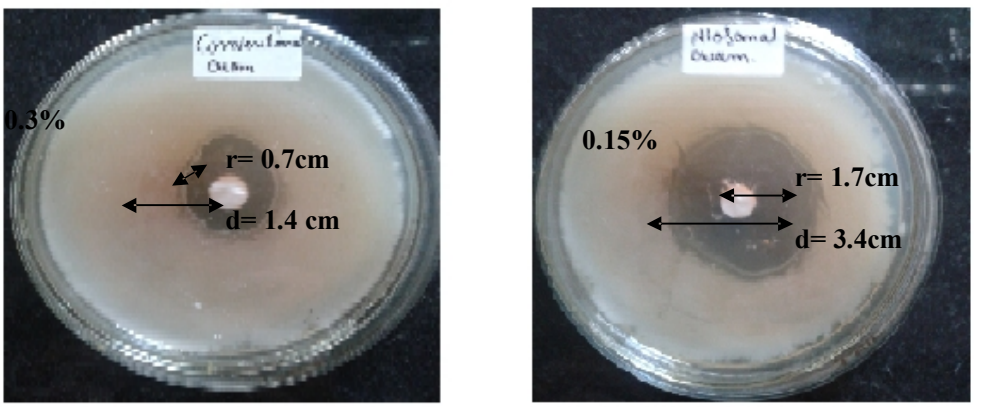


Figure 8: *In-vitro* drug diffusion study of Ciprofloxacin loaded niosomal cream compared with the conventional ciprofloxacin

The % drug diffused of Ciprofloxacin loaded niosomal cream and Conventional Ciprofloxacin cream within 8 hours were found to be 46.22% and 65.81% respectively. Thus it indicates that Ciprofloxacin loaded niosomal cream was shown more sustained release as compared to conventional Ciprofloxacin cream by In-vitro drug diffusion study (Figure 8).

Antibacterial activity study

The ciprofloxacin loaded niosomal cream was found to show more antibacterial activity as compared to the conventional Ciprofloxacin cream. Initially i.e. after 8 hrs there was a sharp increase in the zone of inhibition incase of conventional cream as compared to niosomal cream. This is because the niosomal cream releases the drug at a slower rate and which act on the *Staphylococcus aureus*. After 24 hrs, the zone of inhibition was more in case of niosomal cream indicating controlled release of the drug from the niosomes.



a) Zone of inhibition of Conventional Ciprofloxacin cream in *Staphylococcus aureus culture*
b) Zone of inhibition of niosomal Ciprofloxacin cream in *Staphylococcus aureus culture*

Figure 9: Comparative Zone of Inhibition of Ciprofloxacin loaded niosomal cream and conventional Ciprofloxacin cream

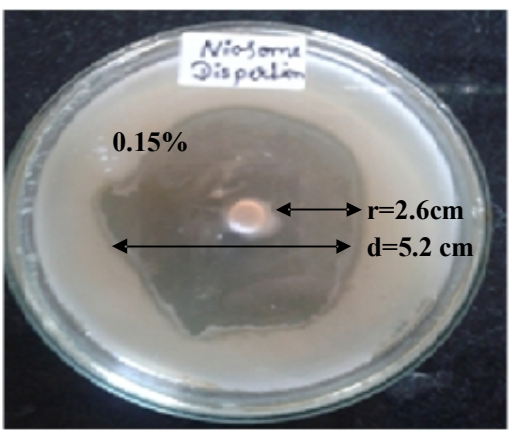


Figure 10: Zone of inhibition of Niosome containing Ciprofloxacin dispersion in *Staphylococcus aureus* culture

Table 3: Comparative Zone of Inhibition of Ciprofloxacin loaded niosomal cream and conventional Ciprofloxacin cream

S. no.	Sample	Drug concentration	Quantity of sample	Zone of Inhibition	
				Radius (r) n=3	Diameter (d) n=3
1	Conventional Ciprofloxacin cream	0.3%	0.25g	0.7 cm	1.4 cm
2	Niosomal Ciprofloxacin cream	0.15%	0.25g	1.7 cm	3.4 cm
3	Niosomal dispersion	0.15%	0.1ml	2.6 cm	5.2 cm

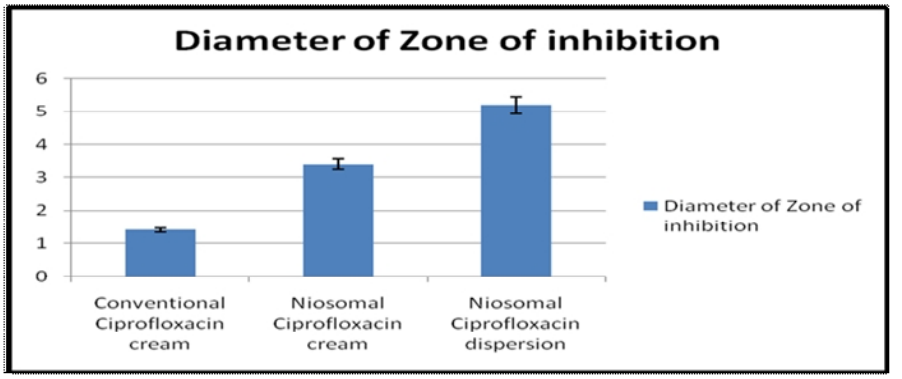


Figure 11: Bar interpretation of Zone of inhibition indicates there is maximum zone of inhibition of ciprofloxacin loaded niosomal cream as compare to conventional ciprofloxacin cream

Skin irritation study

Skin irritation study was conducted on male Wistar albino rats and was observed for skin sensitivity reaction at the end of 12, 24, 48 and 72 hours showed absence of erythema, edema or no signs of rashes and reddening on the dorsal surface of rat, after application of niosomal formulation which was compare with control one. This indicates that prepared formulations do not cause any skin irritation with right choice of ingredients and the niosome formulation was suitable for human application with high safety and efficacy profiles.

CONCLUSION

The encapsulation of Ciprofloxacin into niosomal cream formulation improved skin retention which is require to provide prolonged local effect on the skin infection site for the complete eradication of bacterial infection. Ciprofloxacin loaded niosomes with 86% entrapment efficiency and 71.49% drug retention were successfully developed using combination of Span-60 as non-ionic surfactant and Lipotin as a dispersing agent by thin film hydration method. The optimization of Ciprofloxacin loaded niosomal cream was done on the basis of ex-vivo drug diffusion study. The formulation batch F4 was selected as optimum batch showing 12.62% drug diffusion within 12 hours and 71.49% drug retention, which is necessary for local effect. Invitro drug diffusion study showed sustained release of Ciprofloxacin from Niosomes for 8 hours as compared to conventional. These niosomes vesicles provided better local depot which slowly increases the skin permeation of drug into upper stratum corneum layer of skin and also increased the retention on that site, which indicate prolonged action. Thus, the use of niosomes may be considered as a promising non-invasive, safe, efficacious and non-toxic approach for enhancing topical delivery of Ciprofloxacin through skin, and thus, providing successful local treatment of various bacterial skin infection.

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