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Formulation, Optimization and Characterization of Topical Niosomalal Dosage Forms for Acne Treatment

Mallikarjun Vasam[1]*, Satyanarayana Korutla[1]
[1]Chaitanya (Deemed to be University)-Pharmacy, Hanamkonda, Warangal, Telangana, India
***Corresponding author email: mallikarjunvasam@gmail.com**

ABSTRACT
Acne is a common skin disease that typically affects everyone at least once in their lifespan. With corneocytes surrounded by the mortar of intercellular lipid lamellae, the structure of the stratum corneum is frequently compared to a brick wall. Utilizing elastic vesicles (niosomes) that can be transported through channel-like structures in the skin is one of the most effective methods for drug delivery to the affected area of skin. In this study, niosomes were used to deliver a combination of Adapalene (a keratolytic agent) and benzoyl peroxide (BPO), a potent antibacterial, for the effective therapy of acne by acting on a pathogenic site. In this section, drugs encapsulated within a niosomal gel formulation were evaluated in vitro and ex vivo for their predetermined characteristics. The prepared niosome had a zeta potential of -48 mV and a size of 712 nm; the entrapment efficiency of niosomes was 93.11 ±0.57 %, respectively. A 2^3 full factorial design was conducted, comparison made between span 40 and span 60 loaded niosome, span 60 possessed high EE and low particle size. The release kinetics of selected niosomal formulation was controlled by zero order kinetics. Differential scanning calorimetry and Fourier transform infrared spectroscopy characterization techniques showed that there was no interaction between the drug and excipient.
Keywords: *antiacne combination therapy, retention efficiency, therapeutic index*

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INTRODUCTION

Many therapeutic interventions fail or are ineffective because of undesirable side effects, inefficient drug metabolism, noncompliance by patients, or patient rejection of invasive therapy. There have been many attempts to solve these issues by creating drug carriers, but some of these carriers, such liposomes, niosomes, and micro emulsions, are only able to penetrate the outer layers of the skin. Many strategies have been implemented in an attempt to circumvent this issue caused by the stratum corneum barrier. Penetration enhancers, non-gradient-dependent forces, microneedles, jet injectors, and other advances in drug delivery technology have been developed in recent years, as have modifications to the drug carrier (such as the use of vesicles) to increase skin permeability[1].

Improving how drugs are absorbed by the skin is a crucial part of contemporary medicine. Clearly, the topical route of drug delivery for treating skin illnesses is a promising new frontier in drug delivery research, since it provides an alternative to the more traditional means of drug delivery (oral administration/injection). Acne is a prevalent skin disorder that affects almost everyone at some point in their lives[2].

Acne vulgaris is characterized by open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions such as papules, pustules, or nodules, and can persist for years. Sebaceous follicles are unique pilosebaceous units that can be seen on the face, chest, and back, and they are the target of this skin condition. Acne is characterized by inflammation caused by pus-forming bacteria, such as Propionibacterium acnes and Staphylococcus epidermidis[3, 4].

Sebum triglycerides are hydrolyzed by the organism's extracellular lipases into glycerol and free fatty acids, both of which have proinflammatory characteristics. Acne can be treated topically with a variety of medications, including retinoids, benzoyl peroxide (BPO), azelaic acid, erythromycin, clindamycin, and combination therapy. Itching, redness, scaling, flaring up, photosensitivity, and bacterial resistance are some of the potential side effects of topical antiacne treatments [5, 6]. Individual applications of adapalene and BPO, as well as cyclical applications, are used to treat acne. Due to the effective barrier qualities of skin membranes, many of the standard topical drugs now on the market have a diminished therapeutic impact. The corneocytes that make up the stratum corneum and the intercellular lipid lamellae that surround them

are sometimes likened to bricks in a wall. Elastic vesicles (niosomes), which can be conveyed through the skin via channel-like features, are the greatest solution for effective drug delivery to a damaged area of skin [7, 8].

Vesicular drug delivery systems are flexible, soft, self-regulating, and optimized for maximum efficacy. Mixing appropriate surface-active components in the right ratios results in elastic liposomal membranes with greater pliability[9].

In addition, their nanoscale dimensions prevent the immune system from picking them up, and they can bypass the skin's complicated structure en route to the target site, allowing for lower drug doses and less adverse effects[10, 11]. Nanocarriers' unique properties—such as their small size, high surface energy, high surface area, composition, and architecture—are what ultimately contribute to their usefulness. Because of these characteristics, they are able to reach more deeply into the skin and the bloodstream [12, 13].

Drug reservoirs can be found in colloidal particle carriers such as niosomes and liposomes. Niosomes, also known as unilamellar or multilamellar nonionic surfactant vesicles, are synthetic vesicles created from nonionic surfactants through hydration. Technically speaking, niosomes excel over liposomes due to their higher stability and lack of drawbacks like liposomes' changeable phospholipid purity and high price [14, 15]. The use of these particles as drug carriers in topical medication administration has been the subject of much research. Advantages of these carriers include improved drug stability, enhanced therapeutic effects, prolonged circulation time in a biological environment, and enhanced uptake of the entrapped drugs into the target site, with decreased drug toxicity as a result of decreased nonspecific tissue uptake. Effective drug carriers, niosomes may encapsulate and transport both hydrophilic and lipophilic medicines[6].

In addition to their role as a soluble matrix, vesicles can modulate the systemic absorption of pharmaceuticals through dermal drug delivery by acting as a local depot for sustained drug release, a permeation enhancer of dermally active compounds, or a rate-limiting membrane barrier. Niosome components Span 60 and cholesterol were used for this study, with BPO and tretinoin serving as model medicines for niosomal formulation. Niosomal gels were used in an in vitro penetration and retention investigation for BPO and adapalene[16].

