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Original Paper

FORMULATION AND EVALUATION OF NIOSOMAL GEL CONTAINING TAZAROTENE FOR THE TREATMENT OF ACNE AND PSORIASIS

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ABSTRACT

Psoriasis is a chronic inflammatory skin disorder that may drastically affect the quality of life of an affected person. Acne is a common skin condition that occurs when oil and dead skin cells clog the skin's pores. Acne primarily affects teens; more than 85% experience at least a mild form of this condition. It most commonly occurs on the face, chest, back, shoulders, and neck. Acne affects young men and young women about equally, but there are differences. Men are more likely than women to have more severe, longer lasting forms of acne. In contrast, women are more likely to have intermittent acne due to hormonal changes associated with their menstrual cycle and acne caused by cosmetics. While most people outgrow their acne by their 20's some, especially women, have acne well into adulthood. In Present study aimed to develop niosomal gel for the treatment of acne and psoriasis. The release of the drug in the deep layers of the skin and its transdermal absorption could then be the result of a fusion of niosomes, with skin lipids and drug release at various points along the penetration pathway. It can be concluded that a gel formulation containing niosomes loaded with Tazarotene showed prolonged action and it can be developed successfully to improve the dermal infections.

Key words: Tazarotene, Formulation Development, Niosomal gel, Acne

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disorder that may drastically affect the quality of life of an affected person. Different treatments are available for psoriasis and among this topical therapy are most commonly used in majority of patients. Psoriasis has genetic and life style triggers; the treatment guidelines involve continuous monitoring and lifelong care for the patients. Knowledge of the disease trigger factors and their role in precipitating the psoriasis is quiet important in the disease management. Care should be taken to avoid these psoriasis triggers. In recent years, new biological therapies have been introduced and several existing treatments have been improved giving new hope to people with psoriasis.

Quality of life in a disease whether it's pre-treatment or post-treatment speak a lot about its all round impact on patients. Psoriasis has negatively effects on quality of life. Psoriasis is a lifelong, chronic, and recurrent disease. In a patient surveys conducted by the National

Psoriasis Foundation between 2001 and 2008 in the USA, 33% of patients with mild disease and 60% of patients with moderate-to-severe psoriasis reported that their disease significantly affect their everyday life. Psoriasis can be as debilitating as many other serious medical or psychiatric conditions. The physical, psychological and social dimensions of life are negatively affected by the psoriasis and can be greater than those resulting from life threatening illnesses such as myocardial infarction.

NIOSOME

Niosomes are a novel drug delivery system, in which the medication is confine in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. Constructura, niosomes are similar to liposomes, in that they are also made up of a bilayer. However, the bilayer in the case of niosomes is made up of non-ionic surface active agents alternately phospholipids as seen in the case of liposomes. Most surface active agents when immersed in water yield micellar structures however some surfactants can yield bilayer vesicles which are niosomes. Niosomes may be unilateral or multilateral depending on the method used to prepare them. The niosomes are classified as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size. The origination of vesicular system based on hydration of mixture of a single-alkyl chain nonionic surfactant and cholesterol was firstly reported in 1979. Niosomes might be maked by various types of nonionic surfactants together with polyglycerol alkyl ethers, crown ethers, ester-linked surfactants, glucosyl dialkyl ethers, polyoxyethylene alkyl ethers, Brij, Tweens and Spans. Nonionic surfactants used to prepare niosomes carry no charge and are relatively nontoxic and mild to use.

TYPES OF NIOSOMES

A. PRONIOSOMES

Proniosomes are also termed as 'dry niosomes'. The encapsulation of drugs in the proniosomal vesicular formation maintains their systemic circulation, provides controlled release, increase penetration in the targeted areas and reduces the toxic effects. Proniosomes are dry, free-flowing formulations of the surfactant-coated carrier, which can be rehydrated by revealing agitation in hot aqueous media within minutes. Polar and non-polar both, hydrophobic and hydrophilic drugs can be entrapped by proniosomes. Niosomes physical stability problems such as accumulation, fusion and escaping are minimized by proniosomes and they also provide additional convenience in transportation, distribution, storage, and dosing. proniosomes prolongs the existence of the drug in the systemic circulation and finally reduces the toxicity.

B. ASPASOMES

Mixture of acorbyl palmitate, cholesterol and highly charged lipid diacetyl phosphate leads to the construction of vesicles named aspasomes. Aspasomes are first hydrated with water/aqueous solution and then sonicated to attain the niosomes. Aspasomes are suggested to improve the transdermal permeation of drugs. Aspasomes have also been used to reduce disorders caused by reactive oxygen species due to its intrinsic antioxidant property.

C. VESICLES IN WATER AND OIL SYSTEM (v/w/o)

In this system suspension of aqueous niosomes (v/w) are emulsified into the oily phase at 60°C to form vesicle in water in oil emulsion (v/w/o). Cooling to room temperature forms vesicle in water in oil gel (v/w/o gel). The prepared v/w/o gel can entrap the hydrophilic active ingredients which are susceptible for enzymatic degradation such as proteins/proteinous drugs and also provide a controlled release pattern in drug delivery.

