ORIGINAL ARTICLE

# Preparation and Characterization of Topical NIOSOMAL Gel for Acne Treatment

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## ABSTRACT

Acne is a widespread skin condition that usually impacts individuals at some point in their lives. The structure of the stratum corneum is often likened to a brick wall, with corneocytes surrounded by intercellular lipid lamellae acting as the mortar. Using elastic vesicles (niosomes) that can be transported through channel-like structures in the skin is a highly efficient approach for delivering drugs to the affected area of the skin. This study utilized niosomes as a delivery system for a combination of adapalene and benzoyl peroxide (BPO). The aim was to effectively treat acne by targeting the site of infection. Within this section, the evaluation of drugs enclosed in a niosomal gel formulation was conducted to determine their specific characteristics through *in vitro* and *ex vivo* testing. The drug content in niosomal gel formulation F2 is 91.11%, in F6 is 94.21%, and in F8 is 96.99%. The total percentage of drug release from formulations containing ordinary adapalene gel (F8) was 99.27%. The release kinetics of the chosen niosomal gel were precisely regulated through diffusion, specifically following the Higuchi model. In a span of 24 h, the niosomal gel allowed for a precise permeation of 6.25 ± 0.14 g/cm$^2$ of adapalene, whereas the permeation of BPO amounted to 5.04 ± 0.014 g/cm$^2$. Furthermore, the niosome gel's stability was assessed at various temperatures to identify the necessary storage conditions for preserving the quality of the formulation.

**Key words:** Antiacne combination therapy, retention efficiency, therapeutic index

## INTRODUCTION

Therapeutic interventions often fall short due to unwanted side effects, inefficient drug metabolism, patient non-compliance, or rejection of invasive therapy. Various attempts have been made to address these concerns through the development of drug carriers. However, certain carriers such as liposomes, niosomes, and microemulsions can only penetrate the outer layers of the skin. Various strategies have been employed to address the challenge posed by the stratum corneum barrier. Advancements in drug delivery technology, including penetration enhancers, non-gradient-dependent forces, microneedles, jet injectors, and other innovations, have emerged in recent years. In addition, modifications to the drug carrier, such as the utilization of vesicles, have been made to enhance skin permeability.[1]

Enhancing the absorption of drugs through the skin is an essential aspect of modern medicine. The topical route of drug delivery for treating skin illnesses is a promising new frontier in drug delivery research, offering an alternative to the more traditional means of drug delivery (oral administration/injection). Acne is a common skin condition that impacts a large number of individuals at various stages of their lives.[2]

Acne vulgaris is characterized by the presence of open and/or closed comedones (blackheads and whiteheads) as well as inflammatory lesions such as papules, pustules, or nodules. This condition can last for an extended period of time. Sebaceous follicles are distinct pilosebaceous units that are visible on the face, chest, and back, and they are the focus of this skin condition. Acne is marked by inflammation triggered by bacteria that produce pus, such as *Propionibacterium* acnes and *Staphylococcus epidermidis*.[3,4]

The organism's extracellular lipases break down sebum triglycerides into glycerol and free fatty acids, which both have pro-inflammatory properties. Topical medications such as retinoids, benzoyl peroxide (BPO), azelaic acid, erythromycin, clindamycin, and combination therapy are effective treatments

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for acne. Possible side effects of topical antiacne treatments include itching, redness, scaling, flaring up, photosensitivity, and bacterial resistance.[5,6] Adapalene and BPO, along with cyclical applications, are commonly employed to address acne concerns. Thanks to the remarkable barrier properties of skin membranes, the therapeutic impact of numerous standard topical drugs available in the market has been significantly reduced. The corneocytes comprising the stratum corneum and the intercellular lipid lamellae enveloping them are often compared to bricks forming a wall. Elastic vesicles (niosomes), with their ability to penetrate the skin through channel-like features, offer an optimal solution for delivering drugs precisely to a targeted area of damaged skin.[7,8]

Vesicular drug delivery systems are designed to be highly efficient, with a focus on flexibility, softness, and self-regulation. Combining surface-active components in specific proportions yields liposomal membranes that are highly flexible.[9]

