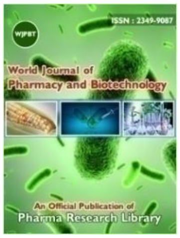

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Formulation, Development and Evaluation of Topical Tazorotene Liposomal Gel for the Management of Acne

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A B S T R A C T

The objective of the present study was to statistically optimize liposomal formulations to enhance the dermal delivery of the model drug tazarotene in combination with a hydroquinone-based gel. A 2^3 factorial design was employed to identify and evaluate significant formulation and process parameters influencing liposome development. Optimization batches (TL1 to TL8) were prepared via the lipid film hydration technique using varying concentrations of lecithin and cholesterol, and different stirring speeds (100 and 200 rpm). The resulting formulations were evaluated for vesicle morphology, particle size, and entrapment efficiency using transmission electron microscopy (TEM). The optimized liposomal formulation, TL6, was further incorporated into gels containing hydroquinone. Three gel formulations (LF1, LF2, and LF3) were prepared using varying concentrations of carbopol (0.5%, 1.0%, and 2%). The optimized tazarotene-hydroquinone gel formulation (1% carbopol) was characterized for pH, spreadability, viscosity (cps), and in vitro drug release. TL6 demonstrated the highest drug entrapment efficiency, with a vesicle size of 180.4 nm and an entrapment efficiency of 69.10%. In vitro diffusion studies showed drug release from the liposomal gel and a marketed conventional gel to be 98.12% and 98.58%, respectively. The findings suggest that the liposomal gel containing tazarotene and hydroquinone holds promise as an effective system for topical drug delivery.

Keywords: Tazarotene, Hydroquinone, Liposome, Gel, Topical Drug Delivery

A R T I C L E I N F O

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1. Introduction

Liposome technology is one of the fastest-evolving scientific domains, with significant contributions in drug delivery, cosmetics, and nanotechnology. The widespread interest in liposomes stems from their unique advantages, including the ability to encapsulate both hydrophilic and lipophilic agents, target specific sites in the body, and offer versatility in terms of size, surface charge, lamellarity, and membrane fluidity [1]. The first evidence demonstrating altered drug deposition following topical application of liposomally encapsulated drugs was presented at the FIP Congress in 1979. In the early 1980s, Mezei and Gulasekharam pioneered research on the use of liposomes for topical drug delivery. These efforts culminated in the commercialization of a liposomal gel containing econazole (Pevaryl™ by Cilag, Switzerland) in 1988 [2]. Their studies revealed that topical application of liposomal triamcinolone acetonide over five days resulted in a fourfold increase in drug concentration within the epidermis and dermis compared to conventional ointments, while significantly reducing urinary excretion. These findings suggested that liposomes enhance local drug activity while minimizing systemic absorption.

The localization of drugs within the liposomal structure depends on their solubility and partitioning behavior. Hydrophilic drugs (log $P \leq 0.3$) tend to reside in the aqueous core, whereas highly lipophilic drugs (log $P \geq 5$) are predominantly retained within the lipid bilayer. Drugs with intermediate partition coefficients ($1.7 \leq \log P \leq 4$) often present formulation challenges, as they readily distribute between aqueous and lipid phases, resulting in poor retention unless stabilized through lipid complexation [3]. On the other hand, drugs with poor biphasic solubility such as mercaptopurine, azathioprine, and allopurinol remain difficult to encapsulate effectively within liposomes [4].

Liposomes function not only as drug transporters but also as drug localizers, making them highly valuable in enhancing localized drug action. Although much of the early research in topical liposomal delivery focused on drug deposition in the stratum corneum, recent studies have increasingly demonstrated their ability to facilitate follicular drug delivery [5].

In this context, the present study aimed to statistically optimize liposomal formulations for the enhanced dermal delivery of the model drug tazarotene, in combination with a hydroquinone-based gel, as a promising approach for targeted topical therapy.

2. Materials and Methods

Preformulation Studies: Preformulation studies are an important tool for determination of physical and chemical properties of the drug before incorporating it in formulation development programme. The nature of the drug highly affects the processing parameters like method of preparation, loading efficiency, compatibility and pharmacokinetic response of the formulation.

Preformulation studies are indispensable protocols for development of safe, effective and stable dosage form as well. Preformulation studies include studies of:

- The physiochemical properties of drug, and an assessment of their relevance to the final formulation.
- The chemical and physical stability of drug.
- Chemical /physical compatibility of the active with potential excipients.