D. DEFORMABLE NIOSOMES

Elastic niosomes are prepared of nonionic surfactants,

ethanol and water. They show superior to conventional niosomes due to their capability to increase penetration efficiency of a compound through intact skin by passing through pores in the stratum corneum, which are smaller than the vesicles. The flexibility of their structure allows them to pass through pores that are less than one-tenth of these vesicles.

APPLICATION OF NIOSOME

Niosomes have been successfully used in drug targeting to various organs such as skin, brain, liver, lung ocular systems, tumor etc. Niosomes show a higher bioavailability than conventional dosage forms Controlled and sustained release of drugs have been achieved by niosomes Permeation of drugs through the skin has been enhanced by niosomes. Noisome, it selfimproves the stratum corneum properties both by reducing transepidermal water lossand skin condition by increasing smoothness via reloading lost skin lipids. Niosomes can be applied for drug protection from biological enzymes and acid thereby increasing the drug stability.

2. MATERIAL AND METHODS

Physiochemical Properties of Tazarotene

A. Physical evaluation

Table 2.1 List of Sensory characters

S. No.	Sensory characters	Result
1.	Colour	Light yellow powder
2.	Odor	Odorless
3.	Taste	Tasteless

A) SOLUBILITY:

Table 2.2 Solubility of Tazarotene

Solvent used	Tazarotene
Distilled Water	Insoluble
0.1 N Hydrochloric acid	Soluble
Ethanol	Freely soluble
Methanol	Freely soluble
Chloroform	Soluble
Acetone	Soluble
DMSO	Soluble
Phosphate buffer pH 7.4	Soluble

B) MELTING POINT:

Table 2.3 Melting point of the Tazarotene

S. No.	Melting Point of Tazarotene	Average Melting Point of Tazarotene
1.	95-96^{o}C	95-96^{o}C
2.	94-95^{o}C	
3.	95-96^{o}C	

C) PARTITION COEFFICIENT:

Table 2.4 Partition coefficient of the Tazarotene

S. No.	Amount of drug in octanol	Amount of drug in water	Partition coefficient ($P_{o/w}$)	Average partition coefficient
1.	370.08	440.47	0.84	0.84
2.	375.50	447.02	0.84	
3.	365.25	440.06	0.83	

D) DETERMINATION OF pH:

Table 2.5 pH of the Tazarotene

S. No.	pH of the solution	Average pH of the solution
1.	6.9	6.9
2.	7.1	
3.	6.9	

E) IDENTIFICATION TEST

Identification of Tazarotene was done by FTIR Spectroscopy with respect to marker compound. Tazarotene was obtained as White or almost white crystalline powder. It was identified from the result of IR spectrum as per specification.

SAMPLE OF PURE TAZAROTENE

The IR spectrum of sample drug shows the peak values which are characteristics of the drug and the graph were shown in figure.

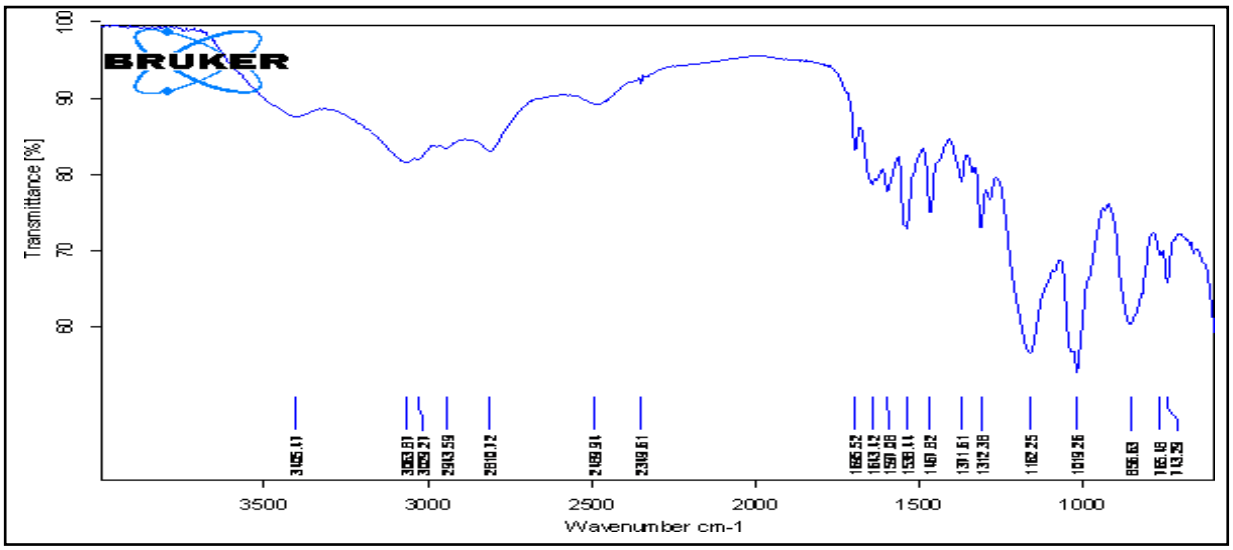

Figure: 2.1 FT-IR Spectrum of Pure Drug (Tazarotene)