Furthermore, the nanoscale dimensions of these particles make them undetectable by the immune system, enabling them to effortlessly navigate through the intricate structure of the skin and reach their intended destination. This not only allows for reduced drug dosages but also minimizes the occurrence of unwanted side effects.[10,11] The unique properties of nanocarriers, including their small size, high surface energy, high surface area, composition, and architecture, are what make them highly valuable. Due to their unique properties, they can penetrate the skin and bloodstream more effectively.[12,13]

Colloidal particle carriers such as niosomes and liposomes are known to contain drug reservoirs. Niosomes are synthetic vesicles formed from non-ionic surfactants through hydration. They can be classified as unilamellar or multilamellar depending on their structure. In terms of technical aspects, niosomes outperform liposomes because of their superior stability and absence of disadvantages such as variable phospholipid purity and high cost.[14,15] Extensive research has been conducted on the utilization of these particles as drug carriers in topical medication administration. The Benefits of these carriers include increased drug stability, improved therapeutic effects, extended circulation time in a biological environment, and improved uptake of the enclosed drugs into the desired location, resulting in reduced drug toxicity due to decreased uptake by non-target tissues. Niosomes are capable of encapsulating and transporting a wide range of medicines, including both hydrophilic and lipophilic drugs.[6]

Vesicles have the ability to affect the absorption of pharmaceuticals through dermal drug delivery. They can serve as a soluble matrix, providing sustained drug release, enhancing the permeation of dermally active compounds, or acting as a barrier that limits the rate of drug release. The study utilized Span 60 and cholesterol as niosome components, whereas BPO and tretinoin were used as model medicines for niosomal formulation. An *in vitro* penetration and retention investigation was conducted using niosomal gels with BPO and adapalene.[16]

## MATERIALS AND METHODS

### Materials

Adapalene was procured from Cipla Pharmaceutical, Ahmedabad, India, whereas BPO was gifted by Sun Pharmaceuticals, Hosur, India. Carbopol 940, cholesterol, stearic acid from Himedia Laboratories, Hyderabad. Span 40, Span 60, Span 85 from Loba Chemie, Mumbai, and all other materials and chemicals were of analytical grade.

### Preparation of niosomal gel formulations

#### *Preparation of adapalene niosomal gel*

The gel bases for carbopol 940 are made by homogenizing 1% (w/w) carbopol dispersion in enough water for 30 min using a magnetic stirrer before letting it equilibrate for 24 h. Then, triethanolamine is used to bring the pH level back down to 4.5–6.5.[19] During the stirring phase, adapalene-loaded niosomes are added to the prepared plain gel base, and the process is carried out in the same manner as described for carbopol plain gel bases.

### Evaluation of niosomal gel formulations

#### *Drug content analysis*

Adapalene niosomal gels (100 mg) are dissolved in phosphate buffer (pH 7.4) in a volume of 50 mL using a microcentrifuge. These solutions are diluted with the same buffer solution after being transferred quantitatively to a volumetric flask. After this, the solutions are filtered using membrane filters (0.45 mm pore size) before being analyzed using a spectrophotometer for the presence of adapalene at 237 nm.[20]

#### *pH measurements*

A pH meter is used to determine the exact pH value of each niosomal gel. Every time you use it, you will need to calibrate it with solutions of known pH 4, 7, and 10. To make a 2-h supply of gel, 1 g is mixed with 100 mL of distilled water. To test the pH of the base solution, just place the pH meter's electrode in the liquid. It is recommended to measure the pH 3 times and use an average.[21]

#### *Rheological studies*

On a Brook-field viscometer with spindle number S-06, the viscosity of a gel formulation is measured in triplicate, and the average of three readings is recorded.[22]

### *Transmission electron microscopy (TEM)*

TEM is used to determine the morphology of the adapalene niosomal gel dispersions.[23]

### *Particle size analysis*

Malvern Mastersizer measurements were carried out at 25°C with a 45 mm focus lens and a beam length of 2.4 mm.[24]

### *In vitro* release studies

The *in vitro* release study is conducted by placing 1 g of gel formulations in a dialysis container containing 100 ml of PBS with a pH of 7.4 and 37 ± 10°C. The beakers were stirred at 50 revolutions per minute atop a magnetic agitator.[25] At specified time intervals, aliquots of samples are withdrawn, analyzed at 237 nm with a UV spectrophotometer to ascertain the percentage of drug released, and replaced with an equal volume of fresh PBS pH7.4.

