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Design of Gatifloxacin Niosomes by film hydration method

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ABSTRACT

A Niosome is a non-ionic surfactant-based Vesicle (biology and chemistry). Niosomes are formed mostly by non-ionic surfactant and cholesterol incorporation as an excipient. Other excipients can also be used. Niosomes have more penetrating capability than the previous preparations of emulsions. Niosomes are lamellar structures that are microscopic in size. They constitute of nonionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. The objective of the work is to design niosomes of a drug meant for infections caused due to Gram-positive and Gram-negative bacteria., the objective of the present work is design to formulate and evaluate niosomes of Gatifloxacin for efficient parentral administration in case of Gram-positive and Gram-negative bacteria.

Keywords: *Niosome, Gatifloxacin, Phaspholipid, Carbapol*

Controlled drug delivery technique presents front line part of today's developed technique, in this includes many scientific approaches, serving for individual care. The drug deliverance technique having abundant advantages than existing conventional type of dosage, it involves enhanced effectiveness, minimized poisoning, enhanced consumer conformity also ease. This type of drug deliverance technique utilizes micro molecules, for caring drugs. As the varieties of forms for dosage are invented like microparticle as well as nanoparticles shown more significance. An ideal and advanced oral drug delivery system is that, which exactly controls speed, time as well as site of release of medicament separately of normal physiological variables such as gastrointestinal tract pH, digestive condition of the gastrointestinal tract, peristalsis movement and circadian rhythm. Therapeutic effectiveness of a drug depends upon the bioavailability and eventually upon the solubility of drug substances. Solubility is prerequisite to achieve desired concentration of drug in systemic circulation, drug absorption and pharmacological response. Oral route of drug administration is the uncomplicated and easiest approach of administration of drugs as it offers good patient compliance, convenience, accurate dosing, easy production, and greater stability.

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Niosome

A Niosome is a non-ionic surfactant-based Vesicle (biology and chemistry). Niosomes are formed mostly by non-ionic surfactant and cholesterol incorporation as an excipient. Other excipients can also be used. Niosomes have more penetrating capability than the previous preparations of emulsions. They are structurally similar to liposomes in having a bilayer, however, the materials used to prepare niosomes make them more stable and thus niosomes offer many more advantages over liposomes. Niosomes are lamellar structures that are microscopic in size. They constitute of nonionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. The surfactant molecules tend to orient themselves in such a way that the hydrophilic ends of the non-ionic surfactant point outwards, while the hydrophobic ends face each other to form the bilayer. Controlled release drug products are often formulated to permit the establishment and maintenance of any concentration at target site for longer intervals of time.

Types of niosomes

The niosomes are classified as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size. (e.g. LUV, SUV) or as a function of the method of preparation (e.g. REV, DRV).

The various types of niosomes are as following:
i) Multi lamellar vesicles (MLV)
ii) Large unilamellar vesicles (LUV)
iii) Small unilamellar vesicles (SUV)

(i) Multilamellar vesicles (MLV): It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the most widely used niosomes (Bangham et al., in 1974). It is simple to make and are mechanically stable upon storage for long periods. These vesicles are highly suited as drug carrier for lipophilic compounds.

(ii) Large unilamellar vesicles (LUV): Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.

(iii) Small unilamellar vesicles: These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion method or, homogenization method. The approximate sizes of small unilamellar vesicles are 0.025-0.05 µcm diameter. They are thermodynamically unstable and are susceptible to aggregation and fusion. Their entrapped volume is small and percentage entrapment of aqueous solute is correspondingly low.

MATERIAL AND METHOD

Niosomes can be prepared by film hydration method,

Materials

Gatifloxacin sesquihydrate was a kind gift from Zydus Cadila, Ahmedabad, India. Water used for experimental purposes was type-I (Millipore®).

Table 1: List of Chemicals.