IR Spectrum of Tazarotene + All EXCIPIENTS

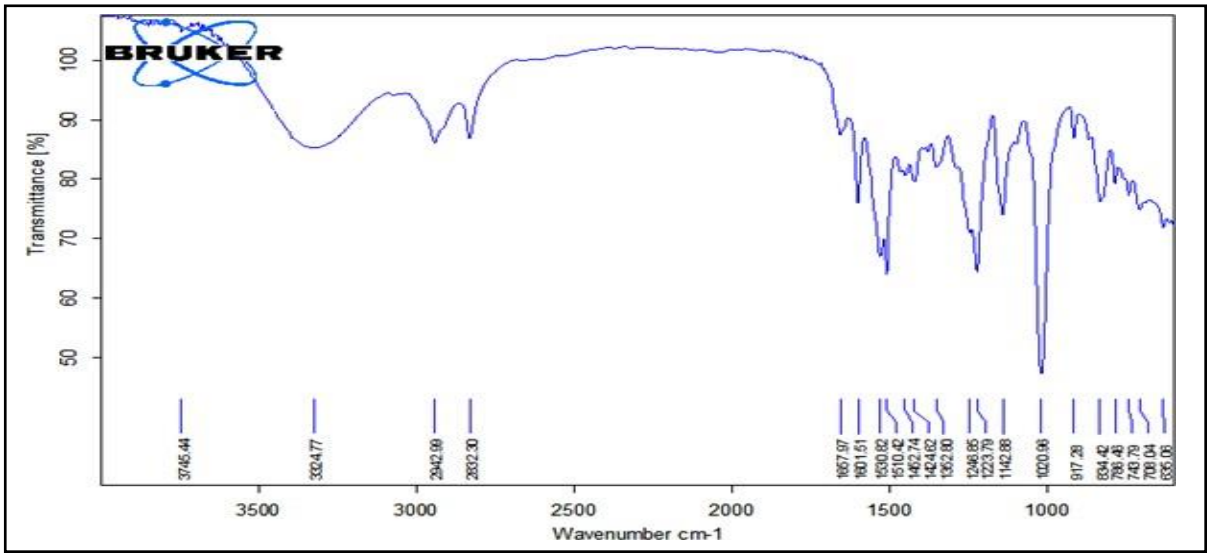

Figure: 2.2 FT-IR Spectrum of Pure Drug and Excipients

F) LOSS ON DRYING:

Table 2.6 Loss of drying of drug sample

S. No.	Initial weight	Final weight after 15 minutes	% loss of drying	Avg. % loss of drying
1.	5gm	4.92 gm	1.67 %	1.672 %
2.	5gm	4.91 gm	1.82 %	
3.	5gm	4.92 gm	1.67 %	

G) BULK PROPERTIES

Table 2.7 Bulk density of Tazarotene

S. No.	Bulk mass	Bulk volume	Bulk density	Avg. bulk density
1.	10 gm	25 ml	0.400 g/ml	0.400 g/ml
2.	10 gm	25 ml	0.400 g/ml	
3.	10 gm	25 ml	0.400 g/ml	

H) TAPPED DENSITY:

Table 2.8 Tapped density of Tazarotene

S. No.	Bulk mass	Tapped volume	Tapped density	Avg. tapped density
1.	10 gm	18 ml	0.555 g/ ml	0.555 g/ ml
2.	10 gm	18 ml	0.555 g/ ml	
3.	10 gm	18 ml	0.555 g/ ml	

I) COMPRESSIBILITY INDEX (Carr's index):

Table 2.9 Carr's index. of Tazarotene

S. No.	Bulk density	Tapped density	C.I.
1.	0.400 g/ml	0.555 g/ml	38.75

J) HAUSNER RATIO:

Table 2.10 Hausner of Tazarotene

S. No.	Bulk density	Tapped density	Hausner ratio
1.	0.400 g/ ml	0.555 g/ ml	1.38

K) FLOW PROPERTIES

Table 2.11 Angle of repose of Tazarotene

S. No.	Height of pile	Radius of pile	Angle of repose	Avg. angle of repose
1.	2.3 cm	5 cm	25 º	**25 º**
2.	2.4 cm	5.1 cm	25 º10'	

3.	2.5 cm	5.4 cm	25 ^{o}	

L) MOISTURE CONTENT DETERMINATION:

Table 2.12: Moisture content determination

S. No.	Drug	KF Factor	Amount of KF Reagent consumed	Moisture content
1	Tazarotene	0.565	0.2ml	0.113

M) DETERMINATION OF λ_{max} OF TAZAROTENE:

The spectrum peak point graph of absorbance of Tazarotene versus wave length was shown in figure:

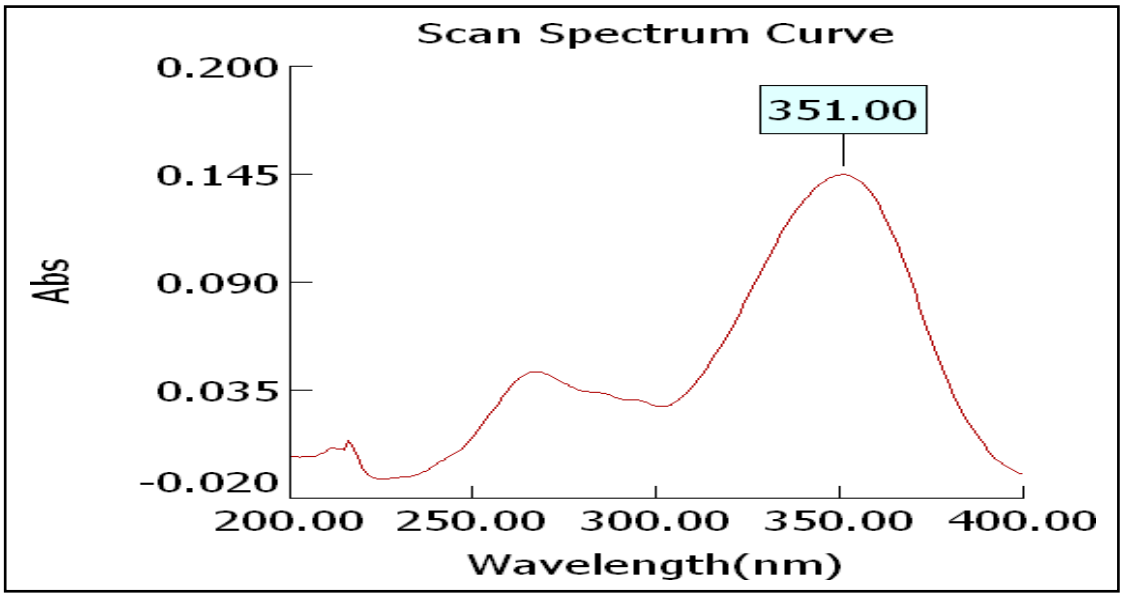

Figure 2.3 Wavelength maxima of tazarotene in phosphate buffer pH 7.4.

N) CALIBRATION CURVE OF TAZAROTENE AT λ_{max} 351nm

Observation table: 2.13 Calibration curve of Tazarotene

S. No.	Conc. (µg/ml)	Absorbance
1	10	0.159
2	20	0.302
3	30	0.452
4	40	0.614
5	50	0.751

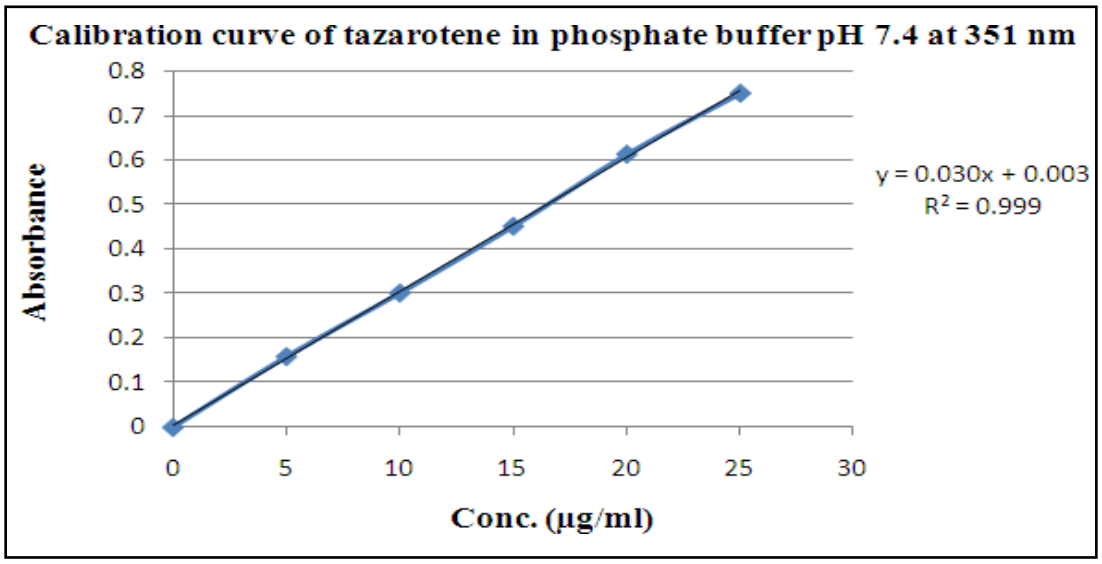

Figure 2.4 Calibration curve of tazarotene in phosphate buffer pH 7.4 at 351nm

3. EXPERIMENTAL AND RESULTS

3.1 Formulation development of Tazarotene loaded niosomes

Table 3.1: Composition of niosomes by varying amount of lipid

Components	Formulation code					
	F1	F2	F3	F4	F5	F6
Drug (mg)	100	100	100	100	100	100
Span 20 (mg)	50	100	150	200	250	300
Phosphatidylcholine	50	50	50	50	50	50
Cholesterol (mg)	10	20	30	40	50	60
Chloroform (ml)	10	10	10	10	10	10
PBS (7.4) (ml)	20	20	20	20	20	20

3.2 EVALUATION OF TAZAROTENE LOADED NIOSOMES

a. Vesicle size determination: Vesicle size was determined using the particle size analyzer.

b. Entrapment efficiency: Surface morphology was determined by TEM, for TEM a drop of the sample was placed on a carbon-coated copper grid and after 15 min it was negatively stained with 1% aqueous solution of phosphotungustic acid.

