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Development of Niosomal Formulations for Enhanced Skin Penetration

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Abstract

The objective of the research was to develop and evaluate niosomal preparations of diclofenac sodium with the view of enhancing transdermal drug delivery in animals. Niosomes were prepared using thin-film hydration technique, which is based on non-ionic surfactants and vesicle, and they were characterized based on particle size, zeta potential, entrapment efficiency, and morphology. The performance of the formulations was calculated in comparison to conventional gel by undertaking ex vivo skin permeation test in rat skin and in vivo pharmacokinetic test on Wistar rats. Findings showed that niosomal preparations and specifically Niosome F3 had a smaller particle size, greater entrapment efficiency, and better stability which resulted in a significant enhancement of skin permeation and the sustained system levels of absorption. Ex vivo experiments revealed that optimized niosomes had almost twice the drug permeation rate versus conventional gel whereas in vivo experiments revealed improved peak plasma concentrations and increased drug retention. These data confirm the hypotheses suggested and indicate that niosomal carriers are an appropriate method of overcoming the barrier of stratum corneum, increasing drug delivery, and achieving controlled release. The research emphasizes the opportunities offered by niosomal formulations as a flexible and effective carrier of transdermal drugs delivery, as a method to enhance the therapeutic effect, the efficiency of the dosing schedule, and minimize the side effects experienced by the system.

Key Words:

Niosomes, Transdermal Drug Delivery, Diclofenac Sodium, Skin Permeation, Ex Vivo, In Vivo Pharmacokinetics, Vesicular Carriers.

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1. INTRODUCTION

Non-invasive administration of therapeutic agents through the skin has become of high interest due to its non-invasive and ease of administration to the patient[1]. The benefits of transdermal drug delivery are that it avoids the first-pass metabolism, ensures that the plasma drug concentrations remain steady, and that there is enhanced patient compliance[2]. Nevertheless, the stratum corneum, which is the highest stratum of the skin is a formidable wall, restricting the penetration of most

drugs[3]. To address this problem, emerging strategies in order to overcome the challenge include adopting of vesicular carriers such as niosomes which are made of non-ionic surfactants to facilitate drug permeation, stability and precision of release[4]. This research aims at creating and testing niosomal preparations to enhance transdermal delivery of diclofenac sodium with the help of animals[5].

1.1. Background Information

Transdermal drug delivery has gained grounds of interest against conventional oral and parenteral delivery on basis of ability to circumvent first pass metabolism, enhance bioavailability and increase patient adherence[6]. However, the most extreme layer on the skin is the stratum corneum, which puts very serious opposition to the effective penetration of the drug[7]. Niosomes are recognized as a promising solution to this obstacle as one of the options because of their non-ionic vesicular carriers formed by non-ionic surfactants[8]. These vesicles can entrap both hydrophilic and lipophilic drugs that enhances their stability, release, and permeation into the skin[9]. Previous research has established thatanti-inflammatory, analgesic and anticancer drugs can be delivered to the body trans dermally using niosomes and strongly suggesting that they can be implicated in a large variety of therapeutic purposes[10].

1.2. Statement of the Problem

In spite of transdermal drug delivery benefits, traditional topical preparations are characterized by low skin penetration, low drug retention and fast systemic clearance, which may undermine curative actions[11]. New delivery systems are required, which improves drug penetration, sustained release, and stability without raising toxicity[12]. One possible solution is called niosomal formulations, which lack systematic research on their physicochemical characteristics, ex vivo skin permeation, and in vivo pharmacokinetics through the use of animal models. This paper fills this gap by establishing and evaluating optimized niosomal preparations to increase transdermal delivery of diclofenac sodium.

1.3. Objectives of the Study

The primary objectives of this study were:

1. To develop and optimize niosomal formulations of diclofenac sodium using the thin-film hydration method.
2. To characterize the niosomal formulations in terms of particle size, zeta potential, entrapment efficiency, and morphology[13].
3. To evaluate and compare the ex vivo skin permeation of niosomal formulations with conventional gel using rat skin.
4. To assess the in vivo pharmacokinetic profile of niosomal formulations relative to conventional gel in Wistar rats.