S No.	MATERIAL	SUPPLIERS
1.	Gatifloxacin sesquihydrate	Zydus Cadila, Ahmedabad
2.	Propylene glycol	Peekay scientific center, Bhopal
3.	Phospholipid	
4.	Carbapol	
5.	Triethyl citrate	
6.	Acrylic resin	
7.	Lecithin	
8.	Ethanol	
9.	Polyethylene	
10.	Polystyrene	

Methods

Formulation of Niosomes(Alisagar *et al.*, 2002) Multilamellar niosomes were prepared by the thin-film hydration method. Accurately weighed quantities of drug, surfactant (Tween or Span), and CHOL were dissolved in chloroform in a round-bottom flask. Different molar ratios of DCP were added to each formulation as a negative charge-inducing agent. The chloroform was evaporated at 60^{o}C under reduced pressure using a rotary flash evaporator at various RPM. After chloroform evaporation, the flask was kept under vacuum overnight in a nitrogen atmosphere to remove residual solvent. 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 interval between successive times. Vesicle suspensions were also sonicated for 5 min and 2 min.

Optimization Of Process-Related Variables In Niosome Formulation The process-related variables of sonication time, hydration medium, hydration time, speed of rotation of flask evaporator and charge-inducing agents were investigated in vesicle formation with 90μm Tween 80 and 20 μm cholesterol with a fixed amount of Gatifloxacin by trial and error method.

Table.2 Formula for Drug loaded niosomes and optimization parameters

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

Characterization

- **Optical Microscopy**

A drop of niosomal suspension was placed on the microscopic glass slide. Photographs of sonicated and nonsonicated formulations were taken at 40x magnification using the digital

camera (Olympus 8 mega pixel) attached to the eye piece of the microscope. Shape and lamellar nature of the nonsonicated vesicles was confirmed with the photographs.

- **Scanning Electron Microscopy**
  The morphology of the niosomal suspension were investigated by SEM. The representative SEM photographs of the niosomal suspension are shown in Figure
  SEM images showed that niosomal suspension were finely spherical and uniform; no entire drug crystals were observed visually. (Crotts G., 1995).
- **Vesicle Size Determination**
  Vesicle size of sonicated formulation was determined by optical microscopy using a pre-calibrated eye piece. Eyepiece was calibrated using stage micrometer at 40x magnification. Size of each division of eyepiece micrometer was determined using the formula

$$\text{Size of each division} = \frac{\text{Number of divisions of stage micrometer}}{\text{Number of divisions of eye piece micrometer}} \times 100$$

  The average diameter of 100 vesicles was counted for 3 times at different time intervals after 4 hours for the prepared formulation.
- **Transmission Electron Microscopy**
  A drop of the sonicated niosomal sample was placed onto a carbon-coated grid to leave a thin film. Before drying of this film on the grid, it was negatively stained with 1% phosphotungstic acid (PTA). For this, a drop of staining solution was added onto the film and the excess of the solution was drained-off with a filter paper. The grid was allowed to air dry thoroughly and was then visualized using a Transmission Electron Microscope (Jain *et al.*, 2004) (TEM) with an accelerating voltage of 80 kV.
- **Determination of Polydispersity Index and Zeta Potential**
  The polydispersity index of vesicles determined using Zetasizer, Nano ZS 90, (Malvern Instruments) working of which is based on dynamic light scattering (Perriea*et al.*, 2004). For the measurement, 100 µl of the formulation was diluted with the appropriate volume of PBS (pH 7.4) and the vesicle diameter was determined. Zeta potential was determined by taking the appropriate diluted formulation in a disposable clear polycarbonate capillary cell.
- **Determination Of Viscosity**
  Viscosity of the formulations was determined using 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:

$$\textbf{Viscosity of sample } (\eta_1) = \frac{p_1 x t_1}{p_2 x t_2} X \eta_2$$

Where,

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

- **Determination Of Drug Entrapment In Vesicles**

Niosomal formulations were centrifuged at 15,700 x g for 90 min at 4ºC using a refrigerated centrifuge (Eppendorf, 5415 R, Germany) to separate niosomes from non-entrapped drug. Concentration of the free drug in the supernatant was determined by measuring absorbance at 267 nm with a UV spectrophotometer (Shimadzu, model UV 1650 PC, Kyoto, Japan). The percentage of drug entrapment in niosomes was calculated using the following formula of Alsarra *et al.*, 2005.