MATERIAL AND METHODS

Materials: Adapalene was procured from Cipla Pharmaceutical, Ahemadabad, India, while BPO was gifted by Sun Pharmaceuticals, Hosur, India. Carbopol 940, Cholesterol, Stearic acid from Himedia Lab, Hyderabad. Span 40, Span 60, Span 85 from Loba Chemie, Mumbai, and all other materials and chemicals were of analytical grade.

Incompatibility studies between drugs (FTIR): "About 300 mg of potassium bromide (KBr) was measured and processed into a fine powder, and before that, about 1 mg of the sample was added and pulverized sufficiently to blend the sample through the KBr. The KBr blender was then pressed using an infrared press at 8 tons of pressure to create a palate[17].

Differential Scanning Calorimetry (DSC): The PHOENIX DSC-204 F1 from Netzsch-Gerätebau GmbH in Germany was used for the thermal analysis. Indium (In) was used for the temperature axis calibration and the cell constant calibration. Two mg samples were transferred to hermetically sealed aluminum pans[18]. Using pin-holed aluminum pans and dry nitrogen purging (50 ml/min), we heated samples between 30 - 200° C.

Preparation of adapalene loaded benzoyl peroxide niosomes: Using the thin film hydration technique, multiple-lamellar niosomes were generated. In a round-bottomed container, surfactant and cholesterol were dissolved in a 2:1 mixture of chloroform and methanol. The organic solvent was evaporated using a rotavapour film evaporator (Rotary vacuuma digital bath, Popular, India) at 45°C, 160 rpm, and reduced pressure. Following the complete evaporation of the organic solvent, the flask was placed under vacuum overnight to remove any residual solvent. Thin films were hydrated with saline (0.9% concentration) and water. Using the same procedure, but without the drug, vacant niosomes were produced for further evaluation[19].

Characterization of Niosomal Formulation

Drug Content Analysis: After lysing the niosomes with 50% n-propanol, the formulation's drug concentration is determined. A Niosomes solution equivalent to 200 g of Adapalene (1 ml) is pipetted into a 100 ml standard vessel. Adding a substantial volume of n-propanol (50%) and vigorously shaking the solution completely lyses the vesicles[20]. The volume is brought to 100 ml with 7.4-pH phosphate-buffered saline. Using a UV-Visible Spectrophotometer (Shimadzu UV-1700 Pharma spec Japan) and a blank of empty niosomes, the absorbance is measured at 237nm. The substance concentration is derived from the standard curve expending the subsequent formula[11].

Drug Content= Sample Absorbance/Standard Absorbance × 100

Entrapment Efficiency: Refrigerated (Eppendorf, 5417R, Germany) centrifugation at 14,000 rpm for 120 minutes at 4oC is used to separate drug-loaded niosome preparations from unentrapped material. The free drug content in the supernatant layer is determined by observing the absorbance at 237 nm of the sample using a Shimadzu UV-1700 Pharma spec Japan UV-Visible Spectrophotometer following centrifugation[21]. Drug entrapment within niosomes can be expressed as a percentage expending the subsequent equation.

% Drug Entrapment= (Total Drug- Unentrapped Drug) / Total Drug × 100

Characterization of niosomes

Morphological analysis: Niosomes were dyed with 1% phosphotungustic acid after being adhered to a carbon substrate by a drop of diluted niosome dispersion placed to a carbon-coated 300 mesh copper grid and left for 1 minute. Using the corner of some filter paper, the last traces of dispersion were soaked up and eliminated[22]. The materials were then analyzed and photographed using a 100 KV Hitachi transmission electron microscope (TEM).

Table 1: Composition table of Niosome

Excipients	F1	F2	F3	F4	F5	F6	F7	F8
Adapalene (mg)	10	10	10	10	10	10	10	10
Benzoyl Peroxide (mg)	70	70	70	70	70	70	70	70
Stearic acid (mg)	25	45	45	25	25	45	45	25
Carbopol 940 (mg)	20	20	20	20	20	20	20	20
Cholesterol (mg)	55	30	30	55	55	30	30	55
Span-40	75	140	75	145	---	----	------	------
Span-60	----	---	----	------	75	145	75	145

Particles size determination: Particle size was measured using a laser diffraction particle size analyser called a Malvern Mastersizer. Particle size was assessed by suspending the produced Niosomes in water inside the particle size analyzer's chamber and reading the results with the instrument's factory-installed software[23].

Zeta potential: Niosomes were diluted into a suspension (1 g/ml) that was prepared. The particle's size and surface charge were quantified with a Zetasizer Nano ZS (Malvern Instruments, UK)[24].

Determination of gel lipid transition temperature (DSC): Niosomes with multiple lamellae were subjected to DSC analysis. 40 L samples contained in conventional aluminum pans were analyzed. At a scanning rate of 10°C/min, thermograms were collected. The reference solution was 0.9% saline. The sample was examined amid 30 and 300 degrees Celsius. The phase transition temperature was determined using the highest surplus heat capacity temperature[25].

Drug release Kinetics: Findings from an in vitro drug release study of niosomes are fitted to pharmacokinetic equations such as the zero order (cumulative percent release versus time), the first order (log percent drug remaining versus time), the Higuchi's model (cumulative percent release versus square root of time), and the korsmeyer-peppas (log cumulative percent release versus log time) to shed light on the pharmacokinetics and mechanism of drug release[26]. The r^2 and k values for the linear curve derived through regression analysis were calculated. For non-Fickian (anomalous/zero order) release, n was between 0.5 - 1.0; for Fickian diffusion, n was less than 0.5; and for zero order release, n = 1. n was predicted using linear regression of log (M_t/M_∞) vs log t[27].