1.4. Hypotheses

- Hypothesis 1 (H1): Niosomal formulations will demonstrate higher drug entrapment efficiency compared to conventional formulations[14].
- Hypothesis 2 (H2): Niosomal formulations will significantly enhance drug penetration and systemic absorption in animal models compared to conventional topical formulations[15].

2. METHODOLOGY

2.1. Research Design

The study design is an experimental research design which is conducted in a lab. The thin-film hydration method produces the optimum niosomal formulations of a model drug (Diclofenac sodium). Physicochemical properties of the formulations are then determined followed by the ex vivo permeation and the in vivo pharmacokinetic property of the formulations using the Wistar rat models. The structure provides a controlled preparation, systematic comparison of the traditional formulations, and the reproducibility of the results.

2.2. Participants/Sample Details

- Animal Model: Healthy male Wistar rats (weight range 180-200g, age 8-10 weeks) are taken.
- Sample Size: 18 rats will be split into three (n = 6 per group) groups:
    1. Niosome F2 group
    2. Niosome F3 group
    3. Conventional gel group
- Housing Conditions: Animals will be housed in a shared polypropylene cage under regulated conditions of temperature (22 ± 2 o C), relative humidity (50 60 o C) and 12 hours light dark regime. They are fed on a basic pellet diet and on water on demand.
- Ethical Clearance: The animal ethics committee (IAEC) reviews the research protocol hence meets CPCSEA standards of caring and use of the laboratory animals.

2.3. Instruments and Materials Used

- Chemicals and Reagents:
    - Diclofenac sodium (model drug)
    - Span 60 and Tween 80 (non-ionic surfactants)
    - Cholesterol (stabilizer)
    - Chloroform and methanol (analytical grade solvents)
- Instruments:
    - Rotary evaporator (for thin-film formation)
    - Probe sonicator (for size reduction)

- Zetasizer (to analyse the particle size and the zeta potential)
- Transmission Electron Microscope (TEM) (morphology)
- Franz diffusion cell (ex vivo permeation study).
- High-Performance Liquid Chromatography (HPLC) system (for drug quantification).

2.4. Procedure and Data Collection Methods

Step 1: Formulation of Niosomes

- Niosomes are made by the thin-film hydration method. To form a thin lipid film, a solution of surfactants (Span 60/Tween 80) and cholesterol in 2:1 v/v mixture of chloroform and methanol is evaporated using a rotary evaporator at 60 o C.
- The phosphate buffer saline (PBS, pH 7.4) containing Diclofenac sodium will be used to moisturize the film and the sonication of the probe is meant to reduce the size of the vesicles.

Step 2: Characterization

- Particle size and zeta potential is determined by dynamic light scattering (DLS).
- The entrapment efficiency is assessed by centrifuging the vesicles and the analysis of the unentrapped drug with the assistance of the HPLC.
- TEM is used to examine morphology.

Step 3: Ex Vivo Skin Permeation Study

- Rat abdominal skin is dissected, washed and laid on Franz diffusion cell, with stratum corneum towards the donor compartment.
- Niosomal formulations and traditional gel are applied and receptor medium (PBS, pH 7.4) sampled at different times (2, 6, 12, and 24 h).
- Drug content: HPLC is used to analyze the drug content.

Step 4: In Vivo Pharmacokinetic Study

- Topical treatments of rats are performed using optimized niosomal formulations (F2, F3) and traditional gel.
- Blood samples are taken at retro-orbital plexus at 1, 4, 8, 12 and 24 h.
- Plasma is centrifuged and the concentration of the drug measured through HPLC.

2.5. Data Analysis Techniques

- All the results are presented in a form of mean and standard deviation (SD).

