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Formulation and in-vitro evaluation of niosomal drug delivery system for aceclofenac

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ABSTRACT

In the past few decades, considerable attention has been focused on the development of new drug delivery system (NDDS). The NDDS should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity to the site of action. Conventional dosage forms including prolonged release dosage forms are unable to meet none of these. At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery. The aim of present work is to develop a niosomal drug delivery system of aceclofenac. To perform drug-polymer compatibility FT-IR studies were carried out and observed that there was no interaction between the APl and excipients. 8 niosomal formulations are prepared by the thin film hydration method using the cholesterol as the phospholipid. Prepared niosomal formulations were characterized by vesicle size, shape, surface charge, entrapment efficiency, drug content and invitro drug release studies. The vesicle size, size distribution and zeta potential of the optimized formulation (F5) was found to be 65.6 nm and zeta potential was found to be -1.5mV. Size distribution curve confirms the normal size distribution of the vesicles. The % entrapment efficiency of niosomal vesicles formulations were found to be in the range of 54.18±0.59 to 92.71±0.56 and optimized formulation was found to be 92.71±0.56 and drug content of niosomes formulations (F1to F8) were determined to be in the range of 94.6 -97.8%. The pH of all topical niosomal gels were found to be in the range of 7.4±0.02 to 7.4±0.08.The best fit with higher correlation (r2> 0.99) was found with the Zero Order Release and follows Korsemeyer peppas equation for all the formulations, which means that release of Aceclofenac from the lipid bilayer vesicles were due to diffusion. The stability studies were carried out and there was no significant change found in the formulations.

Keywords: NDDS, Aceclofenac; niosomes; cholesterol; span; carbopol.

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INTRODUCTION

In the past few decades, considerable attention has been focused on the development of new drug delivery system (NDDS). The NDDS should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity to the site of action. Conventional dosage forms including prolonged release dosage forms are unable to meet none of these. At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery[1]. Approaches are being adapted to achieve this goal, by paying considerable attention either to control the distribution of drug by incorporating it in a carrier system, or by altering the structure of the drug at the molecular level, or to control the input of the drug into the bioenvironmental to ensure an appropriate profile of distribution[2].Niosomes or nonionic surfactant vesicles are microscopic lamellar structures formed on admixture of nonionic surfactant of the alkyl or dial-

kyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media[3]. In niosomes, the vesicles forming amphiphile is a nonionic surfactant such as spans, tweens which is usually stabilized by addition of cholesterol and small amount of charge inducer such as dicetyl phosphate[4].Niosomes can entrap both hydrophilic and lipophilic drugs, either in aqueous layer or in vesicular membrane made of lipid materials. Because of the presence of nonionic surfactant with the lipid, there is better targeting of drugs to tumors, liver and brain. It may prove very useful for targeting the drug for treating cancers, parasitic, viral and other microbial disease more effectively[5].

MATERIALS AND METHODS

Aceclofenac was a gift sample from wockhardt pharmaceutics and spans, cholesterol, carbopol were obtained from Loba Chemie, Mumbai. All other chemicals used were of analytical grade.

Pre formulation parameters

Standard calibration curve of the Aceclofenac

100mg of accurately weighed Aceclofenac in 100ml of methanol (stock solution-1). It contains 1mg/ml of drug. From stock solution-1, 2ml of solution was taken into a 100ml volumetric flask and volume was made up with phosphate buffer pH 7.4 (stock solution-2). It contains 20µg/ml. From this stock solution-2, pipette out 1, 2, 3, 4, 5, and 6ml were taken in 10ml volumetric flask and make up with 7.4 pH phosphate buffer. It contains 2, 4, 6, 8, 10 and 12µg/ml respectively. The absorption maxima obtained at 275nm and absorbances were detected by using UV-visible spectrophotometer[6].