Stability studies: Niosomes were stored in a refrigerator (4-8 °C), at room temperature (25 ±2°C), and in a 45 ±2°C oven to test the vesicle's ability to retain the medication. Glass jars with aluminum foil seals were used to keep niosomal gel compositions stable throughout the research. Drug content was determined by utilizing a UV spectrophotometer to evaluate samples collected at various times throughout the month[28].

Factors study by 2^3 full factorial design

The 2^3 Full Factorial Designs was implemented to asses the factors which contributed significantly in the study design. While performing the study, Design Expert 11.0 V was adopted. Three independent variables such as stearic acid, cholesterol, span 40 and 60 selected. The responses selected are entrapment efficiency and particle size [29]. The quantity of factors included in the study was based on the literature review. A total 8 formulation developed separately with span 40 and span 60 and data are analyzed and reported. Half normal plot, interaction plot, interaction plots as well as 3D response surface plot was developed. The data were interpreted by ANOVA which highlighted the significant factors involved in the niosomal study [30]. The p value fixed at a level of 0.05.

RESULTS AND DISCUSSION

Incompatibility studies between drugs (FTIR): By comparing the combined spectrum to that of either drug individually, infrared spectroscopy showed that the combination of Adapalene and BPO was stable and stable. Using infrared spectroscopy, we found that Adapalene had two distinct bands (1648 cm^{-1} for C=O str and 3092 cm^{-1} for N-H str) and that BPO also had two distinct bands (1,759.4 cm^{-1} C=O str ester, 1,226.7 cm^{-1}, C=O str). Combination (Figure 1) of ADP (containing C=O and N-H group) with BPO (containing C=O for ester group and C=O).

Differential scanning Calorimetry (DSC): The DSC approach is useful for finding incompatible medication and excipient combinations. The non-ionic surfactants Span 40 and Span 60, cholesterol, and physical combinations are shown in DSC thermogram form in Figure 2. A melting endothermic peak was observed for this medication at 221.6°C. The melting endothermic peak of the non-ionic surfactants Span 40 and Span 60 was extremely sharp at 57 °C and 63 °C, respectively. In physical combinations of Span60, cholesterol, and Adapalene, the abrupt melting endothermic peak was observed at 59.19 °C, while in Tween 60, cholesterol, and Adapalene, the peak was observed at 70.69 °C. This finding is consistent with the hypothesis that the formulation's individual components—Span 60, Span 40, cholesterol, and Adapalene—do not combine to form a new chemical entity but instead remain in a heterogeneous state.

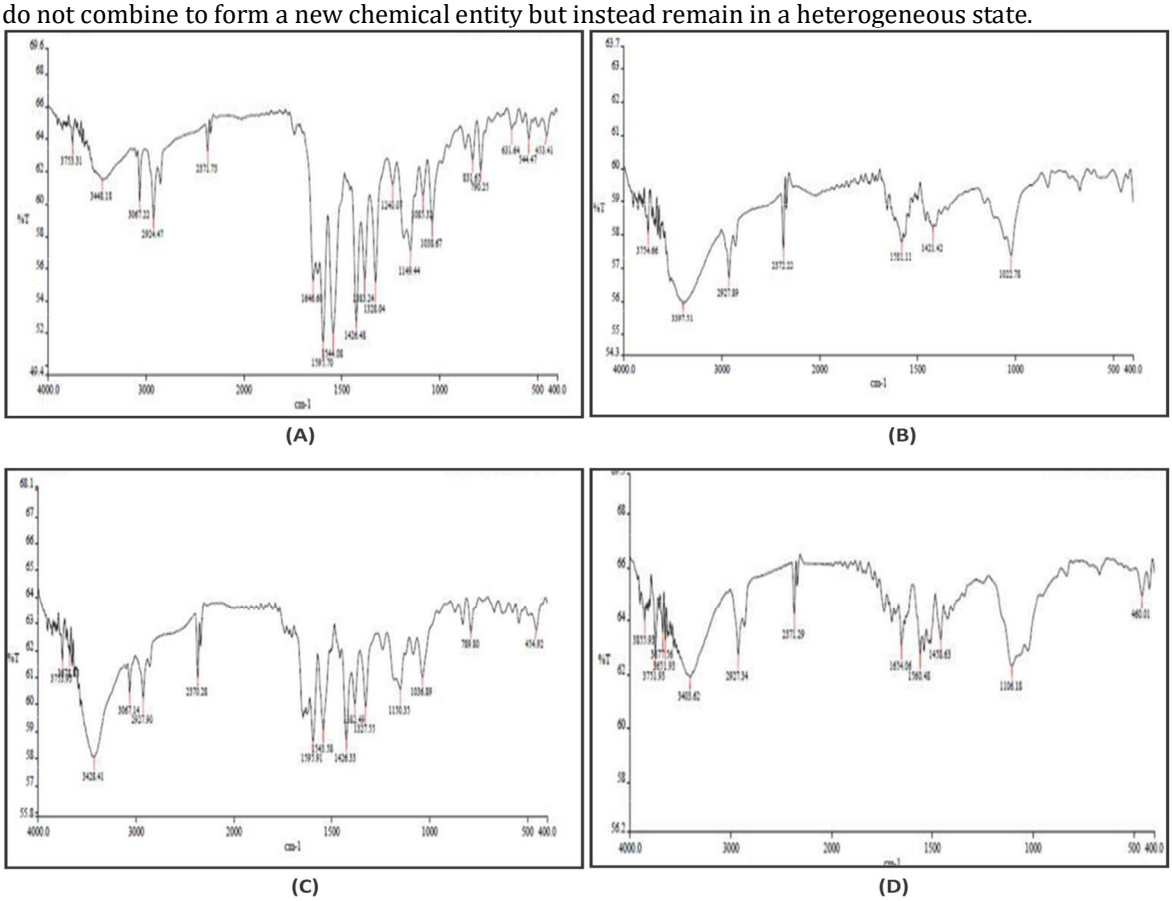

Figure 1: FTIR of (A)- Adapalene, (B)- Benzoyl Peroxide, (C)- Carbopol, (D)- Adapalene+Benzoyl Peroxide+Carbopol+Cholesterol+Span 40.

