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NIOSOMES AS CARRIERS FOR TOPICAL DELIVERY OF ACECLOFENAC: PREPARATION, CHARACTERIZATION AND *IN VIVO* EVALUATION

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ABSTRACT

Aceclofenac-loaded niosomal cream were developed to provide sustained and localised drug delivery into the skin, increasing the medication's anti-inflammatory activity and lowering its systemic adverse effects. Different molar ratios of surfactant, cholesterol, and charge inducers were used to create niosomes using the thin-film hydration method. Formulations were characterized for entrapment efficiency, morphology, size, and zeta potential. In-vitro release and stability studies were conducted on selected formulations. Niosomal cream were evaluated for spreadability, pH, rheological behaviour, and in-vivo anti-inflammatory efficacy. The encapsulation efficiency of the formulations was good, reaching 70%. Vesicles had an entrapment efficacy of 84% to 94%, were spherical in form, and ranged in size from 425 to 485 nm. The study suggested that the F5 formulation had the best trapping efficiency and in-vitro release. In-vivo studies revealed that niosomal cream showed a better sustained anti-inflammatory effect than drug plain gel and the marketed product, which was confirmed by the paw edema test. Niosomal cream are promising formulations for sustained local delivery of Aceclofenac. It will provide a new method for future study.

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most often prescribed medications for treating pain and inflammation.[1] An oral NSAID called aceclofenac has been suggested for the treatment of osteoarthritis and rheumatoid arthritis. [2,3] Additionally, it possesses analgesic, antipyretic, and anti-inflammatory properties.[4] Chronic usage of aceclofenac oral administration results in gastrointestinal bleeding and ulceration. It also results in anaemia because of GI hemorrhage. These adverse effects are avoided when taking medications via the transdermal route, which also improves patient compliance, prevents first-pass metabolism, and keeps the plasma drug level stable for a longer length of time. As a result, enhanced aceclofenac vesicular formulations with high levels of permeation may be helpful in treating locally irritated skin as well as inflammatory and painful conditions of the body's support systems, including the bones, ligaments, joints, tendons, and muscles. Topical vehicle systems with the potential to alter drug penetration through the skin have drawn more attention in recent years. Chemical enhancers and solvents are used in several dermal vehicles to accomplish this. [5] But because many of these chemical enhancers are irritants, using them regularly may be dangerous. Therefore, it would be ideal to create a topical vehicle system that does not require the use of chemical enhancers to promote drug absorption via the skin. Ethosomes, transfersomes, niosomes, and liposomes are a few possible methods for improving drug transdermal penetration. In order to develop and assess the transdermal distribution of new vesicular carriers niosomes containing aceclofenac and compare their in vitro release performance with that of commercially available aceclofenac gel formulation.

MATERIALS AND METHODS

Aceclofenac, Tween 80,dicetyl phosphate (DCP), were purchased from Sigma-Aldrich. Ethanol, Chloroform, Propylene glycol, Ethanol was procured from Qualigens fine chemicals, Mumbai. All other chemicals were of analytical grade and double distilled water used throughout the experiment.

FORMULATION OF ACECLOFENAC LOADED NOISOME

Formulation of niosomes were done by thin film hydration method. Weigh an accurate amount of tween 80, cholesterol and DCP and dissolve it in 10 ml of chloroform by using a magnetic stirrer. Then to the resultant solution add aceclofenac sodium and stir well until aceclofenac sodium gets dissolved. Then the solution is poured into the round bottom flask and is evaporated in the rotary vacuum evaporated until a thin film is formed on the round bottom flask. Then the formed thin film is hydrated by adding the solution of 10 ml of phosphate buffer saline(PBS) of pH 7.4. After hydration, the solution is transferred into the beaker and is sonicated for about 20 minutes using a sonicator. The composition of ingredients in the formulation was given in the Table1.

Table 1 Composition of aceclofenac loaded noisome.

Ingredients	F1	F2	F3	F4	F5	F6
Aceclofenac (mg)	20	20	20	20	20	20
Tween80 (mg)	10	20	30	20	20	40
Chloesterol (mg)	20	20	20	20	30	20
dicetyl phosphate(ml)	2	2	2	2	2	2
PBS (ml)	10	10	10	10	10	10
Chloroform (ml)	10	10	10	10	10	10

EVALUATION OF ACECLOFENAC NIOSOMES:

Vesicle size and shape analysis:

Optical microscopy:

Niosomes may be seen using optical microscope at magnifications of 40X and 100X. The microscopical picture of synthesized niosomes is shown in Figure 1.

Utilising an optical microscope with a calibrated eyepiece micrometre, vesicle size analysis was performed. 200 or more niosomes were measured one at a time, an average was determined, and the mean diameter and size distribution range were computed. The vesicle sizes of the formulationsare displayed in Figure 2.