This process was repeated thrice to ensure that free drug was completely removed.

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

RESULTS

Vesicle Shape and Lamellarity

Gatifloxacin niosomes shape and lamellar structure were determined by optical microscopy method specified for optimized formulations F3, F4 and F6 in figure

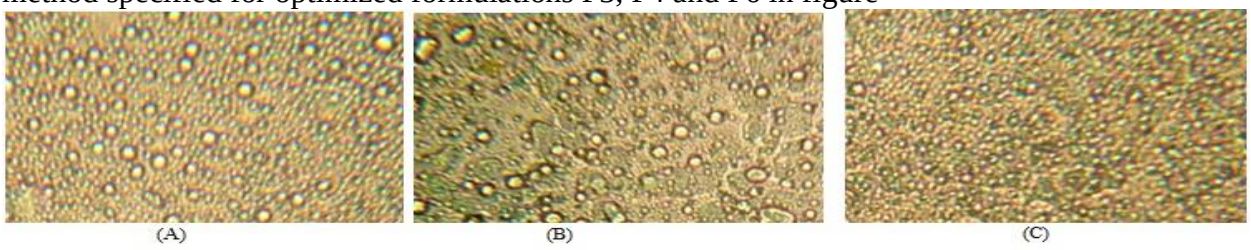

Figure 1.Photomicrographs of formulations (A) F3, (B) F4 & (C) F6.

Drug Content and Physical Parameters

The drug loaded niosomal dispersion was off-white in color, odourless, 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 is shown in table.

Table 3: Drug content in niosomal formulations.

Formulation code	Appearance	pH	Odour	Drug content(% ± S.D.)
F1	Milky white	4.7	Odourless	99.23±1.75
F2	Milky white	4.6	Odourless	89.20±0.61
F3	Milky white	5.1	Odourless	89.13±0.79
F4	Milky white	4.9	Odourless	101.41±0.90
F5	Milky white	4.7	Odourless	98.76±1.50
F6	Milky white	5.2	Odourless	99.52±0.97

Viscosity

Viscosity of noisome formulations was determined using Ostwald viscometer shown in table

Table 4: Viscosity measurement of niosome batches.

S.No	Formulation	Viscosity (centipoise)
1	F1	2.096
2	F2	2.267
3	F3	2.277
4	F4	1.955
5	F5	3.248
6	F6	2.133

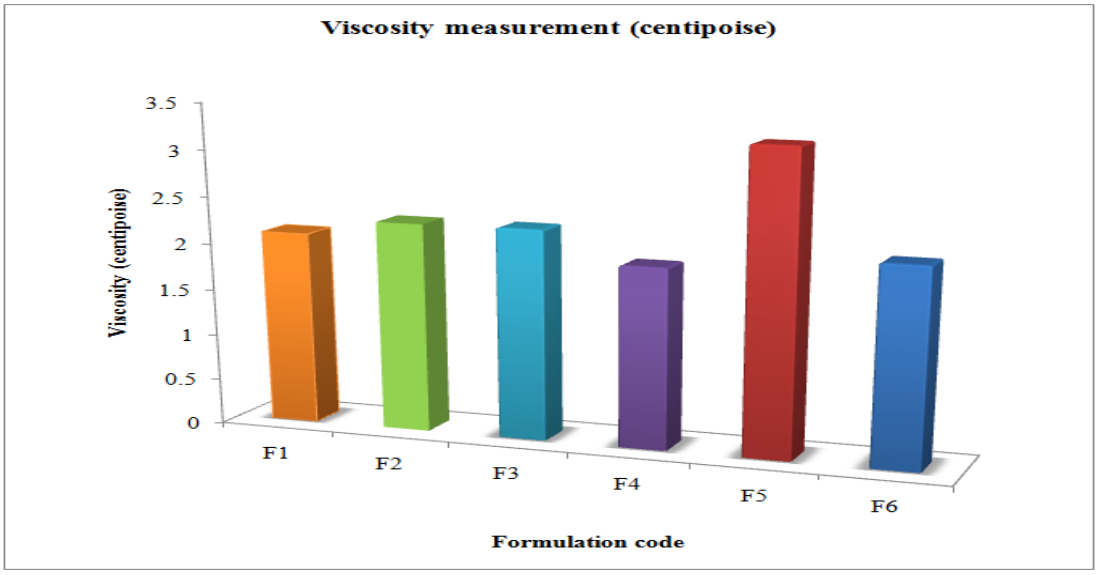

Figure. 2 Viscosity measurements of niosome batches

IN VITRO RELEASE STUDIES

In vitrorelease was studied using a dialysis bag

Table 5: In Vitro Release from Niosome Formulation.