Table 2: Drug content and Encapsulation Efficiency of Niosomes

S. No.	Formulation	Drug Content %	% Encapslation Efficiency
1.	F1	88.87	66.7±0.47 %
2.	F2	94.14	72.27 ±0.14 %
3.	F3	86.87	70.28 ±0.39 %
4.	F4	88.39	76.04 ±0.27 %
5.	F5	93.44	74.09±0.11 %
6.	F6	97.87	84.47±0.89%
7.	F7	96.13	70.79 ±0.11 %
8.	F8	99.78	93.11 ±0.57 %

N=3

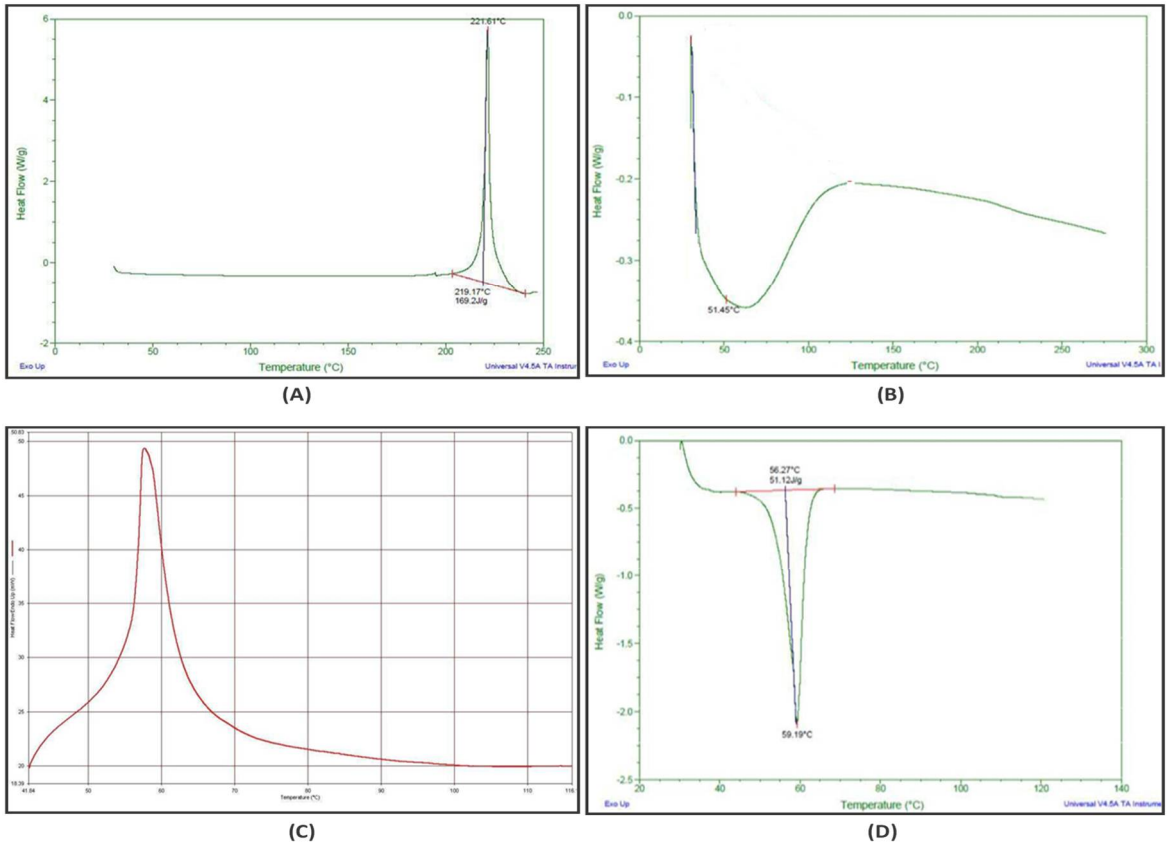

Figure 2: DSC of (A)- Adapalene, (B)- Carbopol 940, (C)- Cholesterol, (D)- Mixture of Adapalene, Benzoyl Peroxide, Carbopol

Drug content analysis: There was consistency in the drug's concentration throughout all eight formulations (F1–F8), with percentages ranging from 86.87% to 99.78% as displayed in Table 2.

Encapslation Efficiency: The niosomal formulations yielded a maximal encapsulation rate of 93.11% for formulation F8 (Table 2). This can be attributed to its longer side chain and its ability to readily diffuse into receptor membrane integrity, orientation, and packaging. In every formulation, surfactants had a significant effect on entrapment efficiency.

Morphology analysis by transmission electron microscopy: For the purpose of determining vesicle formation and morphology, transmission electron microscopy morphology analysis was performed. It was evident from the TEM analysis that a uniform spherical noisome had formed, and a photomicrograph of niosomes was taken at a magnification of 100 X as displayed in Figure 3(A, B, C).

Particle size analysis by photon correlation spectroscopy: The samples were polydispersed (PI = 0.79) according to the dynamic laser light scattering measurements, but the vesicle sizes seemed to be reproducible as shown in Figure 3(D). The average vesicle diameter for both Adapalene and benzoyl peroxide saturation was 712 nm.