Preformulation Studies of Tazarotene and Hydroquinone

Physical appearance: The drugs (Tazarotene and Hydroquinone) were examined for its organoleptic properties like colour, taste and odour. Determination of wavelength maxima (λmax): Individual drugs were accurately weighed (10 mg) and each separately dissolved in 100 ml of PBS (pH 7.4) in a 100 ml volumetric flask. 1 ml of the stock solution was pipette into a separate 10 ml volumetric flask and volume made up to the mark with PBS (pH 7.4). The resulting solution was scanned between 200-400 nm using UV/Vis double beam spectrophotometer (Tejakrishna et al, 2013).

Preparation of Standard Stock Solution:

Individual drugs were accurately weighed (10 mg) and dissolved in 10ml of PBS (pH 7.4) volume was made up to 10 ml with the PBS (pH 7.4) give a stock solution of 1000 ppm or µg/ml.

Preparation of calibration curve of Tazarotene

(a) Calibration curve in phosphate buffer pH 7.4: From stock solutions of Tazarotene 1 ml was taken and diluted up to 10 ml. from this solution 0.1, 0.2, 0.3, 0.4 and 0.5 ml solutions were transferred to 10ml volumetric flasks and make up the volume up to 10 ml with diluents, gives standard drug solution of 1, 2, 3, 4, 5 µg/ml concentration.

The absorbances of were recorded at 351nm against a blank PBS (pH 7.4) for Tazarotene. The calibration curve was plotting the absorbance of Tazarotene and the concentration of Tazarotene. The straight line of best fit was obtained by using linear regression analysis program.

Preparation of calibration curve of Hydroquinone.

Calibration curve in phosphate buffer pH 7.4: From stock solutions of Hydroquinone 1 ml was taken and diluted up to 10 ml. from this solution 1.0, 2.0, 3.0, 4.0 and 5.0 ml solutions were transferred to 10ml volumetric flasks and make up the volume up to 10 ml with diluents, gives standard drug solution of 10, 20, 30, 40, 50 µg/ml concentration. The absorbances of were recorded at 288nm against a blank PBS (pH 7.4) for hydroquinone. The calibration curve was plotting the absorbance of Hydroquinone and the concentration hydroquinone. The straight line of best fit was obtained by using linear regression analysis program.

FTIR Spectroscopy of Tazarotene and Hydroquinone: IR spectra of pure drug individually and physical mixture of drug were recorded by KBr method using Fourier Transform Infrared Spectrophotometer. A base line correction was made using dried potassium bromide pellet. The potassium bromide-and sample individual pellet of approximately l mm diameter was prepared by grinding 3-5 mg of physical mixture of drug- excipients with 100-150 mg of potassium bromide in pressure compression machine.

The sample pellet was mounted in IR compartment and scanned at wavelengths 4000 cm-1 to 400 cm^{-1}. Melting point determination: It is one of the parameters for the purity of drugs. Melting point was determined by open capillary method (Chemline CL-725).The small amount of sample (2-4 mg) was transferred to one sided fused capillary tube and heated in vessel containing silicon oil at a rate of 5ºC/min, Melting point were examined for Tazarotene and Hydroquinone (Lachman et al,1989)

pH measurement:
pH was determined by digital pH meter. In this method 1gm of each Tazarotene and hydroquinone were accurately weighed separately and dissolved separately in 5 ml of ethanol and diluted to 100 ml with distilled water using Sonicator. The solutions were filtered and pH of the filtrate was measured with digital pH meter.

Flow properties:
The flow properties of drugs were characterized in terms of angle of repose, Carr's index and haussner ratio. For determination of angle of repose (θ), the drug powder were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The drug powder was poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The tan-1□ of the (height of the pile / radius of its base) gave the angle of repose.

Drug powders were poured gently through a glass funnel into a graduated cylinder exactly to 10 ml mark. Excess blend was removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0 cm until the time when there was no more decrease in the volume. Bulk density (ρb) and tapped density (ρt) were calculated. Haussner's ratio (HR) and Carr's' index (IC) were calculated according to the equations given below:

$$H_R = \frac{\rho_t}{\rho_b} \quad I_C = \frac{(\rho_t - \rho_b)}{\rho_t} \times 100$$