Table 1: Calibration table of aceclofenac

S.No	Concentration	Absorbance
1	0	0
2	2	0.1374
3	4	0.2604
4	6	0.3912
5	8	0.5188
6	10	0.6425

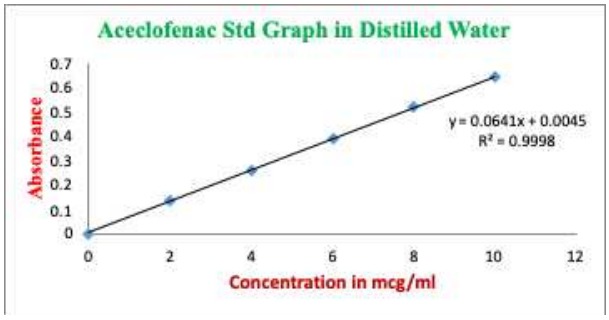

Figure 1: Calibration curve of aceclofenac

Fourier Transform Infrared Spectroscopy (FT-IR)

Fourier transform IR spectra were obtained on Shimadzu FT-IR spectrometer. Samples were prepared in KBr disks (2mg sample in 200mg KBr). The scanning range was 450-4000 cm^{-1} and the resolution was 4 cm^{-1}.

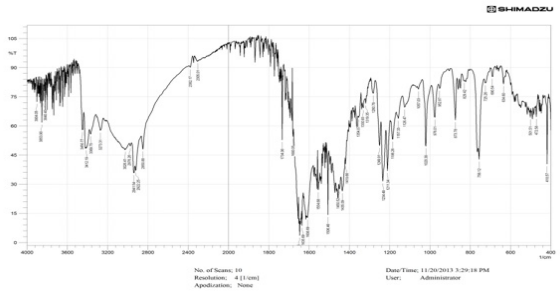

Figure 2: FTIR spectra of Aceclofenac pure drug

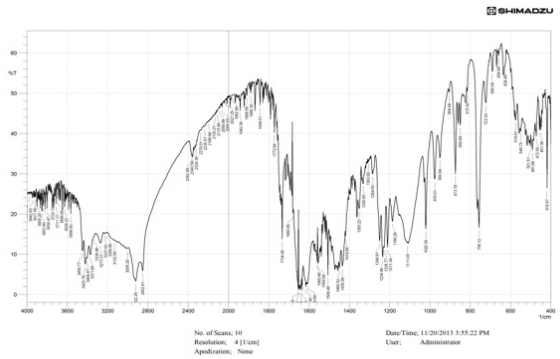

Figure 3: FTIR spectra of optimized niosomal formulation

Preparation of Aceclofenac Niosomes[7]

Aceclofenac niosomes were prepared using thin film-hydration method. Accurately weighed quantities of the surfactant (SpanTM)) and cholesterol in. 1:1 and 1:2 ratios were dissolved in 8 ml of chloroform:methanol mixture (2:1, v/v) in a round-bottom flask. Afterwards, Aceclofenac dissolved in 5mL of chloroform: methanol mixture (2:1, v/v) was added to the lipid solution (Table 1). The organic solvents were removed under vacuum in a rotary evaporator at 40 ◦C for 20 min to form a thin film on the wall of the flask, and kept in a desiccator under vacuum for 2 hours ensure total removal of trace solvents. After removal solvents hydration of the surfactant film was carried out using 10mL of distilled water at 55 ◦C, which is above the gel–liquid transition temperature (*Tc*) of sorbitan monoesters and polyoxyethylene alkyl ether surfactants. The resulting niosomal suspension was mechanically shaken for 1 h using a horizontal mechanical shaking water bath at 55^{0}C. Then, the vesicle suspension was sonicated in 3 cycles of 1min "on" and 1min "off" leading to the formation of multilamellar niosomes. The niosomal suspension was left to mature overnight at 4 ◦C and stored at refrigerator temperature for further studies.