Zeta potential: The formulation of niosomes subjected to zeta potential analysis had a zeta value of -48 mV, which represents the niosomes' net charge. The vesicles repel one another due to the higher charge on their surfaces, making them stable, agglomeration-free, and faster settling, resulting in a suspension that is uniformly distributed as presented in Figure 3(E). This indicates that niosomal formulation exhibits excellent stability.

DSC analysis for determination of gel lipid transition temperature: Niosome phase transformation temperature (gel lipid transition temperature) was calculated using DSC. The niosome changes from a hard gel to a fluid liquid crystal as the system temperature rises because the hydrocarbon chains in the ordered bilayer of vesicles experience a phase shift. When niosomes were created using a span 60: cholesterol (207:52 and 138:52 mg ratio), the gel lipid transition temperature was 56-58°C as represented in Figure 3(F).

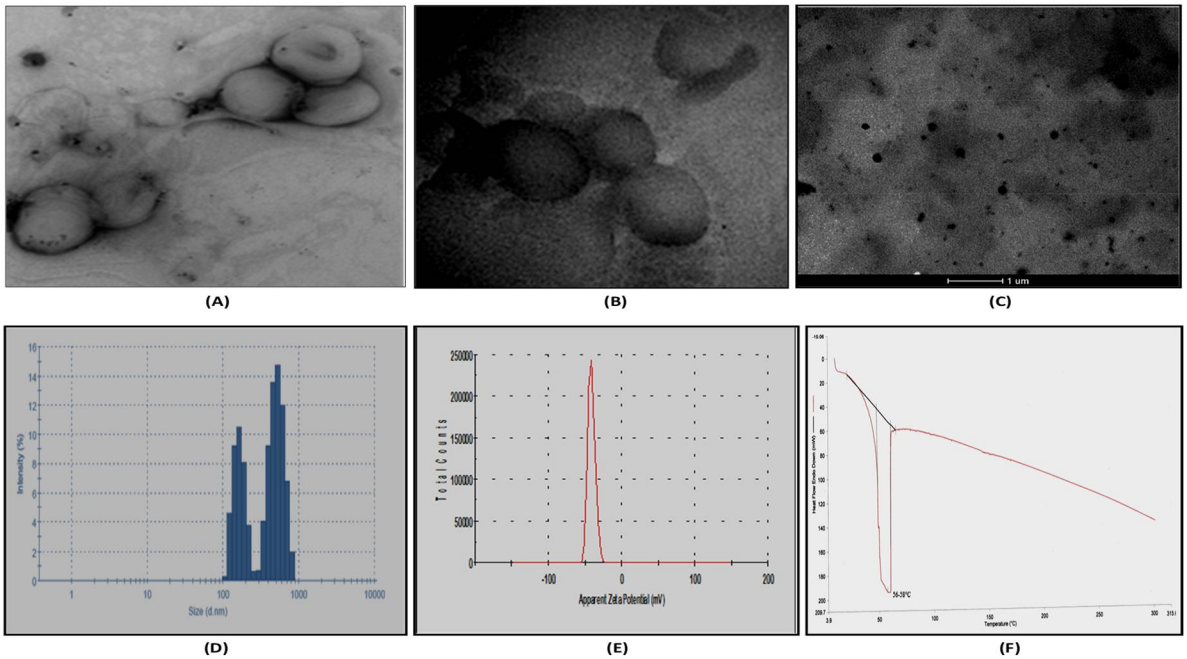

Figure 3: TEM of (A), (B), (C)- Niosomes of F8 Formulation, (D)- particle size distribution in niosomal suspension, (E)- Zeta potential of niosomal suspension, (F)- DSC thermogram of niosomal preparation

Release kinetics of Niosomal Formulations

For the dissolution data, the kinetic model with the highest correlation coefficient was chosen as the best fit. Best fitted with highest co-rrelation coefficient was observed in the Korsemeyer peppas model, zero order followed by Higuchi model given in Table 3.

The drug release from F1-F4 in zero order was found to be between 0.985 and 0.992, while the first order for F1-F4 was between 0.755 and 0.887. It demonstrates that the drug release was greater and the linearity was higher (r^2 = 0.993), which follows first order and thus fit well to the Higuchi model with r2 values ranging from 0.851 to 0.898. Further elucidations of the release mechanisms indicate that F1 to F4 are compatible with the korsemeyer-peppas model, with r2 values ranging from 0.975 to 0.994. Formula F8 was optimized because r^2 values were closer to one and zero order kinetics were followed. The korsmeyer peppas and Higuchi model best accommodated the F8 co-efficient correlation values. This indicates a coupling between the mechanisms of diffusion and erosion, also known as anomalous (non-ficikian) diffusion.

The kinetic model with the maximum correlation coefficient was deemed to be the most suitable for dissolution data. The model with the highest correlation coefficient was the Korsemeyer peppas model, followed by the Higuchi model.

The drug release was greater, and it exhibited higher linearity (0.993) that follows Zero order, thus fitting the Higuchi model with r^2 values ranging from 0.851 to 0.996. Additional elucidations of the release mechanisms indicate that they are compatible with the korsemeyer-peppas model, with r^2 value between 0.957% and 0.987%. Formula F8 was optimized because the n values were closer to one and zero order kinetics was followed.

Table 3: R^2 values-mathematical models dissolution profiles

Formulation code	R^2 Values of mathematical models of dissolution studies				
	Zero order	First order	Higuchi model	Peppas model	
				R^2	N
Niosomal Formulation					
F1	0.992	0.755	0.858	0.981	0.726
F2	0.985	0.854	0.898	0.983	0.922
F3	0.988	0.887	0.851	0.974	0.758
F4	0.990	0.873	0.871	0.961	0.714
F5	0.992	0.868	0.894	0.966	0.707
F6	0.983	0.877	0.989	0.968	0.724
F7	0.989	0.868	0.988	0.987	0.726

F8	0.993	0.874	0.996	0.957	0.711
NIosomal Gel Formulation					
F2	0.980	0.849	0.994	0.985	0.920
F6	0.981	0.871	0.995	0.964	0.728
F8	0.986	0.875	0.997	0.952	0.781

Factors screening and analysis by 2^3 full factorial design

Span 40: Niosomes are developed as per 2^3 full factorial design and the data are recoded in Table 4. The need of the 2^3 full factorial design was to assess the significant factor and variables which could impact on niosomal development.

