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Research Article

FORMULATION AND IN-VITRO EVALUATION OF NIOSOMAL GEL OF GATIFLOXACIN

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ABSTRACT

A novel drug delivery system provides the delivery of drugs at a required rate into the body during the period of treatment as directed by the body. Formulation and evaluation of Noisome containing gatifloxacin using different concentrations of the polymer for controlled release. Pre-formulation study confirms the purity of the drug and compatibility of the drug with excipients using FT-IR. Tween 80 was found significant with the experimental results. An extensive investigation is needed concerning the depth of penetration into the skin, determination of zeta potential, and confirmation of configuration of phospholipids in the lipid bilayer. A significant loss of entrapped drug was found at the end of three month period when liposomal dispersions were stored at high temperature i.e. 25±20C. All gels were found under pH range 7.0 to 7.4, Spreadability under the range 6.6 to 7.6 cm, % drug content 98 to 100%, the viscosity of gels 98 to 115cp, and % permeation found in rage 75 to 91%. Excellent % Permeation Gel formulation GF-4 was found 91%. The drug release at raised temperatures may be associated with the lipid degradation in the bilayers results in membrane packing defects them leaky.

Keywords: Gatifloxacin, Noisome, Gel, lipophilic nature, entrapped drug.

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INTRODUCTION

Novel drug delivery system supplies drugs at an essential rate during the period of treatment into the body and in the direction of the body[1]. Recently, vesicles have been examined extensively due to their flexibility and development on remedial effectiveness of traditionally well-recognized drugs by given that controlled and sustained delivery. Drug encapsulation into the vesicles has the advantage to improve bioavailability that's why investigators attract towards the starting of some liposomal formulations [2]. However, their widespread use is still constrained by their own intrinsic chemical instability and higher cost. A Noisome is a non-ionic surfactant-based Vesicle (biology and chemistry). Mostly, Niosomes are prepared by using cholesterol and non-ionic surfactant as an excipient, also other various excipients may be used. Niosomes possessed more penetrating potential than other preparations. Niosomes are structurally analogous to liposomes in bilayer presence, however, materials utilized to formulate niosomes that make them more stable. Niosomes offer several advantages over liposomes. Niosomes are constructed containing lamellae that are microscopic in size[3].

Topically, niosomes are used for transdermal, ocular, targeting, Immunological, peptide delivery and so many types of other formulations. Gatifloxacin is a fluoroquinolone derivative that belongs to the fourth-generation of antibiotic family like the other members of fluoroquinolone derivative Gatifloxacin also inhibits the bacterial DNA gyrase and topoisomerase IV enzymes.[4]
The present study focus on the formulation and evaluation of Noisome containing gatifloxacin using different concentration of the polymer for controlled release. It can maintain the adequate concentration of the drug on the eye surface and ultimately gave better therapeutic action as compared to other conventional dosage forms.[5]

MATERIALS AND METHODS

Standard drug Gatifloxacin sesquihydrate was obtained from Zydus Cadila, Ahmedabad as gift samples along with their analytical reports. Propylene glycol was purchased from Vedic Orgo LLP. Phospholipid, Carbapol, Lecithin, Polyethylene glycol, Polystyrene, and Acrylic resin were bought from Himedia Chemicals Mumbai. Other solvents and chemicals used in the research were of LR grade. All the studies were carried in distilled water.

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Pre-formulation Study

Determination of Solubility: A fixed amount of drug was taken, and then distilled water was added and observes the solubility visually. Solubility study should be performed for gatifloxacin to determine in which solvent it is soluble, for those various solvents like water, methanol, 0.1N NaOH, 0.1N HCl, Ethyl acetate was used, for determining the solubility the drug should be dissolved in an individual solvent in 1:10 ratio (Drug: Solvent) and visually observed for its solubility.[6]

Melting Point: The Melting point was evaluated by a capillary method using the Digital Melting point apparatus. One end fused capillary tube was filled gently by pure drug sample and packed by tapping so the drug settled in the bottom of the capillary.[7] When the drug was packed into the bottom of the tube, the tube was placed into the slot of the apparatus, the apparatus was started and the temperature was noted at which the drug melt.[8]