Preparation of aceclofenac niosomal gel[8]

Niosomes aqueous dispersion was utilized for the formulation of topical gel. Gel polymer such as carbopol-934 was utilized to prepare niosome gel. 2g of carbopol-934 powder was dispersed into vigorously

Table 2: Composition of Aceclofenac niosomes (F1 to F8)

Ingredients (%)	F1	F2	F3	F4	F5	F6	F7	F8
Aceclofenac	25	25	25	25	25	25	25	25
Cholesterol	38.6	38.6	38.6	38.6	77.2	77.2	77.2	77.2
Span 20	34.6	-	-	-	34.6	-	-	-
Span 40	-	40.2	-	-	-	40.2	-	-
Span 60	-	-	43.6	-	-	-	43.6	-
Span 80	-	-	-	46.3	-	-	-	46.3
Carbopol 934 in %	2	2	2	2	2	2	2	2
Aceclofenac	25	25	25	25	25	25	25	25
Cholesterol	38.6	38.6	38.6	38.6	77.2	77.2	77.2	77.2
Span 20	34.6	-	-	-	34.6	-	-	-
Span 40	-	40.2	-	-	-	40.2	-	-

stirred and allowed to hydrate for 24 hrs. Later 10ml of Propylene glycol was added. The dispersion was neutralized with the drop wise addition of 10% sodium hydroxide, mixing was continued until a transparent gel was appeared. Then the amount of base was adjusted to achieve a gel with pH 6.5 .It can be measured by using pH meter.

Evaluation of Niosomal gel

Size and size distribution: Size and size distribution studies were done for niosomes prepared from Niosomes hydration. The Niosomal suspension (100 mg) was hydrated in a small glass test tube using 10 ml of pH 7.4 phosphate buffer solution. The dispersion was observed under optical microscope at 40X magnification. Size and size distribution of 200–300 niosomes were noted using calibrated stage and ocular micrometers (Elico Instruments, Hyderabad). Similarly, size was noted for niosomes formed spontaneously from Niosomes after hydration without agitation in a cavity slide (B. Vora et al., 1998).

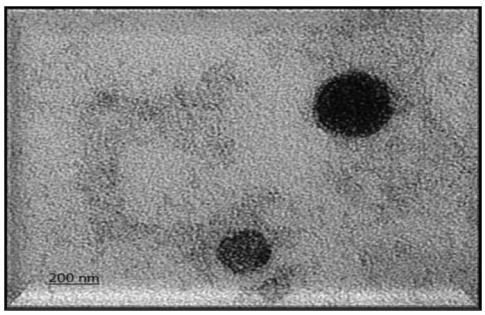

Figure 4: Photomicrograph of Aceclofenac loaded noisome (F5) at 10X

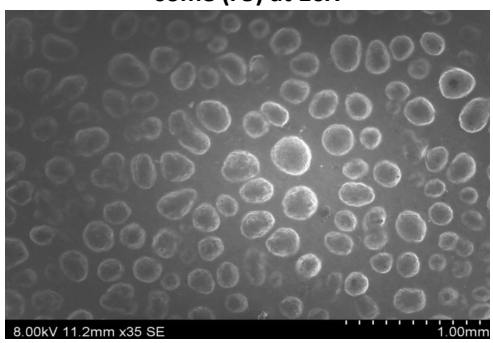

Figure 5: SEM Micrograph of Niosomes (F5)

Entrapment efficiency

To 0.2 g of Niosomal gel, weighed in a glass tube, 10 ml phosphate buffer pH 7.4 was added. The aqueous suspension was then sonicated. Niosomes containing aceclofenac were separated from untrapped drug by centrifugation at 9000rpm for 45 min at 4 ◦C. The supernatant was recovered and assayed spectrophotmetrically using UV spectrophotometer at 283nm.

The encapsulation percentage of drug (EP) was calculated by the following equation

$$\mathrm{EP} = \left[\frac{(C_t) - C_r}{C_t}\right] \times 100$$

where, Ct, concentration of total Aceclofenac , Cr, concentration of free Aceclofenac .