Table 4: Formulations developed as per suggestion from 2^3 full factorial design.

	Factor 1	Factor 2	Factor 3	Response 1	Response 2
Span 40 considered					
Run	**A:Stearic acid**	**B:Cholesterol**	**C:Span 40**	**EE**	**Particle size**
	mg	mg	mg	%	nm
1	40	25	70	71.28	579
2	20	50	70	63.19	341
3	40	50	140	92.37	646
4	40	50	70	84.27	527
5	20	25	70	66.35	518
6	40	25	140	89.25	637
7	20	50	140	73.14	499
8	20	25	140	68.18	521
Span 60 considered					
Run	**A:Stearic acid**	**B:Cholesterol**	**C:Span 60**	**EE**	**Particle size**
	mg	mg	mg	%	nm
1	40	25	70	72.75	526
2	20	50	70	66.91	341
3	20	50	140	89.47	596
4	40	50	140	94.33	638
5	20	25	140	68.15	411
6	40	50	70	88.91	573
7	20	25	70	60.14	308
8	40	25	140	66.72	519

The full factorial design showed that, few terms are significant and exhibited positive effect such as steric acid, span, cholesterol and few interaction terms such as AB and AC. Whereas, there is no effect by BC as seen in Entrapment efficiency determination. Similarly, Particle size estimation was interpretated. It found that, only stearic acid, span 60 possessed positive significant effects.

Interaction curves are obtained to find the possible interaction of excipients. In EE it found that at low amount, ingredients tends to interact however with high amount excipients donot interact. Whereas, at low concentration, there found to be no interaction of stearic acid and cholesterol but at high amount they tends to interact. In contrary, at low amount span 40 and cholesterol interacted whereas in high amount they did not interacted. Similarly, response surface plots were developed and the relationship between each variable and responses recorded as shown in Figure 4. Furthermore, significant factors are analyzed by ANOVA study.