Table: 3.2: Evaluations of niosomes for vesicle size and entrapment efficiency

Formulation	Vesicle Size (nm)	Entrapment efficiency (%)
TE1	230.56 ±4.56	65.65±0.25

TE2	223.40 ±5.69	81.78±0.45
TE3	242.56 ±6.98	76.69±0.85
TE4	270.569±7.45	72.65±0.75
TE5	285.658±8.98	68.98±0.45
TE6	295.658±7.45	60.25±0.56
TE7	298.987±9.65	62.58±0.32
TE8	312.93±8.98	60.25±0.12

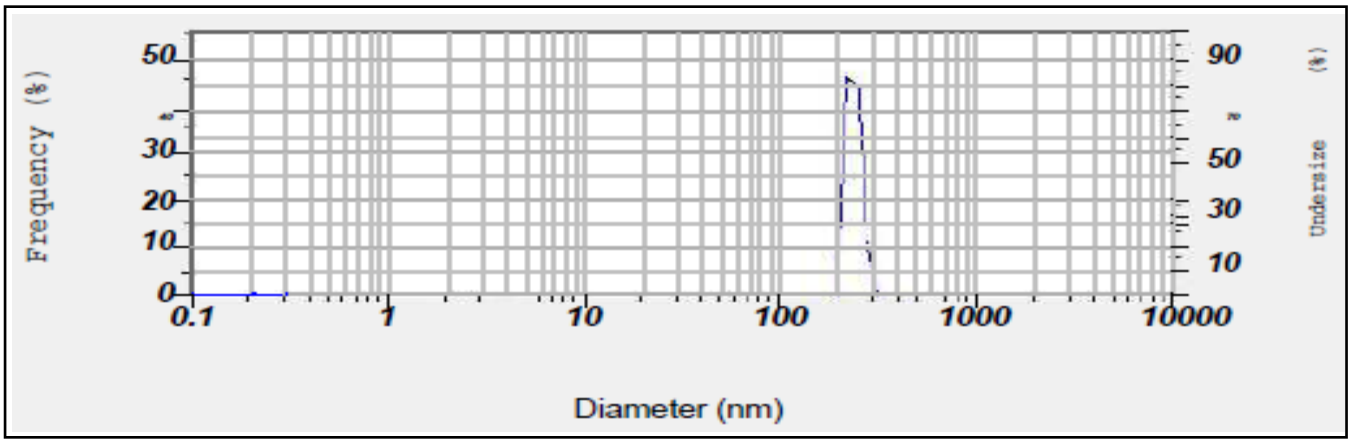

Figure 3.1: Vesicle Size of Optimized niosomes formulation

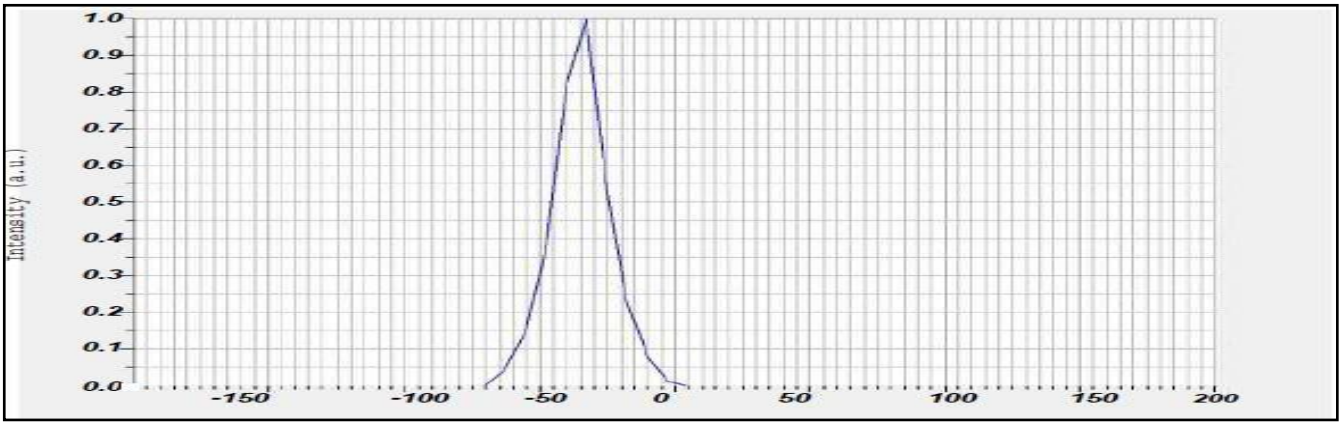

Figure 3.2: Zeta potential of Optimized niosomes formulation Table

3.3: Vesicle size and entrapment efficiency of optimized formulation

Formulation Code	Vesicle Size (nm)	Entrapment Efficiency	Zeta potential
TE4	223.40 ±5.69	81.78±0.45	-35.6