Drug Entrapment:

The dialysis membrane technique was used to determine % entrapment efficiency(EE). Niosomal solution in the amount of 2 ml was transferred to the dialysis membrane. This was added to a 250 ml beaker with 100 ml of distilled water, and a magnetic stirrer was used to agitate it. Every 30 minutes for up to 5 hours, samples were obtained, and an equivalent volume of the new medium was supplied to keep the volume constant. A UV spectrophotometer was used to detect the absorbance at 275 nm. The formulations' entrapment effectiveness is shown in Figure 3.

$$\text{Amount of entrapped drug} = \frac{Amount\,of\,entrapped\,drug}{Total\,amount\,of\,drug} X100$$

***In- vitro* release studies:**

Niosomal solution in the amount of 2 ml was transferred to the dialysis membrane. Using a magnetic stirrer, this was added to a 250 ml beaker that also included 100 ml of phosphate buffer saline. Every 30 minutes for up to 5 hours, samples were obtained, and an equivalent volume of the new medium was supplied to keep the volume constant. To determine the quantity of drug release from the niosomal preparations, the absorbance was measured at 275 nm using pure water as the blank. To assess the manner in which niosomal formulations release drugs, the proportion of drugs released was plotted against time. The drug release of the formulations in vitro is shown in Figure 4.

CREAM FORMULATION

Pharmaceutical creams are semisolid dosage forms that include one or more drugs with ingredients that have been dissolved or dispersed in an appropriate base. Then, the benefits of the cream include prolonged contact at the application site, avoidance of first-pass metabolism, and convenience and ease of use.

Procedure:

The necessary components were precisely weighed before melting the stearic acid and lanolin in a beaker at 60°C. Add glycerine, triethanolamine, and water to another beaker and heat to 70 °C before adding the first beaker's mixture in a second beaker drop by drop while stirring continuously. To create a consistent product, add methyl paraben, propylparaben, and rose oil after chilling. Table 2, provides the formula for the cream preparation.

Table 2Formulation of niosomal cream.

S.No.	Ingredients	Quantity for 100 gm	Quantity for 20 gm
1	Stearic acid	18 g	36 g
2	Glycerine	3 g	0.6 g
3	Lanoline	2 g	0.4 g
4	Triethanolamine	1 g	0.2 g
5	Methyl paraben	0.18 g	0.036 g
6	Propyl paraben	0.02 g	0.04 g
7	Rose water	q.s	q.s
8	Purified water	75.8 ml	15.16 ml

EVALUATION OF ACECLOFENAC NIOSOMAL CREAM

Physical properties [8]:

The cream was observed for colour, odour and appearance.

Determination of pH and Spreadability:

pH:

In a 100 ml beaker, 5 ± 0.01gm of cream were precisely weighed. The cream was mixed with 45 cc of water and added. Using a pH meter at 27°C, the pH of the suspension was measured [9]. Which was displayed in the Table 3.

Spreadability:

Two glass slides with typical dimensions were chosen. A slide was covered with the formulation whose spreadability was to be determined. The formulation was positioned on top of the other slide, which had a gap of 5 cm between it and the other slide. The upper slide was weighed down with a 100g weight. In order to create a thin layer, the formulation between the two slides was uniformly compressed. After the weight was removed, the excess formulation that had adhered to the slides where the formulation had been applied was fixed. A pan and a basic pulley were used to provide force to the second movable slide, which was positioned on top of it. It's one end was secured to a string. A 30gm weight was placed on the pan, and the time it took the upper slide to move 5 cm and separate from the bottom slide under the influence of the weight was recorded. Following that, the spreadability was determined using the following formula. [10,11] spreadability of the cream was given in Table 3.

$$\text{Spreadability} = m \times l/t$$

M = weight tied to the upper slide, l= length of glass slide, t= time taken in seconds.