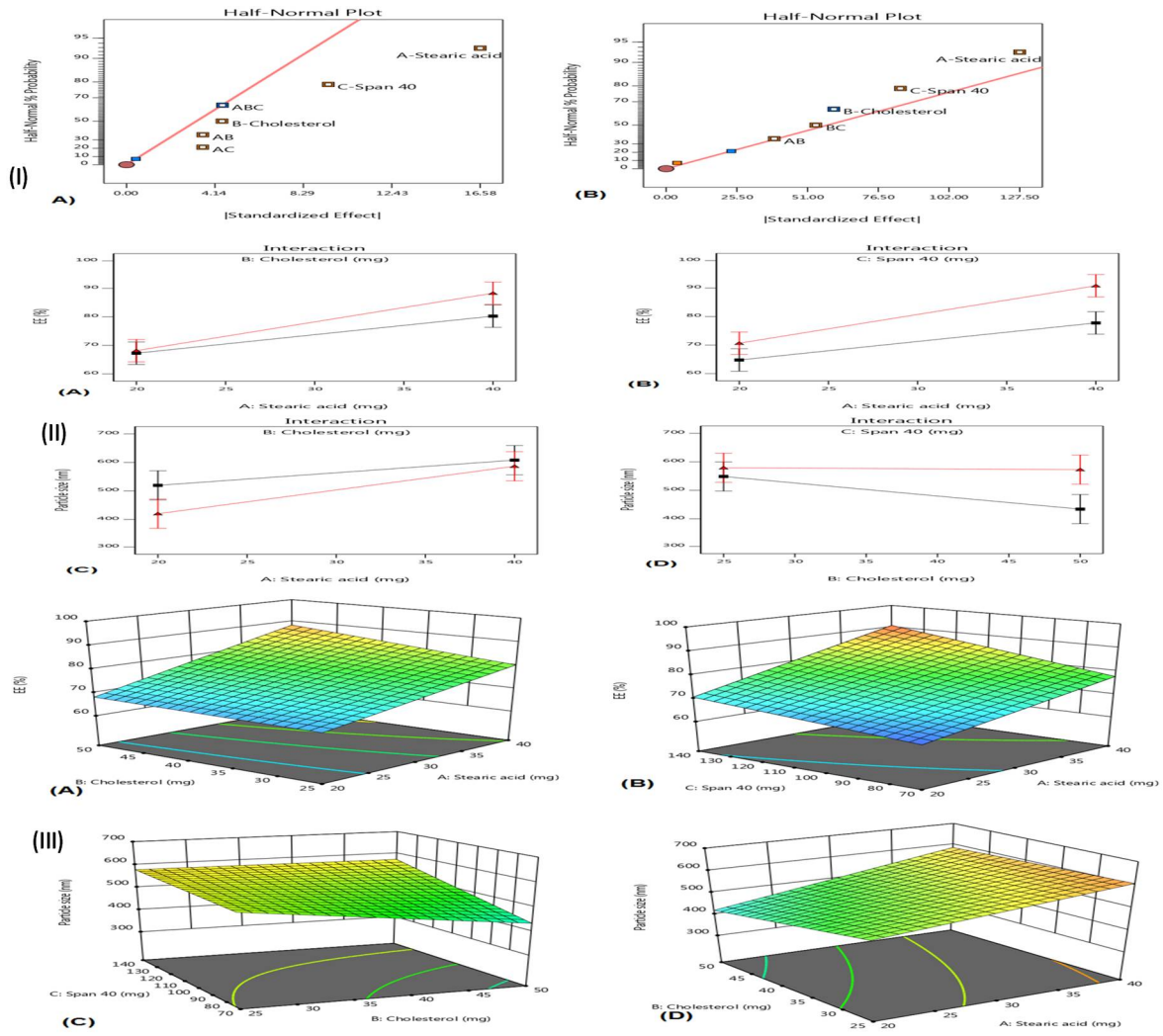

Figure 4: (I)- Half normal plot estimation (A) EE (B) Particle size; (II)- Interaction curves plotted for (A) EE: Stearic acid Vs Cholesterol (B) EE: Stearic acid Vs EE (C) Particle size: Stearic acid Vs Cholesterol (D) Particle size: Cholesterol Vs Span 40; (III)- 3D response surface plot for EE (A) cholesterol Vs Stearic acid (B) Span 40 Vs Stearic acid; plots for particle size (C) Cholesterol Vs Particle size (D) Cholesterol Vs Stearic acid.

The responses are recorded and provided in Table 5. The EE found to be in the range of 63.19 to maximum of 92.37%. It found the formulations with high amount of stearic acid and span 40 as in run 3 posses highest EE. The formulations with low amount of stearic acid and span 40 possessed low EE. The particle size of Niosomes ranged within 341 nm to 646 nm. This data confirms largest niosome developed with formulation loaded with maximum amount of stearic acid, span 40 and cholesterol.

Table 5: ANOVA estimation for EE determination and particle size determination

Span 40						
Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
EE determination						
Model	860.38	6	143.40	374.59	0.0395	significant
A-Stearic acid	***549.63***	***1***	***549.63***	***1435.76***	***0.0168***	significant
B-Cholesterol	40.10	1	40.10	104.74	0.0620	
C-Span 40	***179.08***	***1***	***179.08***	***467.80***	***0.0294***	significant
AB	25.60	1	25.60	66.87	0.0775	
AC	25.53	1	25.53	66.68	0.0776	
ABC	40.46	1	40.46	105.68	0.0617	
Residual	0.3828	1	0.3828			
Cor Total	860.76	7				

Particle size determination						
Model	62987.50	5	12597.50	22.17	0.0437	significant
A-Stearic acid	***32512.50***	***1***	***32512.50***	***57.22***	***0.0170***	
B-Cholesterol	7320.50	1	7320.50	12.88	0.0696	
C-Span 40	***14280.50***	***1***	***14280.50***	***25.13***	***0.0376***	
AB	3042.00	1	3042.00	5.35	0.1468	
BC	5832.00	1	5832.00	10.26	0.0852	
Residual	1136.50	2	568.25			
Cor Total	64124.00	7				
Span 60						
Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
EE determination						
Model	1175.32	6	195.89	163.07	0.0499	significant
A-Stearic acid	***180.88***	***1***	***180.88***	***150.58***	***0.0418***	
B-Cholesterol	***645.48***	***1***	***645.48***	***537.34***	***0.0274***	
C-Span 60	112.20	1	112.20	93.40	0.0656	
AB	30.73	1	30.73	25.58	0.1243	
AC	121.52	1	121.52	101.16	0.0631	
BC	84.50	1	84.50	70.34	0.0755	
Residual	1.20	1	1.20			
Cor Total	1176.52	7				
Particle size determination						
Model	1.034E+05	6	17231.00	50.98	0.0168	significant
A-Stearic acid	***45000.00***	***1***	***45000.00***	***133.14***	***0.0450***	
B-Cholesterol	18432.00	1	18432.00	54.53	0.0857	
C-Span 60	***21632.00***	***1***	***21632.00***	***64.00***	***0.0392***	
AC	11250.00	1	11250.00	33.28	0.1093	
BC	6272.00	1	6272.00	18.56	0.1452	
ABC	800.00	1	800.00	2.37	0.3669	
Residual	338.00	1	338.00			
Cor Total	1.037E+05	7				

ANOVA table showed that, stearic acid and span 40 have significant impact (P<0.05) on EE and particle size of developed niosome.

Span 60: Niosomes are developed as per 2^3 full factorial design and the data are recoded in Table 4. The need of the 2^3 full factorial design was to assess the significant factor and variables which could impact on niosomal development.

The full factorial design showed that, few terms are significant and exhibited positive effect such as steric acid, span, cholesterol and few interaction terms such as AB and BC. Whereas, there is no effect by AC as seen in Entrapment efficiency determination which exhibited negative effect. Similarly, Particle size estimation was interpretated. Similar, TT found that, stearic acid, span 60 as well as cholesterol possessed positive significant effect.

Interaction curves are obtained to find the possible interaction of excipients. In EE it found that at low amount, ingredients tend to interact such as Stearic acid Vs Cholesterol and cholesterol Vs span in however with high amount excipients do not interact as displayed in Figure 5. Whereas, at low concentration, I case of Stearic acid Vs span 60 there found to be no interaction but at high amount they tends to interact.

In contrary, at low amount Stearic acid Vs Span 60 not interacted whereas in high amount they interacted as seen in particle size analysis. Similarly, response surface plots were developed and the relationship between each variable and responses recorded. Furthermore, significant factors are analyzed by ANOVA study.

The responses are recorded and provided in table. The EE found to be in the range of 60.14 to maximum of 94.33%. It found the formulations with high amount of stearic acid and span 60 as in run 4 possess highest EE. The formulations with low amount of stearic acid and span 60 possessed low EE. The particle size of Niosomes ranged within 308 nm to 638 nm. This data confirms largest niosome developed with formulation loaded with maximum amount of stearic acid, span 60 and cholesterol.