Ph 7.4 Buffer: 20.214 g of Na2HPO4-7H2O was added to 800 ml of water in a beaker. Then 3.394 g of NaH2PO4H2O was added to this solution. pH was adjusted using HCl or NaOH and volume make up to 1 liter.[9]

Determination of Wavelength of Maximum Absorbance (λmax):

Gatifloxacin (10mg) was dissolved in 1ml pH 7.4 phosphate buffers and volume was made up to 10 ml volumetric flask using pH 7.4 phosphate buffers. 1 M of stock solution (1mg/ml) was further diluted with pH 7.4 phosphate buffers, up to 10 ml. This solution (100µg/mL) was further diluted to pH 7.4 phosphate buffers to obtain solutions of 2 to 10 µg/mL.[10] The absorption of each solution was measured at 292 nm. Using Systronics UV-2203 UV/V is a double beam spectrophotometer and pH 7.4 phosphate buffers, as a reference standard.[11]

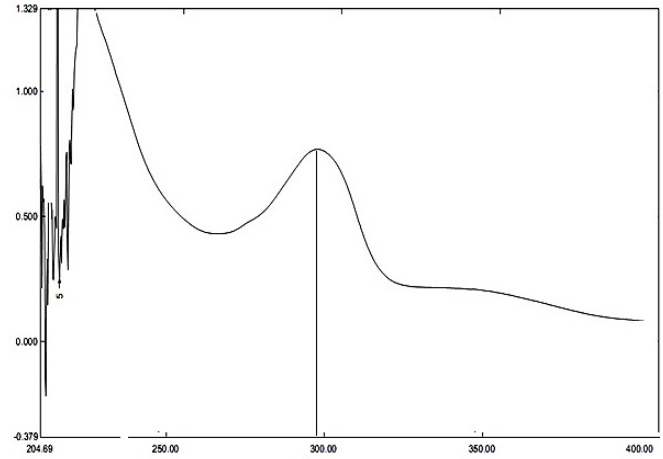

Figure 1: Absorption spectra of Gatifloxacin (10 µg mL^{-1})

Preparation of Calibration Curve

From this stock solution 2, 4, 6, 8, 10 ml was pipette out in 100 ml calibrated volumetric flask, and dilutions of 2, 4, 6, 8, 10µg/ml were obtained. The absorbance of these solutions was taken on a double beam U.V. spectrophotometer using λ_{max} at 292 nm. The calibration curve was plotted absorbance between concentrations (µg/ml).

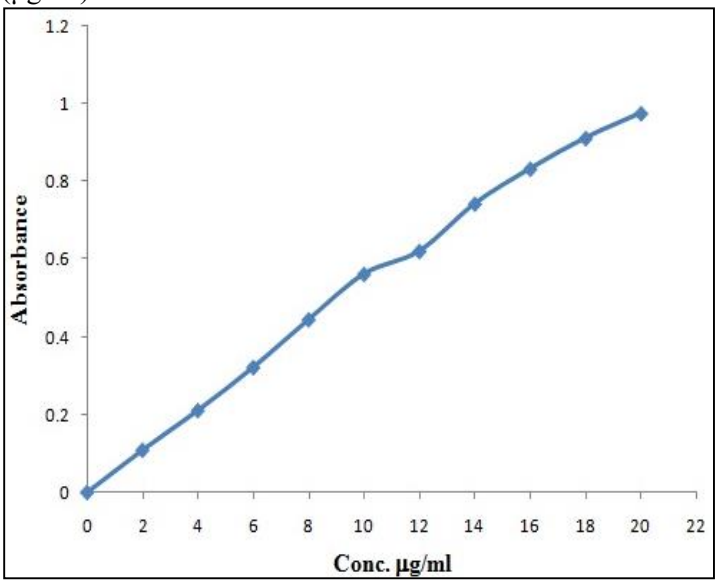

Figure 2: Calibration curve of Gatifloxacin at 292 nm

Partition Coefficient

In chemistry and the pharmaceutical sciences, a partition- (P) or distribution coefficient (D) is defined as the ratio of concentrations of a drug in a mixture of two immiscible phases at equilibrium. This coefficient is the measure of the hydrophilic or lipophilic nature of the drug.