### Kinetics of drug release

Findings from an *in vitro* drug release research of niosomes gel are fitted to many pharmacokinetic equations (including zero order, first order, Higuchi's model, and the Korsmeyer–Peppas equation) to better understand the pharmacokinetics and mechanism of drug release.[11,17]

### *Stability studies*

"Stability testing of new drug substances and products was carried out using International conference on harmonization (ICH) Q1A (R2)." [26,27] The final niosomal formulation combining niosomal loaded BPO and adapalene did not change in viscosity. According to the results of the stability test, the niosomal gel formulation was reliable.

### *In vitro* permeation study

### *Permeation study of prepared antiacne niosomal gel*

Vertical Franz diffusion cells with an effective diffusion area of 2.54 $cm^2$ were used for the *in vitro* skin permeation tests. Wistar rat skin was used in the experiment. After attaching the skin to the receptor compartment, the stratum corneum side was facing up into the donor compartment. Niosomal gel containing 0.1% adapalene and 0.600% BPO was weighed and a total of 200 mg was placed in the donor compartment. For the receptor medium, we employed a 25-mL aliquot of a 1:1 (ethanol/methanol: saline) v/v mixture. A magnetic bar agitated the receptor compartment at a rate of 600 rpm while keeping the temperature at 37°C. Up to 24 h, 3 mL aliquots of the receptor medium were taken out at regular intervals and replaced with fresh receptor solution. UV spectrophotometer readings for BPO (234 nm) and adapalene (237 nm) were taken from the samples.[28] Niosomal gel formulation employing skin from Wistar rats was used to determine the flow of each component.

### *In vitro skin retention study*

By measuring how much drug was kept in the skin samples used in permeation trials, researchers were able to examine vesicles' potential to aid in retaining the drug inside the skin milieu (i.e., depot-effect). After the permeation experiment was completed, the skin affixed to the diffusion cell was removed. To remove any adhering formulation, the epidermis was cleaned with cotton dipped in saline solution, and blotted with tissue paper. Following homogenization of the skin sample in 20 mL of chloroform: methanol/ethanol mixture (2:1, v/v), the resulting homogenate suspension was filtered through filter paper, and the drug concentration was determined with a UV spectrophotometer at the absorption maxima for BPO and adapalene.[29]

### *Stability studies of niosomal gel*

A stability study of the final formulation was conducted by placing the formulation in a stability chamber at 45°C and 65% RH for 1 month and measuring the viscosity of the formulation at various time intervals such as 1, 7, 14, and 30 days and observed the changes in the viscosity of final formulation using Brookfield viscometer."

## RESULTS AND DISCUSSION

### *Evaluation of niosomal gel formulations*

### *Preparation of niosomal gel formulations*

The production of carbopol 940 gel bases entails dispersing 1% (w/w) carbopol in sufficient water, homogenizing the mixture for 30 min using a magnetic stirrer, and then letting the mixture equilibrate for 24 h. Then, stearic acid is added until the pH is in the range of 5–7. Plain gel bases prepared as stated for carbopol are then agitated with adapalene-loaded niosomes, and the procedure is finished as described for carbopol plain gel bases.

### *Drug content analysis*

Accurately weigh 50 mL of phosphate buffer (pH 7.4) and add 100 mg of adapalene niosomal gel to it. These solutions are then diluted with the same buffer solution before being transferred quantitatively to a volumetric flask. Following adapalene spectrophotometric measurement at 237 nm, the resultant solutions are filtered through membrane filters (0.45 mm pore size). Niosomal Gel Formulations F2 (91.11), F6 (94.21), and F8 (96.99) were evaluated for their respective drug content.