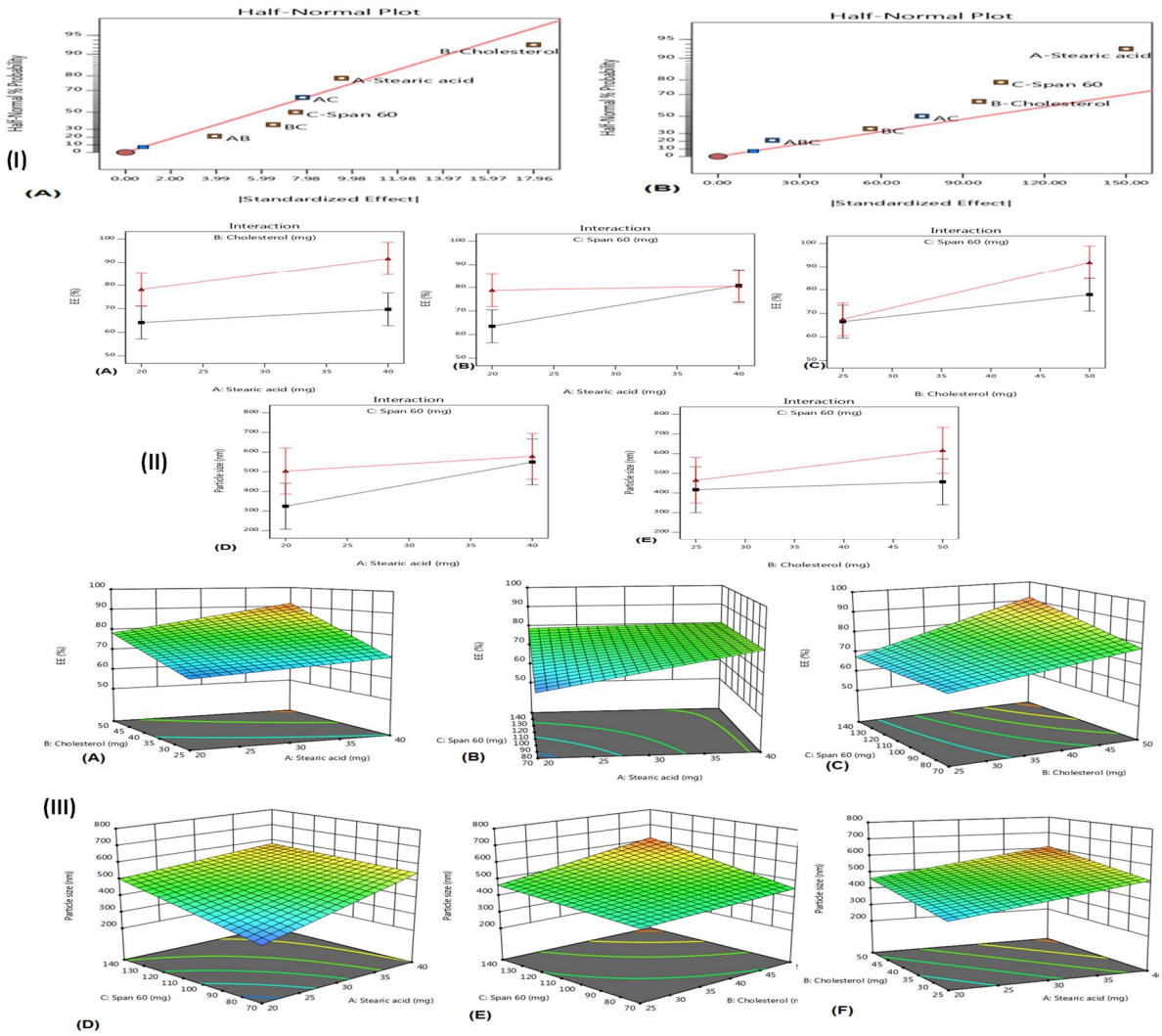

Figure 5: (I)- Half normal plot estimation (A) EE (B) Particle size; (II)- Interaction curves plotted for (A) EE: Stearic acid Vs Cholesterol (B) EE: Stearic acid Vs span 60 (C) EE: cholesterol Vs span 60 (D) Particle size: Stearic acid Vs Span 60 (E) Particle size: Cholesterol Vs Span 60; (III)- 3D response surface plot for EE (A) cholesterol Vs Stearic acid (B) Span 60 Vs Stearic acid (C) cholesterol Vs Span 60; plots for particle size (D) Span 60 Vs Stearic acid size (E) cholesterol Vs Span 60 (F) Stearic acid Vs cholesterol.

A comparison was made between span 40 and span 60 loaded niosome. It ascertained that, Niosomes with span 60 possessed high EE and low particle size as compared to span 40 based formulations. This confirms span 60 have significant contribution in niosomal dosage form development. ANOVA table showed that, stearic acid and cholesterol have significant impact (P<0.05) on EE and particle size of developed niosome.

CONCLUSIONS

Niosomes are non-ionic surfactant vesicles formed by the hydration of synthetic nonionic surfactants of the alkyl or dialkyl polyglycerol ether class, with or without cholesterol or other lipid incorporation. This study aimed to encapsulate Adapalene within niosomes and incorporate these niosomes into a suitable dermatological foundation. The thin film hydration technique using rotary flask evaporator shows good vesicle forming properties as well as better efficiency.

Ethical Approval: In this study, animal experiment was not applicable.

Consent to Participate: In this study, animals and human trails not applicable

Consent to Publish: Not applicable.

Authors Contribution

MV: Conceptualization, Data curation, Validation, Supervision, writing – review & editing, **SK:** Conceptualization, Project administration, Validation, Writing – original draft.

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