FT-IR Spectra Analysis

FT-IR Spectroscopy technique is used to predict interactions between different components therefore this technique was applied to the selection of chemically appropriate compatible excipients. While selecting the ingredients, we would choose those which are stable, compatible, and therapeutically acceptable. Compatibility study aimed to test, whether there is any interaction between the excipients and the drug and compatibility between the drug and excipients.

Levels of investigation

IR Spectrum = Pure drug (Levofloxacin)
IR Spectrum = Levofloxacin + Excipients

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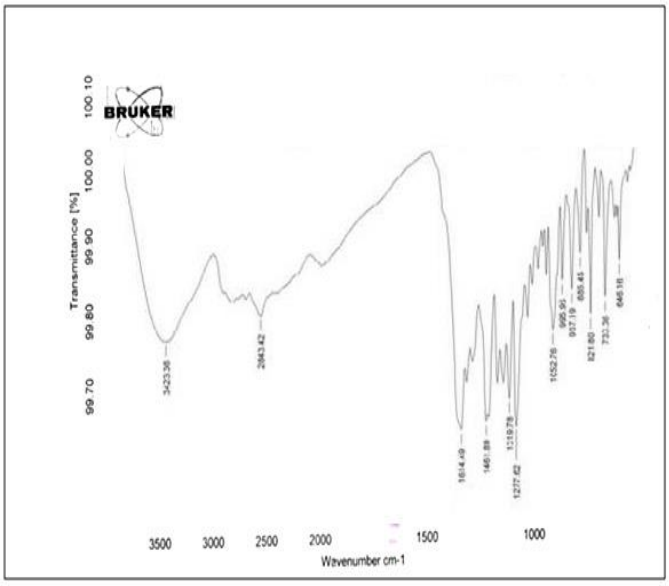

Figure 3: FT-IR of Gatifloxacin drug sample

Formulation of Niosomes

Multilamellar niosomes were prepared by the thin-film hydration method. Non-solvent chloroform was taken in a round-bottom flask and the drug, surfactant, and Cholesterol was weighed accurately and dissolved in it. Dicetylphosphate (DCP) was used as a negative charge-inducing agent in different molar ratios. Rotary flash evaporator used to evaporate chloroform then kept overnight. pH 7.4 phosphate-buffered saline (PBS) (6 ml) was used to hydrate formed thin film by sonication on bath-sonicator. Vesicle suspensions were also sonicated for 5 min and 2 min.[12]

Optimization of process-related Variables in Noisome Formulation

The process-related variables of sonication time, hydration time, a hydration medium, speed of rotatory evaporator, and charge-inducing agents were investigated in vesicle formation with 90 µm, Tween 80 and 20µm cholesterol with a fixed amount of Gatifloxacin by trial and error method.

Table no. 1: Optimization of process-related Variables in Noisome Formulation

Batch No.	CHOL: Tween		Hydration medium	Hydration volume (ml)
	µM ratio	Wt (mg)		
F1	1:1.5	7.6:39.3	PBS pH 7.4	6
F2	1:2.5	7.6:65.5	PBS pH 7.4	6
F3	1:3.0	7.6:78.6	PBS pH 7.4	6
F4	1:3.5	7.6:91.7	PBS pH 7.4	6
F5	1:4.5	7.6:117.9	PBS pH 7.4	6
F6	1:6.0	7.6:157.2	PBS pH 7.4	6

Formulation of niosomal Gel of Gatifloxacin

Dissolve different concentrations of HPMC in ethanol and propylene glycol in water was mixed using a magnetic stirrer, at 25 rpm. By keeping Neem extract loaded phytosome concentration constant in all the formulations. The Neem extract-loaded phytosome was poured into the polymer solution. The solution was kept under stirring and then the pH was adjusted using 0.1M NaOH and the formulated gel was taken for further analysis.