### *pH measurements*

Using a pH meter, the pH of each niosomal gel is determined. Before each use, this is calibrated with buffered solutions

at pH 4, 7, and 10. A gram of gel is dissolved in 100 mL of distilled water and left to store for 2 h. The pH level is determined by placing the pH meter's electrode in a stockpile of prepared base solution. The pH is determined in triplicate, with an average value of 6.8 being recorded [Table 1].

### *Rheological studies*

Using a viscometer (Brookfield+ II LV viscometer), the viscosities (in cps) of the polymers were measured. The spindle (TF 59) was rotated at speeds between 0.5 and 100 rpm. Before taking measurements, samples of the gels were to settle for 30 min at the assay temperature (28 ± 1°C). It was determined that the viscosity of F8 gel was 23,500 cps at 0.5 rpm. At 0.5 rpm, the viscosity of F2 gel was determined to be 18500 cps.

### *TEM*

The figures show the outcomes of a TEM analysis of niosomal gel made using either the FG2 or FG3 formulations. Most vesicles could be seen at a glance; they were typically round, had distinct edges, and held substantially of water [Figure 1].

### *Particle size analysis*

The particle size evaluated for niosomal gels F8 was found to be 106 nm as displayed in Figure 1c.

### *In vitro* release studies

Niosomal gel's *in vitro* release was studied using the dialysis bag technique. Formulations using (F8) conventional adapalene gel had a cumulative percentage of drug release of 99.27% after 12 h. A formulation incorporating (F2) span 60 niosomal gel showed a cumulative percentage of drug release of 68.93% after 12 h. After 12 h, 88.91% of a drug-containing formulation (F6) niosomal gel had been released [Table 2]. According to the findings, F8 was more efficient than F6, and F2 was more efficient than F6.

**Table 1:** pH Values of niosomal gel and rheological studies of niosomal gel

| pH values of niosomal gel | | | |
|---|---|---|---|
| **S. No.** | **F2** | **F6** | **F8** |
| 1 | 6.46 | 6.77 | 6.82 |
| 2 | 6.77 | 6.68 | 6.96 |
| 3 | 6.98 | 6.79 | 6.78 |
| Average | 6.73 | 6.74 | 6.85 |
| **Rheological studies of Niosomal Gel** | | | |
| **RPM** | **Viscosity in CPS** | | |
| | **F8** | **F6** | **F2** |
| 0.1 | 23500 | 19500 | 18500 |
| 0.5 | 7000 | 5500 | 4700 |
| 1.0 | 4500 | 2500 | 1650 |
| 5.0 | 2400 | 1620 | 1200 |
| 10.0 | 950 | 650 | 550 |
| 20.0 | 640 | 350 | 200 |
| 50.0 | 310 | 200 | 118 |
| 100.0 | 180 | 95 | 70 |

### Kinetics of drug release

To establish the best order for drug administration, a linear regression analysis was conducted. The kinetics of all formulations is determined by zero order. The Higuchi correlation coefficient calculation has confirmed that the release of the drug is directly proportional to the square root of time [Figure 2]. This indicates that the diffusion process controls the release of adapalene from the niosomal gel. The Higuchi diffusion-controlled model was utilized to develop formulations F8 (0.997), F2 (0.994), and F6 (0.995).