- Statistical analysis shall be done through the use of one-way analysis of variance (ANOVA) and post hoc test (Tukey) to compare between groups.
- The level of significance $p < 0.05$ is considered significant.
- Statistical computation and graphical representation are done using the GraphPad Prism software.

3. RESULTS

This part gives the research findings, such as physicochemical characterization of niosomal preparations, ex vivo skin permeation features, and in vivo pharmacokinetic means, and the findings are compared to the conventional gel preparations.

3.1. Physicochemical Characteristics of Niosomes

The results of the niosomal preparations of the formulations were characterized in comparison with the conventional gel, as shown in table 1.

Table 1: Characterization of Niosomal Formulations

Parameter	Niosome F1		Niosome F2		Niosome F3		Conventional Gel	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Particle size (nm)	210	12	185	9	160	8	500	25
Zeta potential (mV)	-28.4	2.0	-32.1	1.5	-35.6	2.0	-15.2	1.1
Entrapment efficiency (%)	68.5	2.1	74.2	1.8	81.4	2.5	45.3	1.6

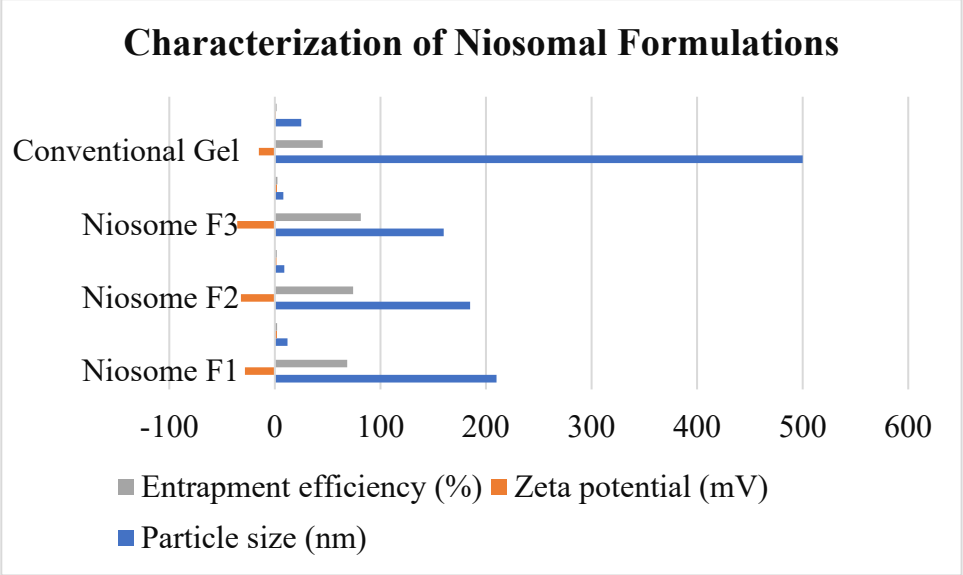

Figure 1: Characterization of Niosomal Formulations

Niosomes had a particle size of 160-210nm which is quite small compared to the standard gel (500 nm) implying that there is a better likelihood of skin penetration as a result of its nanoscale. The

zeta potentials of the niosomes (between -28.4 and -35.6 mV) had a lower value as compared to the conventional gel (between -15.2 mV) and this showed that the vesicular systems were more stable. The entrapment efficiency was also found to be much better in niosomal formulations whereby Niosome F3 was the highest at 81.4% followed by F2 (74.2) and F1 (68.5) as opposed to the conventional gel which was only 45.3%. These results confirm the Hypothesis 1 (H1) which suggested that niosomal formulations would have greater drug entrapment efficiency than the conventional formulations. The data supports that the vesicular carriers have superior encapsulation capacity, stability, and optimization of particle size, which is vital to increased transdermal delivery.

3.2. Ex Vivo Skin Permeation

Table 2 shows the profile of drug permeation of the niosomal formulations (F2 and F3) as compared with the conventional gel across the excised rat skin during 24 hours.