***In vivo* anti-inflammatory studies of aceclofenacniosomal cream**

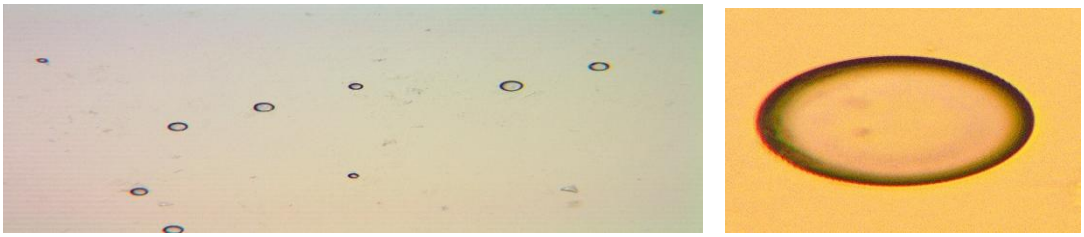
Male rats weighing 200-250 g were used for the in vivo studies. They were given free access to water but were not permitted to eat for 12 hours before the trial.The approval of the institutional animal ethical committee 2009/PO/Re/18/CPCSEA on 13-04-2018was obtained before starting the study.The animals were split into four groups of four each. Animals in Group I, which served as a drug-free control, were fed saline. Group II received normal treatment with aceclofenac cream. In the paws of the rats in Groups III and IV, ordinary niosome and Aceclofenacniosome cream, respectively, were administered. On the same right hind paw of the rats, 0.1ml of 1% carrageenan in normal saline was injected to cause inflammation. Then, for five hours, at 30-minute intervals, the paw oedema was assessed using a plethysmometer. Figure 5 represents the *in vivo* anti-inflammatory activity of aceclofenacniosomal cream.

RESULTS AND DISCUSSION

Evaluation of aceclofenacniosomes:

Vesicle shapeand sizeanalysis:

Optical microscopy technique was used for the analysis of vesicleshape and size of aceclofenacniosomes.



(a) (b)

Figure 1 Microscopical picture of synthesized niosomes under (a) 45X and (b) 100X.

Vesicle sizes of formulation (F1 -F6) was analyzed by optimal microscopy method.

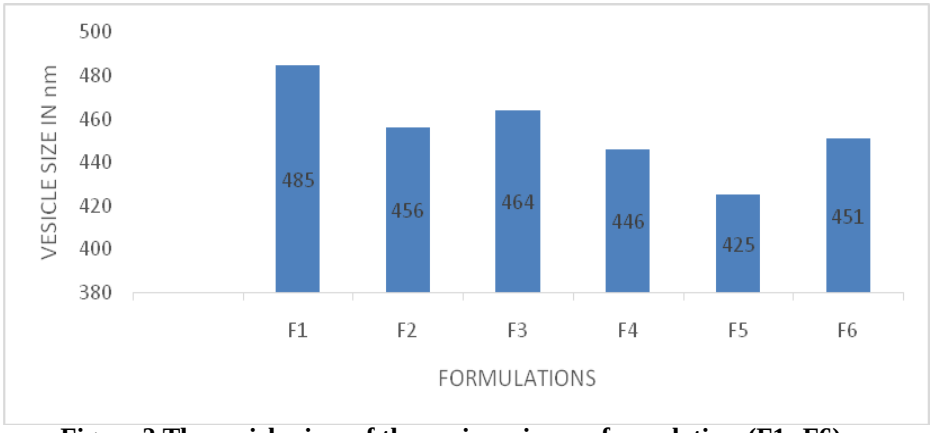


Figure 2 The vesicle sizes of the variousniosomeformulations(F1 -F6).

Drug Entrapment:

The entrapment efficiency of all formulations was evaluated. Based on the entrapment efficiency evaluation results, it turned out that all formulations (F1-F6) had good entrapment, with the F5 formulation exhibiting the greatest entrapment among them.

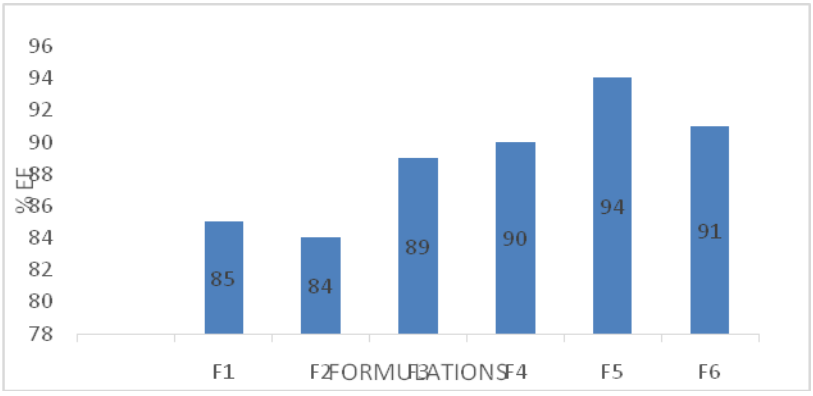


Figure 3 Drug Entrapment of different formulation.

***In-vitro*drug release studies:**

In-vitro dissolution tests were performed on all aceclofenacentrappedniosomeformulations. Based on in vitro dissolution results, all formulations (F1-F6) demonstrated drug release after determining the lag period, which was made feasible by pH-dependent and site-specific drug release polymers, and the F5 formulationshows excellent drug release as 70.012% at the end of 180 minutes.