**Table 2:** Cumulative percentage of drug release of niosomal gel

| Time (Min) | Cumulative % drug release of GELS±S.D* | | |
|---|---|---|---|
| | **F8** | **F2** | **F6** |
| 0.25 | −0.03±1.67 | −2.11±1.6 | −2.24±3.56 |
| 0.50 | −0.08±1.88 | −1.33±3.1 | −1.22±2.35 |
| 0.75 | 2.49±2.25 | −3.75±2.7 | −0.56±2.61 |
| 1.0 | 5.48±1.27 | −1.23±2.35 | 0.39±4.15 |
| 1.5 | 6.78±3.88 | −0.83±2.66 | 4.82±1.66 |
| 2.0 | 9.01±1.13 | 0.34±2.17 | 8.34±1.78 |
| 2.5 | 11.06±2.64 | 1.88±2.57 | 9.77±2.16 |
| 3.0 | 17.90±2.27 | 2.16±1.25 | 14.27±2.53 |
| 3.5 | 22.98±2.84 | 6.47±1.59 | 18.65±3.62 |
| 4.0 | 27.23±2.68 | 8.21±2.81 | 22.47±3.14 |
| 4.5 | 30.64±2.83 | 15.47±1.96 | 25.11±3.58 |
| 5.0 | 35.81±2.11 | 18.15±2.16 | 28.34±3.12 |
| 5.5 | 38.29±2.59 | 18.75±2.88 | 32.65±3.13 |
| 6.0 | 42.32±2.14 | 24.15±3.14 | 36.68±3.44 |
| 6.5 | 47.83±3.17 | 26.77±3.85 | 39.98±3.69 |
| 7.0 | 52.10±3.55 | 2814±3.16 | 45.26±2.19 |
| 7.5 | 54.08±3.16 | 32.07±3.19 | 49.46±3.77 |
| 8.0 | 59.74±3.19 | 36.13±3.26 | 52.13±2.97 |
| 8.5 | 64.32±2.95 | 41.28±2.47 | 57.58±2.13 |
| 9.0 | 69.03±3.13 | 44.14±2.15 | 60.28±2.86 |
| 9.5 | 76.85±3.26 | 40.45±2.18 | 64.47±2.13 |
| 10.0 | 78.39±3.44 | 55.78±2.84 | 69.43±2.55 |
| 10.5 | 81.45±2.65 | 58.38±3.14 | 73.33±3.17 |
| 11.0 | 88.04±2.17 | 66.39±2.55 | 78.16±2.22 |
| 11.5 | 92.13±3.58 | 67.77±3.27 | 82.65±1.35 |
| 12.0 | 99.27±3.22 | 68.13±1.25 | 88.91±1.51 |

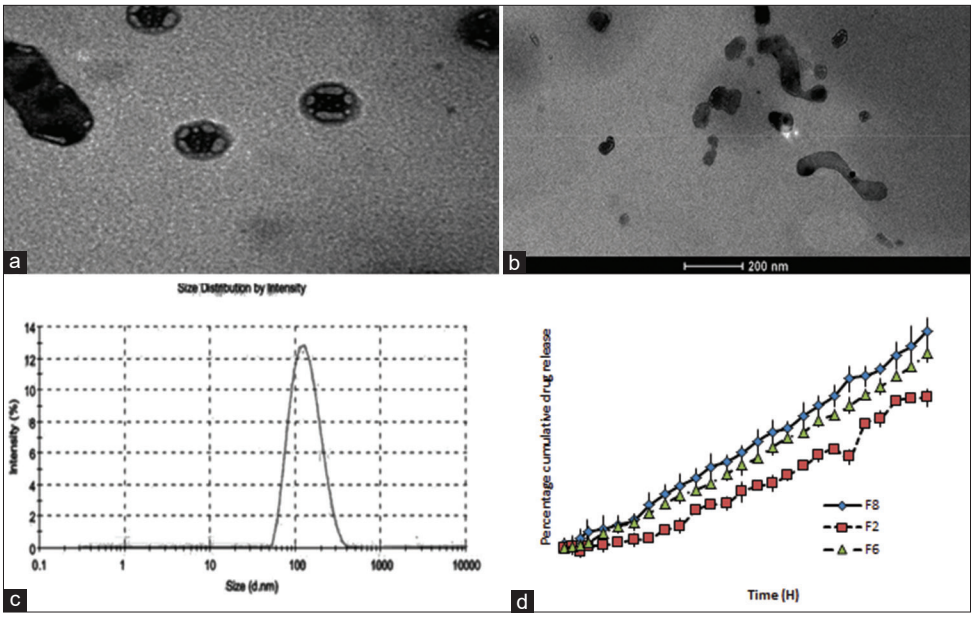


**Figure 1:** TEM image of niosomal gel (a) F8, (b) F2, (c) Particle size distribution of niosomal gel F8, (d) Cumulative % drug release of Niosomal Gel