Vesicle physical analysis

The shape, surface characteristics, and size of the niosomes were observed by scanning electron microscopy. Once again, 0.2 g of the Niosome gel in a glass tube was diluted with 10 ml of pH 7.4 phosphate buffer. The niosomes were mounted on an aluminum stub using double-sided adhesive carbon tape. Then the vesicles were sputter-coated with gold palladium (Au/Pd) using a vacuum evaporator (Edwards) and examined using a scanning electron microscope (Hitachi 3700N, Germany) equipped with a digital camera, at 10 kV accelerating voltage.

Viscosity determination

The viscosity of the optimized formulations was determined by using rotational viscometer (Brookfield viscometer, DV-II, USA). The sample (100 g) was allowed to equilibrate for 5 min after placing in a beaker and dial reading was measured using 62 spindle at 0.3, 0.6 & 1.5 rpm. The measurements were carried in duplicate at ambient temperature (Maria et al., 2009).

Ex-Vivo Release Study

Ex vivo release studies were carried out using unjacketed vertical franz diffusion cells with a diffusional surface area of 6.154 cm^2 and 20 mL of receptor cell volume. Prior to the study, the dialysis membrane (Himedia laboratories Pvt Ltd., Mumbai) was soaked

Table 4: *In-Vitro* drug release of Niosomes gel (F1to F8)

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8
0.25	4.90±0.11	5.62±0.27	5.07±0.76	5.54±1.28	5.91±1.81	3.66±0.32	4.19±0.29	3.99±0.18
0.5	7.25±0.80	8.18±0.20	7.30±0.66	8.63±0.30	8.36±1.95	5.51±0.06	6.36±0.43	5.74±0.19
1	13.05±1.38	13.06±0.20	10.33±0.02	12.19±0.87	13.43±2.90	9.37±0.47	10.98±2.96	7.93±0.13
2	20.20±2.44	20.10±0.37	15.14±0.34	17.79±0.66	22.61±4.29	14.48±0.45	18.75±4.12	12.16±0.35
4	27.64±3.40	28.31±0.16	19.48±0.47	23.74±0.71	34.63±2.38	21.91±2.18	28.96±0.81	18.41±0.44
6	41.76±5.36	39.25±0.23	26.37±0.26	31.90±1.10	44.44±8.31	27.97±2.44	42.40±2.94	26.13±0.45
8	50.06±7.58	48.88±0.30	33.60±0.67	40.19±1.29	53.30±7.97	36.12±4.00	52.70±3.67	34.97±0.27
10	59.69±6.50	61.35±0.59	48.39±1.27	48.77±2.75	59.25±10.29	46.89±3.43	58.95±5.24	49.78±3.74
24	75.71±1.47	88.18±1.76	64.48±1.22	69.06±1.76	97.65±0.70	58.75±1.03	79.10±1.14	59.45±0.86

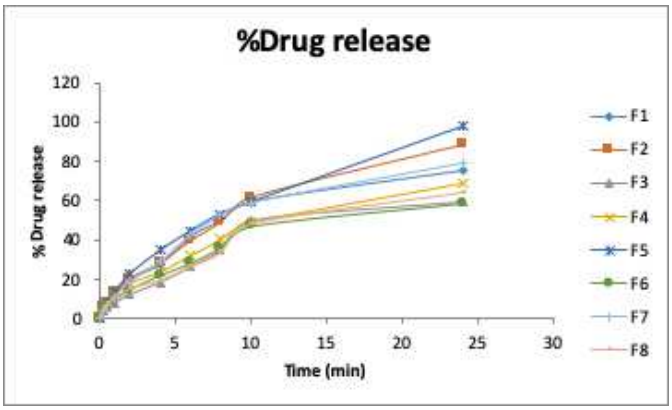

Figure 6: % Drug release profile of Aceclofenac Niosomal gel formulations (F1-F8)