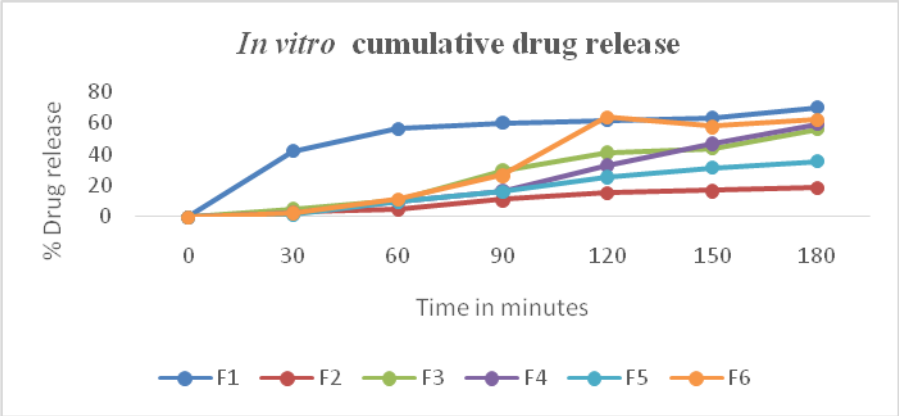


Figure 4 *In-vitro* cumulative drug release of the formulations (F1-F6).

EVALUATION OF ACECLOFENAC NIOSOMAL CREAM

The physical parameters of the niosomal cream were performedas per procedures given in standard references.

Determination of pH and Spreadability:

The pH of the niosomal cream was determined using a pH meter and spreadability by the standard procedure.

Table 3 pH and Spreadability of the Niosomal cream.

Formulation	pH	Spreadability cm/5 min
F1	4.34	4.4
F2	4.55	4.4
F3	4.2	4.3
F4	5.05	4.1
F5	4.88	3.8
F6	4.72	3.7

***In vivo* anti-inflammatory studies of niosomal cream:**

Male rats were used for the in vivo studies.The animals were split into four groups of four each andfor five hours, at 30-minute intervals, the paw oedema was assessed using a plethysmometer.

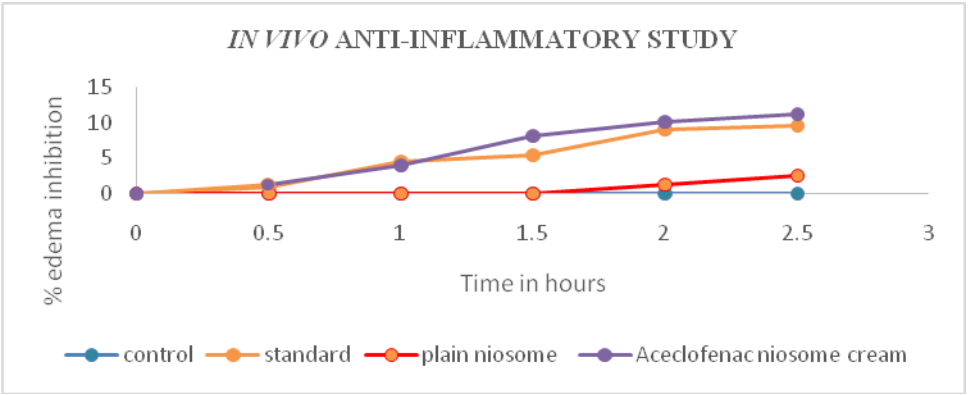


Figure 5 *In vivo* anti-inflammatory activity of aceclofenacniosomal cream.

CONCLUSION

The formulation of aceclofenacniosomal cream provides a practical strategy for achieving an effective therapeutic effect by releasing the drug. Aceclofenacniosomes were effectively generated by thin film hydration utilising tween 80 and cholesterol in various ratios in the current study. The manufactured niosomes were assessed in terms of vesicle size, entrapment efficiency, and in-vitro drug release. It was then developed as a niosomal cream, and the formulated cream was examined for its physical characteristics, pH, spreadability, and in-vivo anti-inflammatory studies on rats. The best and most optimised F5 formulation has been identified. This new technique would be suggested for future components of the system.

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Conflicts of interest

Nil.

Abbreviation

NSAID	- Nonsteroidal anti-inflammatory drugs
GI hemorrhage	– Gastrointestinal hemorrhage
DCP	- Dicetyl phosphate
PBS	- Phosphate buffer saline
UV	– Ultra violet
% EE	- Percentage entrapment efficiency
nm	– Nano meter
ml	– milli liter

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Ethical Approval and Consent to Participate No	2009/PO/Re/18/CPCSEA and 13-04-2018
Availability of Data and Material/ Data Access Statement	Not relevant
Authors Contributions	Equal contribution by all authors.

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