3. Results and Discussion

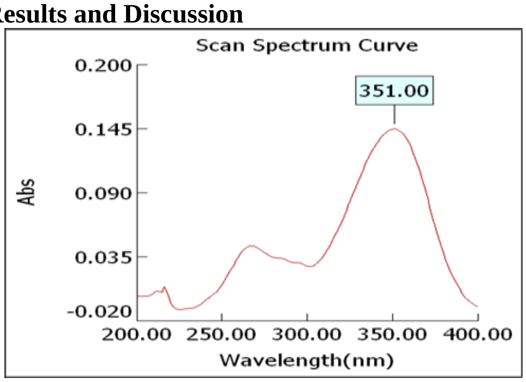

Fig.1: Wavelength scan of Tazarotene in PBS pH 7.4

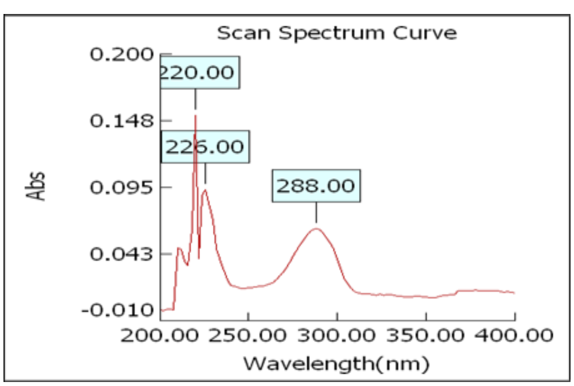

Fig.2: Wavelength scan of Hydroquinone in PBS pH 7.4

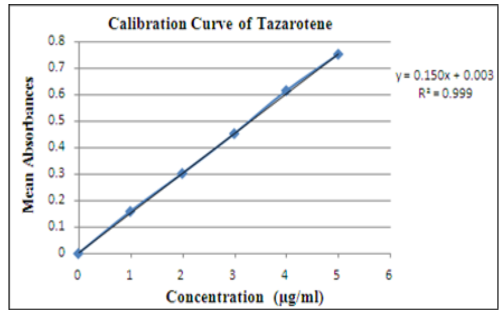

Fig.3: Calibration curve of Tazarotene in PBS (pH 7.4) at 351nm

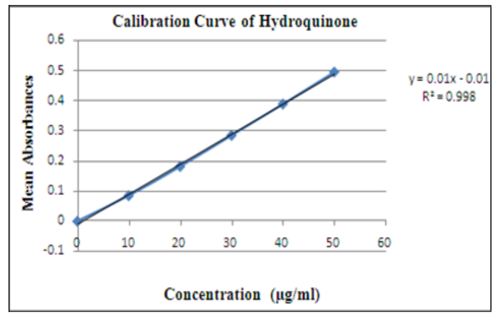

Fig.4: Calibration curve of Hydroquinone in PBS (pH 7.4) at 288 nm

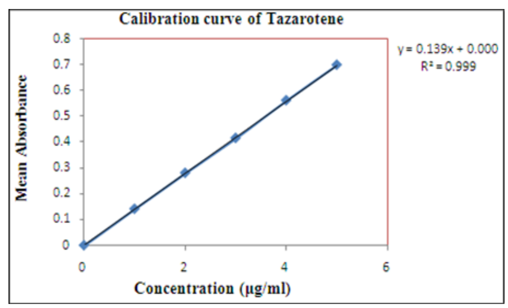

Fig.5: Calibration curve of Tazarotene in PBS (pH 6.8) at 351 nm

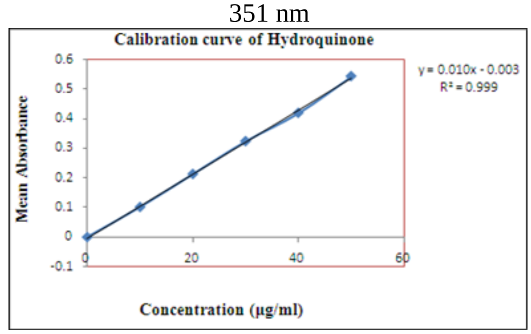

Fig.6: Calibration curve of hydroquinone in PBS (pH 6.8) at 288 nm

Fig.7: Photograph showing antibacterial activity

Table 1: Organoleptic property of Tazarotene and Hydroquinone

Parameter	Tazarotene	Hydroquinone
Colour	Light yellow powder	White crystalline powder
Odor	Odorless	Odorless
Taste	Tasteless	Tasteless

Table 2: Calibration curve of the proposed method for the estimation of Tazarotene and Hydroquinone