Time in 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**

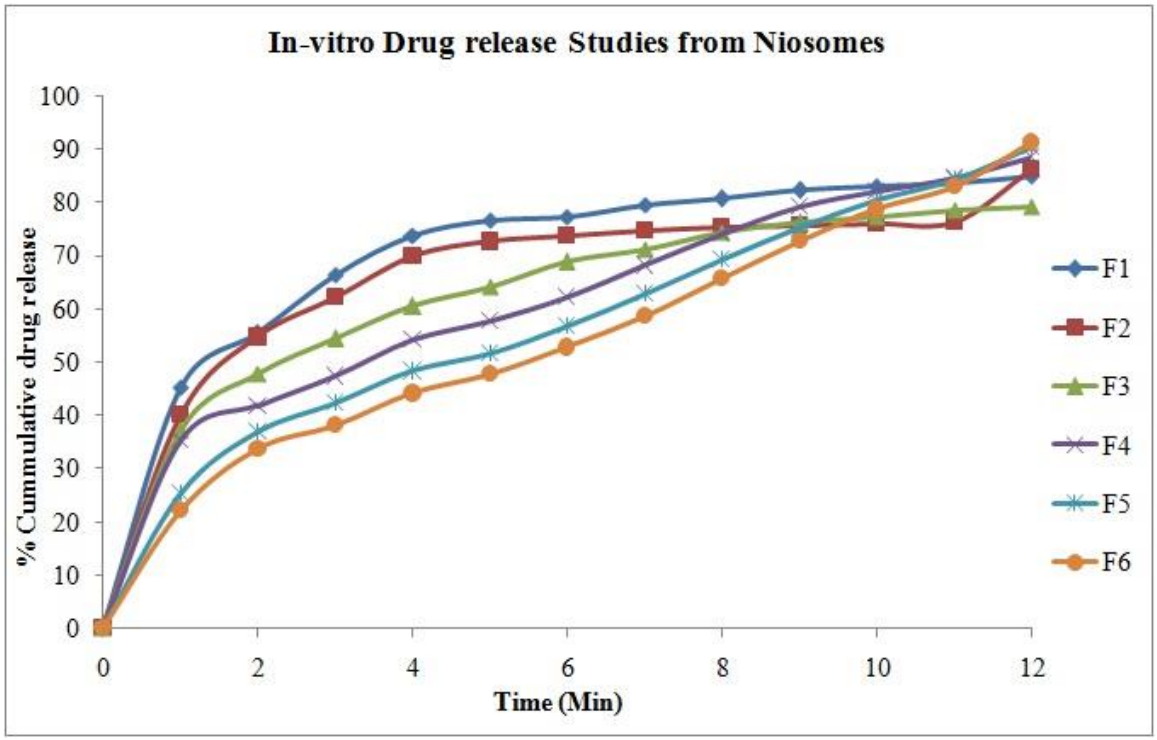

Figure 3: In Vitro Release of drug from Niosome Formulation.

CONCLUSION

From the trial-and-error optimization design, drug loaded Gatifloxacin Niosomes were successfully evaluated. Preformulation study confirms purity of drug and compatibility of drug with excipients using DSC study. Effect of edge activators SPAN 80 and TWEEN 80 were found significant with the experimental results. It was confirmed that the increasing the concentration of Edge activator increases the deformability of niosomes. From characterization parameters of TEM 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 with reference to depth of penetration into the skin, determination of zeta potential and confirmation of configuration of phospholipids in lipid bilayer. There is a need to develop suitable transdermal 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 Niosomal formulation.

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Conflict of Interest
The author declared no conflict of interest.

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