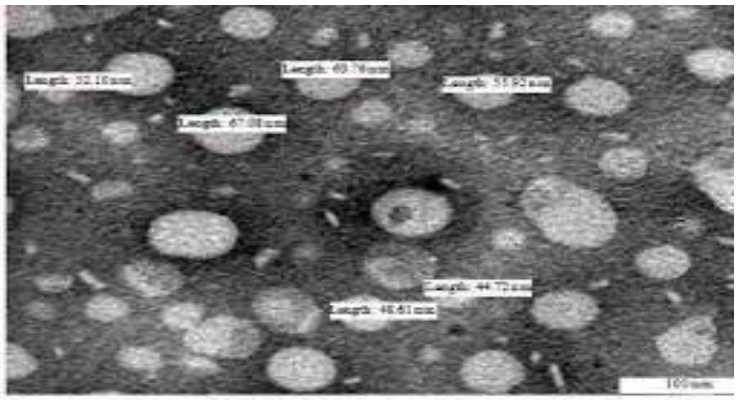

Figure 3.3: TEM image of niosomes

3.3 PREPARATION OF GELS

Preparation of carbopol gel base: 0.5 g Carbopol 934 was weighed and dispersed in water with mild stirring and allowed to swell for 24 hours to obtain 0.5% gel. Later 2 ml of glycerin was added to for gel consistency. Similarly 1 and 2% carbopol gels were prepared.

Table 3.4: Composition of different gel base

Formulation	Carbopol (%)
F1	0.5
F2	1.0
F3	2.0

Preparation of niosomes gels: Equivalent to 1g of niosomes formulation was dissolved in 10ml of ethanol and centrifuged at 6000 rpm for 20 minutes to remove the unentrapped drug. The supernant was decanted and sediment was incorporatedinto the gel vehicle. The incorporation of the niosomes into gels was achieved by slow mechanical mixing at 25 rpm for 10 minutes. The optimized formulation was incorporated into three different gel concentration 0.5, 1 and 2% w/w.

3.4 EVALUATION OF GELS

a. Determination of pH: Weighed 50 gm of gel formulation were transferred in 10 ml of beaker and measured it by using the digital pH meter. pH of the topical gel formulation should be between 3–9 to treat the skin infections.

b. Spreadability: A modified apparatus suggested was used for determining spreadability. The spreadability was measured on the basis of slip and drag characteristics of the gels.

c. Viscosity: The viscosity of gels was determined by using a Brook Field viscometer DV-II model. A T-Bar spindle in combination with a helipath stand was used to measure the viscosity and have accurate readings.

d. Drug content: 1 gm. of the prepared gel was mixed with 100 ml. of ethyl alcohol. Aliquots of different concentrations were prepared by suitable dilutions after filtering the stock solution and the absorbance was measured at 242 nm. Drug content was calculated by linear regression analysis of the calibration curve.

Table 3.5: Results of niosomes gel formulations

Code	Drug content (%)	pH	Spreadability (Gm.cm/sec.)	Viscosity (cps)
F1	99.25 ±0.027	7.0±0.021	23.75±0.075	6589±32
F2	98.68 ± 0.021	7.2±0.040	24.08±0.042	6895±24
F3	96.56 ± 0.017	7.3±0.060	20.75±0.059	72587±25

e. *In-vitro* diffusion study: An *in-vitro* drug release study was performed using modified Franz diffusion cell. Dialysis membrane was placed between receptor and donor compartments. Niosomal gel equivalent to 500 mg of drug was placed in the donor compartment and the receptor compartment was filled with phosphate buffer, pH 7.4 (24 ml). The diffusion cells were maintained at 37±0.5°C with stirring at 50 rpm throughout the experiment. At different time interval, 5 ml of aliquots were withdrawn from receiver compartment through side tube and analyzed for drug content by UV Visible spectrophotometer.

***In-vitro* drug release data of niosomes gel formulation**

Table 3.6: *In-vitro* drug release data for optimized formulation F1

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1.000	0.000	20.250	1.306	98.694	1.994
2	1.414	0.301	38.690	1.588	98.412	1.993
3	1.732	0.477	55.650	1.745	98.255	1.992
4	2.000	0.602	69.960	1.845	98.155	1.992
6	2.449	0.778	85.650	1.933	98.067	1.992
8	2.828	0.903	95.690	1.981	98.019	1.991