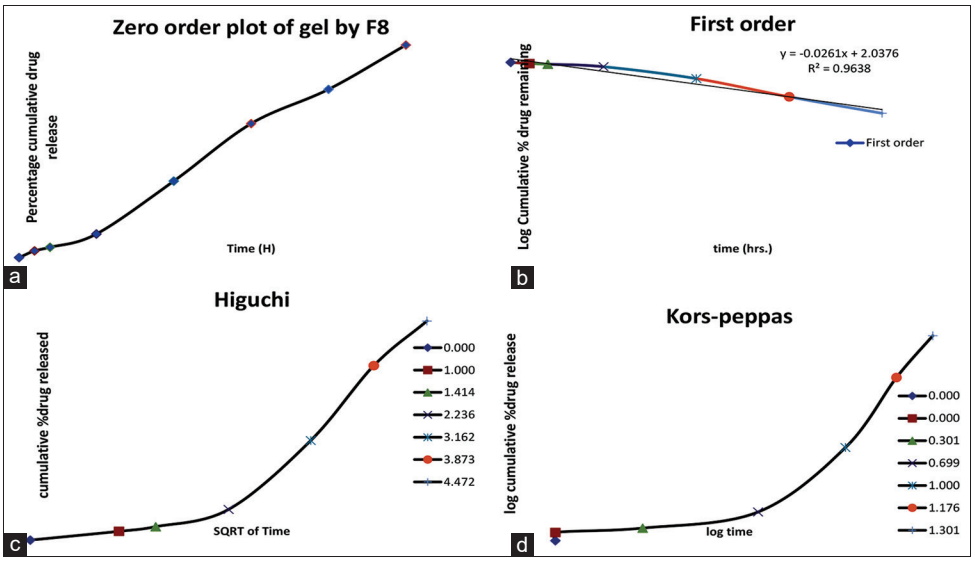


**Figure 2:** Release kinetics of formulation F8 niosomal gel plots of (a) zero order, (b) first order, (c) Higuchi, (d) Korsemeyer–Peppas

### *In vitro permeation study*

During experiments lasting 24 h, the mean quantity of adapalene and BPO permeated per unit of surface area was determined. Permeation profiles of niosomal gel (cumulative quantities of adapalene and BPO permeated versus time) are depicted in Figure 3c. The quantity of adapalene that permeated from niosomal gel in 24 h was 6.25 ± 0.14 g/cm$^2$ and the amount of BPO that permeated was 5.04 ± 0.014 g/cm$^2$.

### *In vitro skin retention study*

The drug content retained in the layers of skin from the cream was 3.36 µg from the F2 formulation, 12.28 µg from the F4 formulation, 16.27 µg from the F5 formulation, 60.11 µg from the F6 formulation, 69.37 µg from F7 formulation, and 148.12 µg from the F8 formulation from niosomal gel.

### Stability studies

The results indicated that the formulation of niosomal gel was quite stable at refrigeration and ambient temperatures, as there was little drug leakage at these temperatures. Due to the dissolving of the formulation's surfactant and lipid, the amount of drug retained at 45°C may have decreased as represented in Figures 3a and b. Consequently, niosomal gel formulations can be refrigerated or stored at ambient temperature. There was no change in the niosomal