Table 5: % Entrapment efficiency and % Drug content after stability studies

Number of Days	% Entrapment Efficiency at temperatures			% Drug Content at temperatures		
	4±2°C	25±2°C	37±2°C	4±2°C	25±2°C	37±2°C
15	91.8	91.63	91.29	97.65	97.19	96.81
30	90.6	90.42	89.75	97.16	96.14	95.37
45	90.27	88.67	84.54	96.23	95.28	94.18
90	89.93	85.42	78.83	95.45	94.39	92.86

in phosphate buffer pH 7.4 Formulation equivalent to 5mg of Aceclofenac was placed in the donor compartment. The receptor compartment consisting of PB pH 7.4 (containing 0.02% w/v of ethanol to retard microbial growth) was maintained at 37±2°C under constant stirring upto 24 hrs . The donor chamber and the sampling port were covered with lid to prevent evaporation during the study. Aliquots of 5 mL were withdrawn periodically at different time intervals (0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hrs) and replaced with equal volume to maintain constant receptor phase volume. At the end of the study, the samples were suitably diluted and the amount of drug was determined spectrophotmetrically at 275 nm.

Stability Studies

The formulations stored in glass vials covered with aluminum foil were kept at room temperature and in refrigerator (4°C) for a period of 30 days. At definite time intervals (10, 20, and 30 days), samples were withdrawn and hydrated with phosphate-buffered saline (pH 7.4) and observed for any sign of drug crystallization under optical microscope. Furthermore, the samples were also evaluated for particle size and percent retention of Aceclofenac.

RESULTS AND DISCUSSION

Entrapment efficiency: The % entrapment efficiency of niosomal vesicles formulations were found to be in the range of 54.18±0.59 to 92.71±0.56. Entrapment efficiency of the F5 formulation was high (maximum 92.71±0.56 for F5).

Table 6: Drug entrapped and % Drug content in niosomes

Formulation	% Entrapment Efficiency
F1	77.12±1.05
F2	88.50±0.83
F3	63.19±0.96
F4	67.66±0.69
F5	92.71±0.56
F6	59.44±0.33
F7	80.24±0.48
F8	54.18±0.59

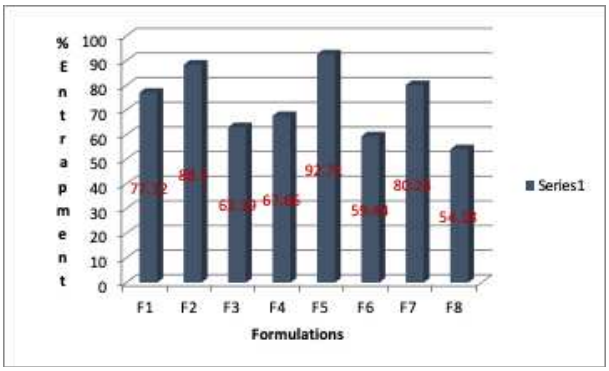

Figure 7: Entrapment efficiency of different formulations

pH value of topical niosomes gel: The value of pH of topical niosomal gels was measured by using digital pH meter (LabindiaSab 5000 pH meter) at the room temperature. The pH of all topical niosomal gels was found to be in the range of 7.4±0.02 to 7.4±0.08.

In-vitro **drug release study:** The *in-vitro* release study in phosphate buffer saline pH 7.4 was carried out using Franz diffusion cell according to procedure. The results are shown in below tables.

CONCLUSION

Aceclofenac belongs to non-steroidal anti-inflammatory drug (NSAID) is considered to be the first-line drug in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The drug is having a narrow therapeutic index, short biological half-life (about 4 h) as well as two third (70-80%) of the dose is excreted by renal transport and it makes aceclofenac dosing frequency more than once a day. As this dosage form would reduce the dosing frequency. In niosomes, the vesicles forming amphiphile are a nonionic surfactant such as span 60 which is usually stabilized by addition of cholesterol.

Finally, it can be concluded from the results of present study that niosome gel improve the transdermal delivery, prolong the release, and improve the site specificity of the drug Aceclofenac. Niosomes formed with F5 formulation is a promising approach to improve the permeability of aceclofenac in a period of time. Niosomes creates a new opportunity for the well-controlled transdermal delivery of a number of drugs that have a problem of administration by other routes.

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