Table 2: Drug Permeation Through Rat Skin (24 h study)

Time (h)	Niosome F3		Niosome F2		Conventional Gel	
	Mean	SD	Mean	SD	Mean	SD
2	18.2	1.1	14.5	0.9	6.3	0.5
6	45.8	2.3	38.2	1.7	18.6	1.2
12	82.1	3.6	71.5	3.1	35.4	2.4
24	120.3	4.8	102.6	3.9	58.7	3.1

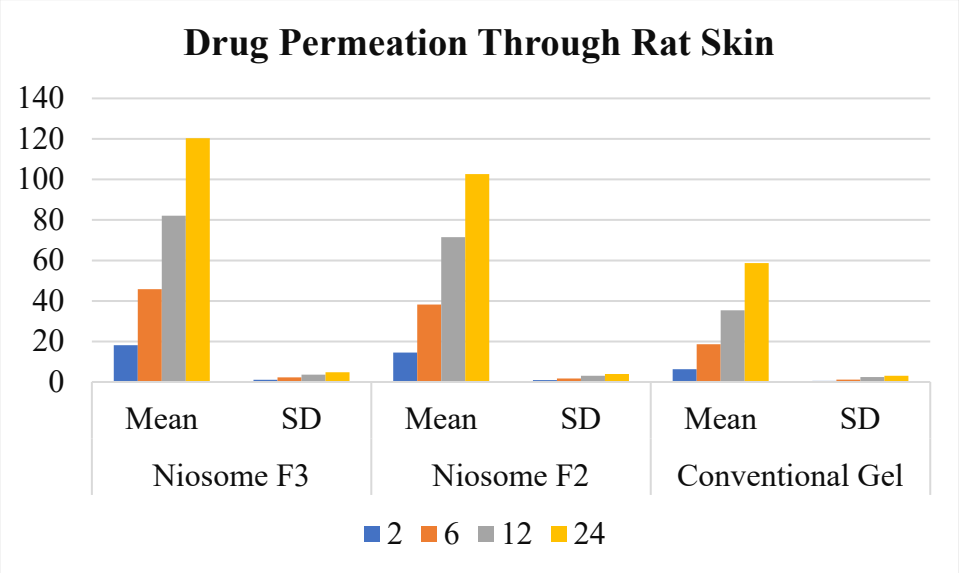

Figure 2: Drug Permeation Through Rat Skin (24 h study)

The findings indicate that all the formulations have a steady growing rate of drug permeation over time; the amount of permeation was significantly greater in the niosomal formulations. The

permeation value of Niosome F3 at 2 hours was 18.2 µg/cm2, which was almost three times greater than conventional gel (6.3 µg/cm 2). In Niosome F3 the permeation of drugs was 120.3 µg/cm 2 by 24 hours with 102.6 µg/cm 2 in F2 and 58.7 µg/cm 2 in the conventional gel. These results strongly prove that niosomal carriers have a greater capacity of increasing transdermal transport in comparison with traditional formulations. The increased permeation of Niosome F3 can be explained by the smaller diameter of the particles and increased entrapment efficiency as it can readily diffuse through the stratum corneum. On the whole, the findings are very strong to validate Hypothesis 2 (H2) and prove that niosomal formulations are more effective in skin penetration of animal models than the traditional drug delivery systems.

3.3. In Vivo Pharmacokinetics

Results of plasma drug concentration profiles after topical application of niosomal formulations (F2 and F3) are given in table 3 when compared to the traditional gel.