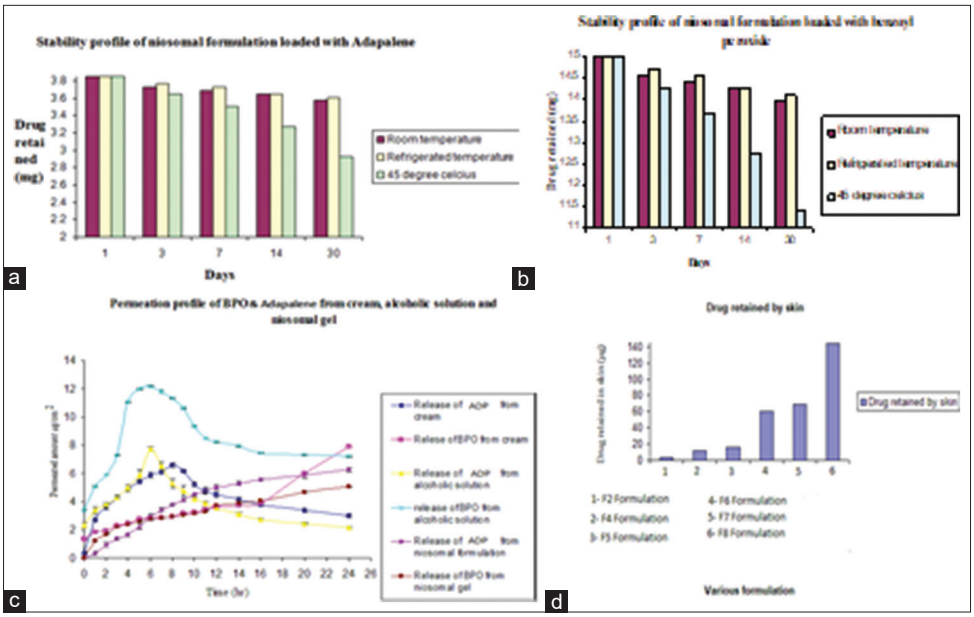


**Figure 3:** Retained in niosomes at various temperatures for 30 days (a) adapalene, (b) benzoyl peroxide, (c) permeation profile of BPO and adapalene from niosomal gel, (d) comparison of *in vitro* retention study of niosomal gel

**Table 3:** Percentage assay at various conditions at specific time intervals

| Formulation | Condition | Percent drug retained (Time in weeks) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Initial | 1 | 2 | 3 | 4 | 6 |
| Niosomes | 2–8°C | 101.26 | 100.47 | 98.44 | 97.15 | 96.87 | 94.83 |
| | 25°C/60% RH | 101.38 | 99.57 | 97.68 | 96.55 | 94.81 | 92.75 |
| | 40°C/75%RH | 101.16 | 96.85 | 91.13 | 85.52 | 80.58 | 71.77 |
| Niosomal Gel | 2–8°C | 100.27 | 100.69 | 98.82 | 97.55 | 96.19 | 93.43 |
| | 25°C/60%RH | 100.27 | 98.15 | 97.74 | 96.84 | 95.27 | 90.76 |
| | 40°C/75%RH | 100.11 | 92.25 | 84.16 | 81.51 | 72.47 | 61.63 |

formulation containing loaded BPO and adapalene [Table 3]. Based on the stability study we can concluded that niosomal gel formulation was stable.

## CONCLUSIONS

Niosomes are vesicles formed through the hydration of synthetic non-ionic surfactants, specifically those belonging to the alkyl or dialkyl polyglycerol ether class. These vesicles may or may not include cholesterol or other lipids. The *ex vivo* skin-retention study revealed that the niosomal gel exhibited exceptional skin retention of BPO and ADP precisely at the affected site. After analyzing the data provided, it is evident that the dosage forms developed using nanovesicles (niosomes) would offer superior therapeutic efficacy at a lower dose compared to conventional dosage forms. The release of adapalene was found to be higher in the plain gel formulation with a strength of 0.01% compared to the niosomal gel formulation at the same time interval. The niosomal gel exhibited remarkable sustained release properties. Based on the findings of this research, it can be determined that the novel niosomal gel formulation is significantly superior to the conventional gel for topical use.

## ETHICAL APPROVAL

In this study, animal experiments were not applicable.

## CONSENT TO PARTICIPATE

In this study, animal and human trials are not applicable

## CONSENT TO PUBLISH

Not applicable.

## AUTHORS CONTRIBUTION

MV: Conceptualization, Data curation, Validation, Supervision, Writing review, and Editing. SK: Conceptualization, Project administration, Validation, and Writing-original draft.

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## DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## DATA AVAILABILITY

Data are available on request from the authors.

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