Characterization of Niosomes

Optical Microscopy:

Glass slide was loaded with a drop of formulated niosomal suspension mount on the microscope. Photographs of sonicated and non-sonicated formulations were taken at 40x magnification using the digital camera attached to the eyepiece of the microscope. The shape and lamellar nature of the non-sonicated vesicles were confirmed with the photographs.

Scanning Electron Microscopy (SEM):

The morphology of the niosomal suspensions was investigated by SEM. The representative SEM photographs of the liposomal suspension are shown in Figure SEM images showed that liposomal suspension was finely spherical and uniform; no entire drug crystals were observed visually.

Vesicle Size Determination:

The vesicle size of the sonicated formulation was observed by optical microscopy using a pre-calibrated eyepiece. The eyepiece was calibrated using a stage micrometer at 40x magnification. The size of each division of eyepiece micrometer was determined using the formula:

$$\textbf{Size of each division} = \frac{\text{Number of divisions of the stage micrometer}}{\text{Number of divisions of the eyepiece micrometer}} \text{ X } 100$$

The average diameter of 100 vesicles was counted for 3 times at different time intervals after 4 hours for the prepared formulation.

Determination of Viscosity: The viscosity of the formulations was determined using the Ostwald viscometer. The time taken for water and formulations to flow from point A to B was calculated and substituted in the formula and the viscosity was calculated as:

$$\boldsymbol{viscosity\ of\ sample}(\eta 1) = \frac{\rho 1 * t1}{\rho 2 * t2} \times \eta 2$$

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Where,

ρ1 – density of the sample
ρ2 – density of water
η1 – viscosity of a sample
η2 – viscosity of water
t1 – time is taken by the sample to flow from point A to B
t2 – time is taken by water to flow from point A to B

Table no. 2: Evaluation of Gatifloxacin Niosomal batches

Formulation code	Polydispersibility index	Entrapment efficiency (%)± S.D	Zeta potential (Mv)± S.D
F1	0.411	75.52±1.13	-27.77±1.55
F2	0.389	73.60±1.39	-24.84±0.79
F3	0.420	69.05±1.14	-20.29±1.03
F4	0.385	79.60±2.26	-25.44±0.92
F5	0.325	78.09±1.94	-21.07±1.75
F6	0.370	74.84±1.60	-24.57±0.16

Determination of Drug Entrapment in Vesicles: centrifuged the Niosomal formulations at 15,000 rpm for 15 min at 4ºC using to separate niosomes from the non-entrapped drug. The concentration of the free drug in the supernatant was determined by measuring absorbance at 292 nm with a UV spectrophotometer. Percentage drug entrapment was obtained by the formula given below:

$$\% \text{ Drug entrapment} = \frac{\text{Total drug} - \text{Drug in supernatant}}{\text{Total drug}} \times 100$$

Table no. 3: Drug content in liposomal formulations

Formulation	Appearance	pH	Odor	Drug content (% ± S.D.)	Vesicle size (µm)	Viscosity (centipoise)
F1	Milky white	4.7	Odourless	99.23±1.75	3.0	2.096
F2	Milky white	4.6	Odourless	89.20±0.61	2.72	2.267
F3	Milky white	5.1	Odourless	89.13±0.79	2.48	2.277
F4	Milky white	4.9	Odourless	99.41±0.90	2.68	1.955
F5	Milky white	4.7	Odourless	98.76±1.50	2.64	3.248
F6	Milky white	5.2	Odourless	99.52±0.97	2.94	2.133

***In-vitro* Release Studies:** a dialysis bag was used as a 'donor compartment' for *in-vitro* drug release. The release study was performed by re-suspended the Niosomes containing Gatifloxacin in 1 ml of pH 7.4, PBS. The artificial membrane was activated by warm water, one end was sealed with a clip, the Niosome preparation or drug in solution was pipetted into the bag and another end was clipped to prevent leakage. Then the dialysis bag was put in 50 ml of pH 7.4, PBS, at 37 ± 2ºC. The medium, which acted as the receptor compartment, was stirred at 100 pm. Samples of medium (5ml) were withdrawn hourly and replaced with fresh buffer and Gatifloxacin absorbance at 292 nm was measured using PBS as blank. Results represented were mean values of thrice runs.