*Average of three readings

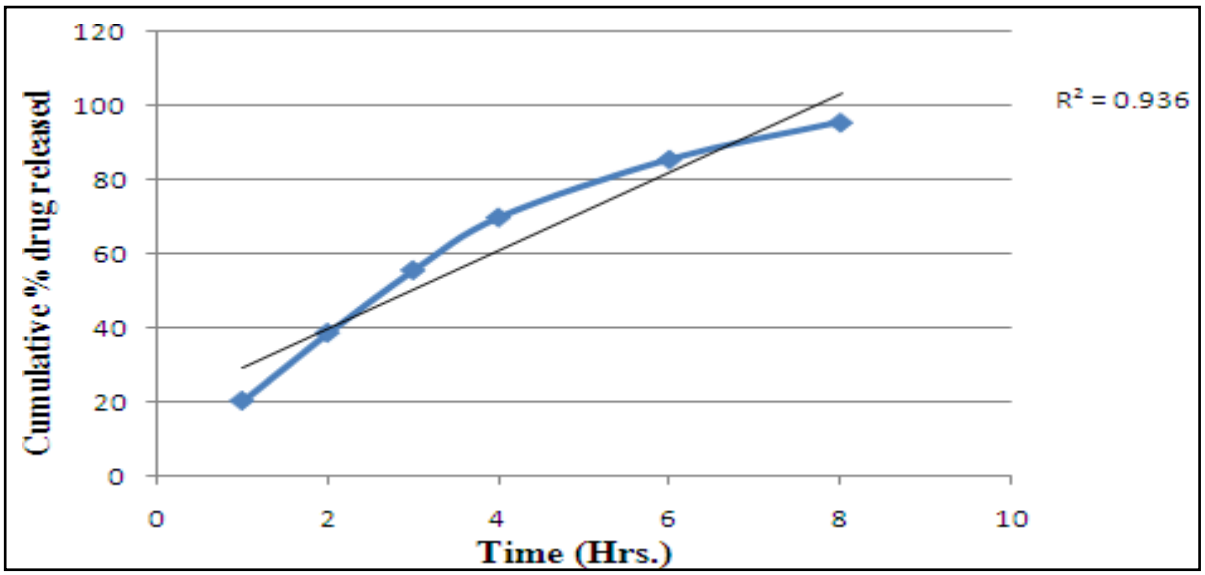

Figure 3.4: Cumulative % drug released Vs Time

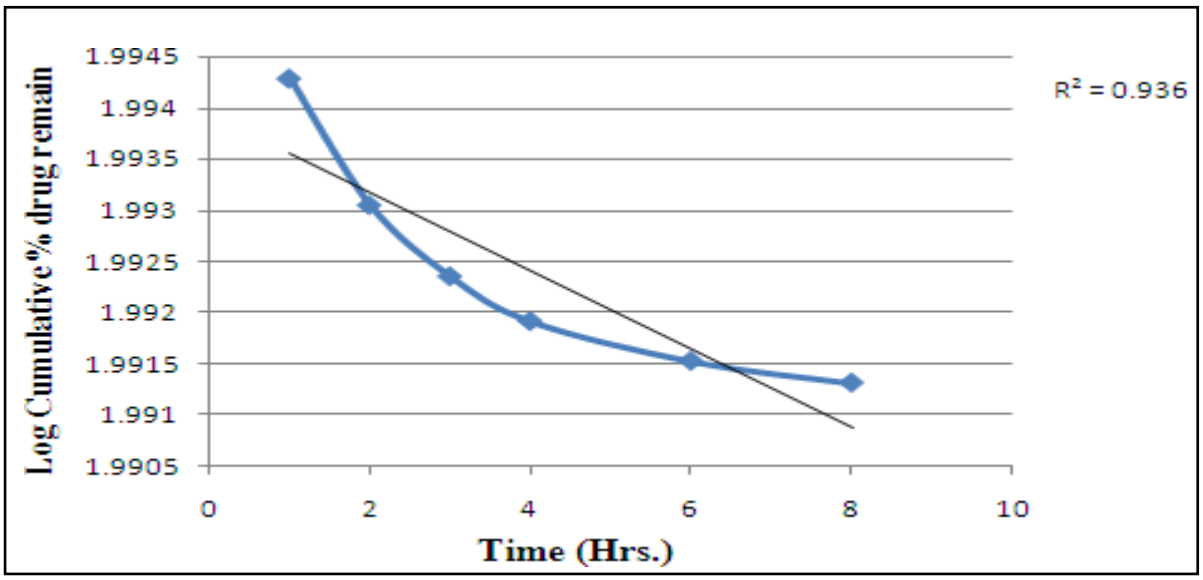

Figure 3.5: Log cumulative % drug remaining Vs Time

Table 3.7: Regression analysis data of niosomes gel formulation

Batch	Zero Order	First Order
	R^2	R^2
F1	0.936	0.936

f. Result of stability studies: Stability studies for optimized formulations were carried out at 28 ± 0.5ºC for a period of four weeks. There was no significant variation found in physical appearance, average particle size and % drug content of the niosomes gel.

3.5 ANTIBACTERIAL ACTIVITY

3.5.1 Pathogenic bacteria used: The pathogenic

bacteria used in the current study *Propioni bacterium acnes* was obtained from Microbial type culture collection, Institute of microbial technology, Chandigarh, Punjab, India.

3.5.2 Antimicrobial sensitivity: The antimicrobial sensitivity test is employed on to the microbes used under present study with Niosomes gels compared with marketed formulation. For this experiment 6 mm diameter wells, stock of equivalent to 100 µg/ml of Niosomes gels applied on it. A nutrient agar plate is seeded with particular bacteria with the help of spread plate technique prior and left for 5 minutes then incubated for 24 hours at 37^{o}C.

3.5.3 Antibiogram studies: Broth cultures of the pure culture isolates of microorganisms *Propionibacterium acnes* which are sensitive towards the 100 µg/ml concentration of gel formulation used in present study were prepared by transferring a loop of culture into sterile nutrient broth and incubated at 37^{o}±0.5^{o}C for 48 hours. A loop full was taken from these broths and seeded onto sterile nutrient agar plates through sterile cotton swab to develop diffused heavy lawn culture.

The well diffusion method was used to determine the antibacterial activity of gel formulation using standard procedure. There were 3 concentration used which are 25, 50 and 100 µg/ml for gel formulation for antibiogram studies. Undiluted over night broth cultures should never be used as an inoculums. The plates were incubated at 37^{o}±0.5^{o}C for 48 hour and then examined for clear zones of inhibition around the wells impregnated with particular concentration of drug.