Conc. (μg/ml)	Tazarotene (351nm)	Conc. (μg/ml)	Hydroquinone (288nm)
	Absorbance*		Absorbance*
1	0.141±0.001	10	0.102±0.001
2	0.280±0.002	20	0.214±0.002
3	0.415±0.001	30	0.325±0.001
4	0.561±0.001	40	0.421±0.001
5	0.698±0.002	50	0.545±0.002

Table 3: Calibration curve of the proposed method for the estimation of Tazarotene and hydroquinone

Conc. (μg/ml)	Tazarotene (351nm)	Conc. (μg/ml)	Hydroquinone (288nm)
	Absorbance*		Absorbance*
1	0.159±0.001	10	0.085±0.001
2	0.302±0.002	20	0.182±0.001
3	0.452±0.001	30	0.285±0.001
4	0.614±0.001	40	0.389±0.002
5	0.751±0.002	50	0.495±0.001

Table 4: Effect of storage temperature on the vesicle size of drug (Tazarotene) loaded liposomal gel LF2

Time (Days)	Average Vesicle Size (nm)	
	4.0 ± 1°C	25 ± 1ºC
0	168.3	168.2
7	168.5	175.8
14	159.2	179.4
21	156.2	183.7
28	153.5	187.2

Table 5: Effect of storage temperature on the % drug content of Tazarotene loaded liposomal gelLF2

Time (Days)	**Drug Content (%)**	
	4.0 ±1°C	**25 ± 1ºC**
0	99.181 ± 0.020	98.182± 0.020
7	98.864± 0.124	98.102± 0.123
14	98.426± 0.256	98.012±0.458
21	98.114 ± 0.421	97.014 ±0.754
28	98.954 ± 0.411	96.425 ±0.412

Table 6: Effect of storage temperature on the % drug content of Hydroquinone loaded liposomal gelLF2

Time (Days)	**Drug Content (%)**	
	4.0 ±1°C	**25 ± 1ºC**
0	99.211± 0.010	98.125± 0.010
7	98.621± 0.0112	98.101± 0.112
14	98.321± 0.143	98.011± 0.323
21	98.012± 0.322	98.012± 0.643
28	98.824± 0.312	97.324±0.334

Table.7. Table 8.33: Antibacterial activity of Marketed and optimized gel formulations against Propionibacterium acnes

Sample	**Zone of Inhibition (mm)**		
	25μg/ml	**50 μg/ml**	**100μg/ml**
Marketed Gel	15±0.22	20±0.12	22±0.11
Liposomal Gel (LF2)	18±0.12	24±0.10	26±0.20

Table 8: Solubility studies of Tazarotene and Hydroquinone in different solvent

Solvent used	Solubility (mg/ml)	
	Tazarotene	**Hydroquinone**
Distilled Water	0.00075	11.26
0.1 N Hydrochloric acid	16.36	22.56
Ethanol	17.57	25.65
Methanol	26.26	31.25
Chloroform	18.56	5.26
Acetone	15.58	8.56
DMSO	35.15	15.56
Phosphate buffer pH 7.4	8.12	22.15
Phosphate buffer pH 6.8	9.25	25.37

Discussion

UV spectrographic studies results in the development of standard graph equation displaying a linear curve for both the drugs; wherein the R^2value of 0.99 was observed for both the drugs which shows a linear relationship between the concentration and absorbance. This indicates good correlation in the concentration range considered for the present study and that the equation can be utilized for calculating of the amount of the drugs present in a particular solution. The λmax is 351.0 nm for Tazarotene and 288.0 for Hydroquinone and hence the drugs will not have tendency to interact in terms of absorbance and quantification through the UV spectrographic studies. The spectrum of drug was authenticated by FTIR spectroscopy. The characteristic peaks present are obtained due to specific structural characteristics of the drug molecule were noted.

4. Conclusion

The in-vitro permeation study in pH 6.8 phosphate buffer revealed that Hydroquinone exhibited $98.89 \pm 0.56\%$ release within 30 minutes, while Tazarotene showed $98.12 \pm 0.45\%$ release over 12 hours, indicating a controlled and prolonged release pattern. Drug release kinetics best fit the Higuchi model (R^2 = 0.976 for LF2 formulation), suggesting diffusion-controlled, non-Fickian release from the gel matrix and liposomal vesicles. Liposomal gel showed greater percentage of inhibition of microbial infection against *Propionibacterium acnes*- On comparison of formulated gels with marketed gel of Tazarotene, Liposomal gel showed greater percentage of inhibition of bacterial infection against *Propionibacterium acnes.* This may be due to the fact that the liposomal gel released the drug in more efficient manner.

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