$$\% \text{ Drug release} = \frac{\text{Conc. obtained from graph (µg/ml)} \times \text{Total vol. of dissolution medium} \times 100}{\text{Amount of drug present in 1 ml of niosomal formulation} \times 100} \times \text{Dilution factor}$$

Table no. 4: *in-vitro* Release from Noisome Formulation

Time (Hours)	Cumulative % release					
	F1	*F2*	*F3*	*F4*	*F5*	F6
0	*0*	*0*	*0*	*0*	*0*	0
1	*45.32*	*40.15*	*37.32*	*35.32*	*25.32*	22.12
2	*55.32*	*54.76*	*47.83*	*41.82*	*36.86*	33.82
3	*66.38*	*62.23*	*54.42*	*47.36*	*42.42*	38.12
4	*73.78*	*69.9*	*60.48*	*54.12*	*48.32*	44.14
5	*76.68*	*72.65*	*64.12*	*57.82*	*51.72*	47.72
6	*77.38*	*73.73*	*68.83*	*62.32*	*56.82*	52.82
7	*79.49*	*74.8*	*71.12*	*68.21*	*62.81*	58.64
8	*80.62*	*75.38*	*74.34*	*74.14*	*69.32*	65.78
9	*82.3*	*75.7*	*76.13*	*79.26*	*75.21*	72.72
10	*83.14*	*76.01*	*77.38*	*82.12*	*80.36*	78.76
11	*83.57*	*76.26*	*78.61*	*84.46*	*84.28*	83.13
12	*84.94*	*86.32*	*79.28*	*88.56*	*90.32*	91.25

*Each value was an average of three determinations

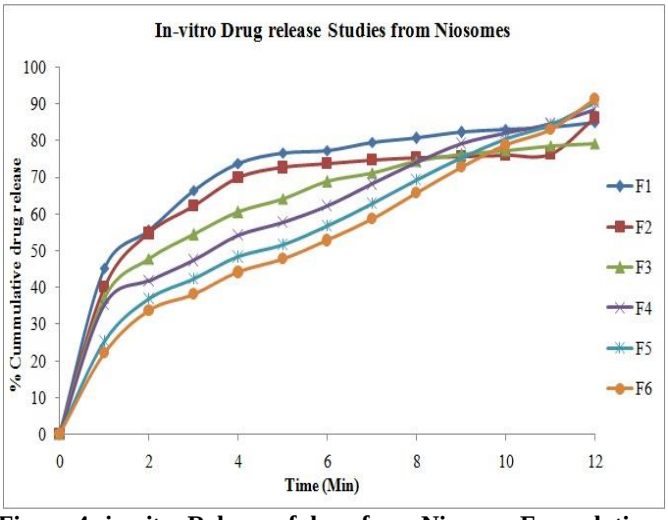

Figure 4: *in-vitro* Release of drug from Niosome Formulations

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Evaluation of Niosomal Gel

Table no. 5: Formulation of Niosomal gel of Gatifloxacin

Formulation	GF-1	GF-2	GF-3	GF-4	GF-5
Phytosome(g)	0.4	0.4	0.4	0.4	0.4
HPMC(g)	0.5	0.5	0.5	0.5	0.5
Ethanol (ml)	10	10	10	10	10
Propylene glycol (g)	2	2	2	2	2
Distilled water (g)	7.1	7.1	7.1	7.1	7.1

pH Measurements:

The pH of the gel formulations is delivered by using a digital pH meter. Before measurement by pH meter should calibrate then readings were taken by dipping the electrode directly into the gel formulations.

Viscosity Measurement:

Brookfield viscometer was used to determine the viscosity of gel formulations. 25.0 g gel was used to determine at 50 rpm with spindle number 4.

Spreadability:

The Spreadability of gel formulations determine by using Spreadability apparatus. Gel sample (1.0 g) was put between lower and upper slide. The Spreadability determine by the formula where Spreadability, is weight tied to the upper slide, is length travel by upper slide, and is the time taken.