3.5.4 Results of Antibacterial activity: *Propionibacterium acnes* were inhibited bythe standard antibacterial used in present work i.e., niosomes gels at all the concentration (20, 50 and 100 µg/ml) used in the study for comparison. The results of anti-bacterial activity are shown in Table

Table 3.8: Antibacterial activity of niosomes gels formulation against *Propionibacterium acnes*

Sample	Zone of Inhibition (mm)		
	20µg/ml	50 µg/ml	100µg/ml
Marketed Gel	12±0.76	15±0.5	17±0.57
Niosomes gels	14±0.5	16±0.57	18±0.86

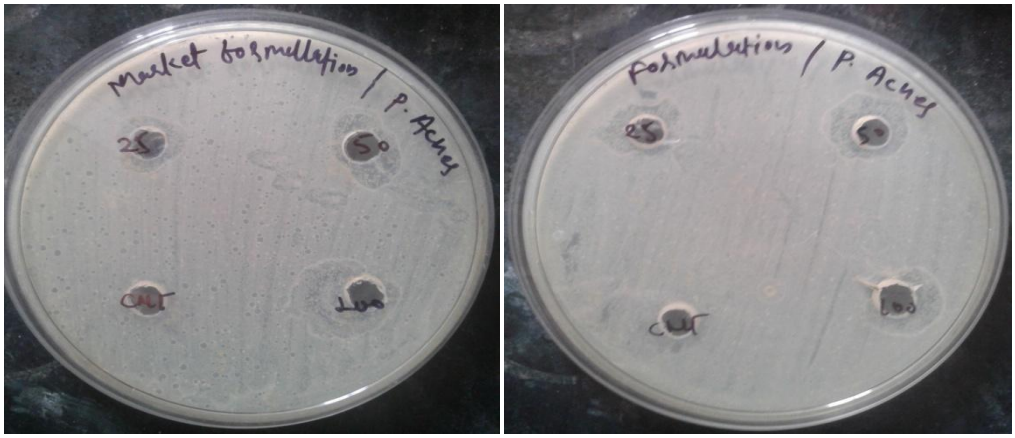

Figure 3.6: **Photograph showing antibacterial activity**

Niosomes gels showed greater percentage of inhibition of microbial infection against *Propionibacterium acnes*- on comparison of formulated gels with marketed gel of Tazarotene, niosomes gels

SUMMARY

Tazarotene is a prescription topical retinoid sold as a cream or gel. This medication is approved for treatment of psoriasis, acne, and sun damaged skin (photodamage). This compound belongs to the class of organic compounds known as retinoids. These are oxygenated derivatives of 3,7-dimethyl-1-(2,6,6-trimethylcyclohex-1-enyl)nona-1,3,5,7-tetraene and derivatives. Psoriasis is a chronic inflammatory skin disorder that may drastically affect the quality of life of an affected person. Different treatments are available for psoriasis and among this topical therapy are most commonly used in majority of patients. Psoriasis has genetic and life style triggers; the treatment guidelines involve continuous monitoring and lifelong care for the patients. Knowledge of the disease trigger factors and their role in precipitating the psoriasis is quiet important in the disease management. Care should be taken to avoid these psoriasis triggers. In recent years, new therapies have been introduced and several existing treatments have been improved giving new hope to people with psoriasis

From the FTIR data of the physical mixture it is clear that functionalities of drug have remained unchanged including intensities of the peak. This suggests that during the process drug and cholesterol has not reacted with the drug to give rise to reactant products. So there is no interaction between them which is in favor to proceed for formulation of vesicular drug delivery system. The UV study shows thatthe drug and excipients are compatible with each other. Partition coefficient value of drug was found to be 0.84 in n-octanol/water system which indicates the lipophilic nature of drug. Preformulation studies reported that the formulation of niosome and Tazarotene can be prepared with appropriate methods.

The aim of the work was to prepare and characterize Tazarotene encapsulated niosome, incorporated in to a suitable dermatological base, and assess its comparative efficacy in the treatment of dermal infections. Drug encapsulated niosomes was prepared by thin film hydration method using different ration of drug, cholesterol and surfactant ration Vesicular carriers were characterized for drug entrapment efficiency, vesicle size, vesicle shape and *in-vitro* diffusion study. Vesicular size, drug entrapment efficiency and zeta potential of the optimized niosomes were determined. Microscopic examination suggests niosomes to be multilamellar vesicles with smooth surface. *In-vitro* diffusion study demonstrated that the drug diffused from

optimized batch (F1) niosomal gel was found to be 95.69%.Stability studies for optimized formulations were carried out at 4.0 □ 0.5□C and 28 ± 0.5ºC for a period of four weeks. There was no significant variation found inphysical appearance, average particle size and % drug content of the niosomes gel.

CONCLUSION

The enhanced delivery of actives using niosomes can be ascribed to aninteraction niosomes and skin lipids. The release of the drug in the deep layers of theskin and its transdermal absorption could then be the result of a fusion of niosomes, with skin lipids and drug release at various points along the penetration pathway. It can be concluded that a gel formulation containing niosomes loaded with Tazarotene showed prolonged action and it can be developed successfully to improve the dermal infections.

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