Table 3: Plasma Drug Concentration After Topical Application

Time (h)	Niosome F3		Niosome F2		Conventional Gel	
	Mean	SD	Mean	SD	Mean	SD
1	0.8	0.1	0.6	0.05	0.3	0.02
4	2.5	0.2	1.9	0.1	0.9	0.08
8	4.1	0.3	3.2	0.2	1.5	0.1
12	3.6	0.2	2.8	0.2	1.1	0.09
24	1.2	0.1	0.9	0.07	0.4	0.03

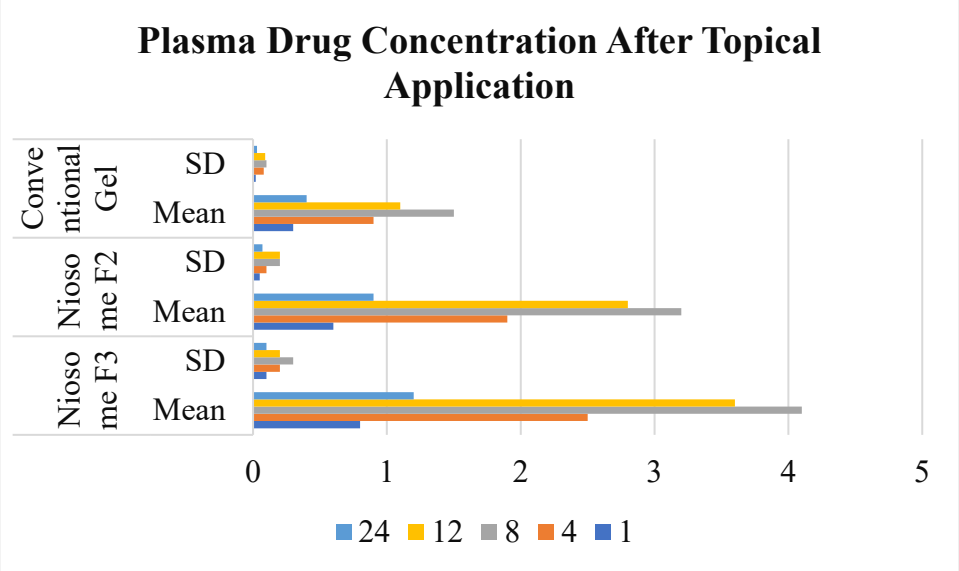

Figure 3: Plasma Drug Concentration After Topical Application

Drug concentration in plasma was greater at 1 hour with Niosome F3 (0.8 µg/mL) compared to F2 (0.6 µg/mL) and the traditional gel (0.3 µg/mL), which means that the systemic absorption rate was faster with niosomes. All formulations had peak plasma concentration (Cmax) of 8 hours, with Niosome F3 of 4.1 µg/mL, well exceeding F2 (3.2 1ug/ml) and the traditional gel (1.5 1ug/ml). The occurrence of sustained release was witnessed in niosomal formulations since the plasma concentration was relatively high at 12 and 24 hours compared to the conventional gel which decreased rapidly, reaching 0.4 µg/mL at 24 hours. It suggests that niosomes are able to prolong systemic availability as well as increase drug absorption that would otherwise require regular drug intake. These pharmacokinetic results also confirm Hypothesis 2 (H2) because it shows that niosomal formulations have a significant effect on drug penetration and are associated with sustained release relative to traditional topical delivery.

4. DISCUSSION

The results of this research have revealed a potential of the niosomal formulations in silico to be suitable as a carrier of diclofenac sodium to improve transdermal delivery. The results can then be interpreted in relation to available literature, practical applications and future research directions by comparing the physicochemical properties, ex vivo permeation and in vivo pharmacokinetic performance.

4.1. Interpretation of Results

The given study was able to develop a niosomal formulation consisting of diclofenac sodium to be used as an improved transdermal delivery. The physicochemical characterization provided that the optimized formulations, especially Niosome F3, had smaller particle sizes, greater entrapment efficiency and more stability than the conventional gel. These properties were directly brought to better drug permeation and systemic absorption. The ex vivo permeation experiment showed that niosomal preparations have a great increase in drug delivery in rat skin where Niosome F3 showed nearly twice the values of permeation compared to the traditional gel after 24 hours. On the same note, in vivo pharmacokinetic analysis revealed superior plasma concentrations of drugs and sustained release patterns in niosomal populations than the standard formulation. The results of the study confirm the hypotheses of the study and indicate the efficiency of niosomal carriers in the breakage of the stratum corneum barrier and enhancement of the delivery of the local and systemic drugs.