Stability Studies:

Niosomal formulation was selected based on entrapment efficiency and in-vitro release studies. Stability studies will be assessed by keeping both liposomal suspension and liposomal gel in vials and sealed. These vials were stored in two conditions e.g. refrigeration temperature (4^0C) and hotter temperature (40^0C) for 30 days. The samples were withdrawn at fixed intervals within one month and the residual content was determined spectrophotometrically.

Table no 6: Evaluation of Niosomal gel of Gatifloxacine

Formulation	Clarity	Odour	Phase separation	Wash ability	Homogeneity	Grittiness
GF-1	Clear	No	No	Washable	Yes	No
GF-2	Clear	No	No	Washable	Yes	No
GF-3	Clear	No	No	Washable	Yes	No
GF-4	Clear	No	No	Washable	Yes	No
GF-5	Clear	No	No	Washable	Yes	No
GF-6	Clear	No	No	Washable	Yes	No

Table no. 7: Evaluation of Niosomal gel of Gatifloxacin on following parameter

Formulation	pH	Spreadability (cm)	% Drug Content	Viscosity (cp)	% Permeation
GF-1	7.1	6.6±0.5	100±1.2	110±1.8	78%
GF-2	7.4	7.6±0.0	100±1.3	113±2.0	89%
GF-3	7.4	7.6±0.1	98±2.1	115±1.2	87%
GF-4	7.2	7.0±0.4	99±1.7	100±0.8	91%
GF-5	7.0	7.1±0.3	100±0.6	98±2.0	75%
GF-6	7.1	7.3± 0.4	99±0.2	115±1.9	79%

Table no 8: Stability of Niosomal gel of Gatifloxacine at 4ºC and 40 ºC with 75% relative humidity

Formulation code	Phase separation		pH		Drug content (%)	
	4ºC	40 ºC	4ºC	40 ºC	4ºC	40 ºC
GF-1	No	No	6.9	7.0	100±1.1	95±2.0
GF-2	No	No	7.4	7.3	100±1.8	99±1.9
GF-3	No	No	7.4	7.2	98±1.9	98±1.8
GF-4	No	No	7.2	7.1	99±0.6	92±1.0
GF-5	Yes	Yes	7.1	7.4	101±1.9	97±2.1
GF-6	Yes	Yes	7.5	7.5	99±1.4	98±1.2

RESULT AND DISCUSSION

The objective of the work was to design niosomes of a drug meant for infections caused due to Gram-positive and Gram-negative bacteria. The drug Gatifloxacin sesquihydrate powder was examined for its organoleptic properties found it was observed that Gatifloxacin sesquihydrate was white crystalline odorless powder. When tested for its solubility in various solvents, it was determined that the drug sample was slightly soluble in water and 0.1 HCl, soluble in methanol, ethanol, and Buffer 7.4 pH. melting point observed 183-184°C. Gatifloxacin sesquihydrate solution was scanned in the U.V. range of 200-400 nm using UV Visible spectrophotometer.

The spectrophotometric method of analysis of Gatifloxacin at λ_{max} 292 nm was found to be reproducible and highly sensitive. The standard curves were prepared in Methanol at λ_{max} 292 nm. The data were regressed to obtain the straight line. The correlation coefficient greater than 0.997 was observed in all the cases, which indicated that the drug follows Beer-Lambert's law in the concentration range of 2-20 µg/ml and equation were Y = 0.018X + 0.001. The partition coefficient value of Gatifloxacin was 2.61 revealed its lipophilic nature. The IR spectrogram of the drug was used to identify an interaction between drug and excipients based on characteristic peaks present which denoted structural characteristics of the drug molecule was noted. -COOH (O-H Stretch) 3000; -COOH

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(C=O Stretch) 1685; CH3 (C-H Stretch) 2870 and Aromatic C-H (C-H Stretch) 900 – 750. Drug and polymer compatibility study reveals that there is no interference between drug and polymer.

The thin-film hydration method was used to prepare Multilamellar niosomes. The thin films were hydrated with 6 ml of phosphate-buffered saline (PBS), pH 7.4, and the formulations were sonicated 3 times at 50 Hz in a bath-sonicator for 15 min with 5 min intervals between successive times. Vesicle suspensions were also sonicated for 5 min and 2 min. The process-related variables of sonication time, a hydration medium, hydration time, speed of rotation of flask evaporator, and charge-inducing agents were investigated in vesicle formation with 90 μM, Tween 80 and 20 M cholesterol, with a fixed amount of Gatifloxacin by trial and error method.

Gatifloxacin niosomes shape and lamellar structure were determined by the optical microscopy method specified for optimized formulations. Photomicrographs revealed that liposomes formulated with tweens were spherical and Multilamellar. Sonicated vesicles were in the submicron size range. In the absence of cholesterol, micelles are formed with the tween 80, 60, and 40. The drug-loaded liposomal dispersion was off-white in color, odorless, and fluid in nature. It was stable and did not show sedimentation. pH was found to be in the range of 4.7-5.2. Summarize data of all the six batches of factorial design. Percentage drug content found 89 to 99.52 %. Formulations F1, F4, and F6 had 99.23, 99.41and 99.52 respectively, F5 had also shown good % drug content 98.76%.

The values of zeta (ζ) potential of the drug-loaded liposomal formulation were in the range of-20.29 to -27.77mV. Values of zeta (ζ) potential showed that the drug-loaded noisome had sufficient charge and mobility to inhibit aggregation of vesicles. Polydispersibility index and entrapment efficiency were also excellent. The DSC thermal profile of Gatifloxacin loaded niosomes (F4) are shown in figure DSC thermal profile of pure Gatifloxacin showed a sharp endothermic peak attributed to melting of a drug during DSC run. The viscosity of liposomal formulations found in under the ideal range from 1.955 to 2.277centipoise.

Liposomal Gatifloxacin formulations with fast drug release in the initial hours may be due to the release of adsorbed drug from the lipophilic region of niosomes which will help to achieve the optimal loading dose. When the concentration of cholesterol was high in Tween 80 (cholesterol: surfactant micro molar ratio 1:1.5) the drug release was 47.36 % in 3 h, and in formulations with a low concentration. Formulated niosomal preparation incorporated in gels in a fixed amount. That gel formulations were evaluated and found all formulations were clear, odorless, washable, homogeneous, and free from grittiness, and also no phase separation found. All gels were found under pH range 7.0 to 7.4, Spreadability under the range 6.6 to 7.6 cm, % drug content 98 to 100%, the viscosity of gels 98 to 115cp, and % permeation found in rage 75 to 91%. Excellent % Permeation Gel formulation GF-4 was found 91%.

Drug stability concerns about drug product safety, efficacy, and quality found it to appropriate. The percentage drug loss from the formulations was used as a measure of storage stability. The initial entrapped drug in the vesicular system was considered as 100%. The leakage of drugs from niosomes vesicles was not more significant in refrigerated conditions. This fact can be justified as 98.57%, 98.24% & 98.17% drug was remaining in niosomes after 1, 2 & 3 months respectively at 4±20C. A significant loss of entrapped drug was found at the end of three month period when niosomal dispersions were stored at high temperature i.e. 25±20C. It can be concluded that for better stability, the formulations should be stored at low temperatures in a refrigerator.

CONCLUSION

From the trial-and-error optimization design, drug-loaded Gatifloxacin Niosomes were successfully evaluated. Pre-formulation study confirms the purity of the drug and compatibility of the drug with excipients using FT-IR and DSC study. Tween 80 was found significant with the experimental results. It was confirmed that increasing the concentration of Tween 80 increases the deformability of niosomes. From characterization parameters and stability study, it was concluded that the formulation has acceptable morphology and particle size, no any chemical interaction, and was stable at refrigerated condition respectively.

An extensive investigation is needed regarding the depth of penetration into the skin, determination of zeta potential, and confirmation of configuration of phospholipids in the lipid bilayer. There is a need to develop a suitable formulation for commercial exploitation. Thus, the specific objective listed in the plan of work of this thesis were achieved namely design, characterization, and release studies of Gatifloxacin liposomal formulation.

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