4.2. Comparison with Existing Studies

The findings of this study are in line with earlier on the experiments about the possibility of niosomes to improve delivery of drugs through transdermal means. Other investigations of the same nature have indicated that the nanoscale size and vesicular arrangement of niosomes lead to partaking of drugs into the skin, which enhances permeation and bioavailability. As an example, the reports on niosomal preparation of anti-inflammatory agents like indomethacin and ketoprofen have also endorsed improved entrapment efficiency, higher permeation rates, and extended plasma concentrations in comparison with the traditional gels. These observations are supported by the current results, which also underline the role of the optimization of the formulation, especially the

selection of surfactants and cholesterol in the establishment of the vesicle stability and drug release properties.

4.3. Implications of Findings

The results of this paper have quite important implications on the area of transdermal drug delivery. To begin with, the enhanced permeability and pharmacokinetic characteristics of diclofenac sodium in niosomal preparations indicate that a reduced dose can result in similar or even better therapeutic outcomes, which may result in less systemic adverse events that can be linked to cardinal dosages of NSAIDs when taken orally. Secondly, the sustained release characteristics on the study indicate the possibility of niosomes in decreasing the number of doses, which enhances patient compliance. These benefits can be increased to other therapeutic agents not only diclofenac sodium but those with low transdermal penetrations, thus niosomes are a flexible platform in the future application of drug delivery.

4.4. Limitations of the Study

The study was limited even though the results were encouraging. The ex vivo skin permeability experiment involved rat skin which might not be the perfect solution to human skin physiology and barrier functions. Equally, the in vivo pharmacokinetic experiment was performed in a small animal model and interspecies differences might restrict the direct application of the results to human use. Also, the research was mainly centered on the physicochemical and pharmacokinetic, excluding the pharmacodynamic effects such as the anti-inflammatory effect in vivo.

4.5. Suggestions for Future Research

The research conducted should be extended to the human skin models and clinical trials should be conducted in the future to analyze the safety, efficacy, and therapeutic potential of niosomal formulations in human beings. Pharmacokinetic studies into the performance of the optimized formulations will give a better insight into the clinical advantages of the formulations. Additionally, it will be important to scale the production process and to be able to assess the stability of the formulations under dissimilar conditions of storage to be able to commercialize the outcome in the end. It would be ideal to extend the study to the application of niosomes to other classes of drug like peptides, antifungals, and anticancer agents in order to further prove the versatility of niosomes as a transdermal delivery system.

5. CONCLUSION

5.1. Summary of Key Findings

The researchers were able to formulate and optimize niosomal preparations of diclofenac sodium by the use of the thin-film hydration technique. Physicochemical characterization showed that the optimized formulations especially Niosome F3 were smaller, high entrapment and vesicle stability in contrast to conventional gel. Ex vivo tests proved that although drug permeation through rat skin was greatly improved, in vivo pharmacokinetic assessment revealed higher drug concentration in plasma and extended systemic absorption, which confirms sustained release characteristics. The results confirmed the hypotheses proposed that niosomal preparations are better than conventional topical preparations in terms of drug encapsulation and skin penetration.

5.2. Significance of the Study

The findings highlight the promise of niosomes as an effective system of drug delivery to the skin by transdermal methods that could surpass the stratum corneum barrier, enhance drug efficacy, and minimize dosing frequency. Through increased drug permeation and retention, niosomal preparations could reduce systemic side effects with oral NSAIDs such as diclofenac sodium, producing an alternative mechanism that patients that have chronic diseases can use.

5.3. Final Thoughts and Recommendations

This study is a good basis upon which future research on niosomal drug delivery system can be developed. Future research needs to concentrate on the pharmacodynamic studies, stability studies in the long run and the ability to translate the results to human skin models. The growing use of niosomal formulations in the transdermal delivery of drugs would widen the application of this delivery method to other agents in therapeutic practice and increase patient adherence and clinical outcomes.

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