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(RESEARCH ARTICLE)

Development and in vitro characterization of the proliposome gel of terbinafine hydrochloride

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Abstract

The study was conducted to prepare the Proliposome Gel of Terbinafine Hydrochloride to improve the drug loading and to sustain the drug release of terbinafine hydrochloride. Proliposome gel of terbinafine hydrochloride were prepared by modified coacervation phase separation method by varying the concentrations of PC to cholesterol. The prepared proliposome gel was evaluated for its pH, viscosity, drug loading, and In vitro drug release studies. The appearance, particle size and drug entrapment of each produced formulation was also evaluated. All proliposome gel formulation made were consistent, homogenous, and white creamy gel.

Keywords: Proliposome gel; Terbinafine; Novel drug delivery system; Liposomes

1. Introduction

Proliposomes are a new type of carrier mediated drug delivery system having many benefits over conventional liposomes. The stability of proliposomes is far superior to liposomes making them more suitable for the delivery of drugs. They are a dry, free-flowing, granular material that immediately forms a liposomal dispersion on contact with water or a biological fluid

The technology is based upon the intrinsic property of hydrated membrane lipids to form vesicles on contact with water. It involves layering of the phospholipids onto a finely divided particulate support which results in the formation of dry powders. When the dry powders are hydrated with an aqueous solution followed by gentle mixing, phospholipids on the solid support rapidly disperses to give a liposomal suspension.

Proliposomes have been employed as a basis for a number of site-specific drug delivery approaches. Proliposomal formulations suggest increases solubility and bioavailability of some poorly soluble drugs. Being available in dry powder form, they have an additional convenience in transportation, distribution, storage, processing, packaging, providing optimal flexibility, unit dosing as capsule and stable during sterilization. All these advantages make them a promising candidate for industrial production.

Proliposomes have been studied for various routes of administration including oral, transdermal, mucosal, nasal, ocular, pulmonary and parenteral. Proliposomes derived liposomes showing advantages as drug carriers, comprising lower cost and toxicity, easy storage and handling and increased stability.

Terbinafine is an antifungal drug. It is mainly effective on fungi of the group Onygenales and some yeasts in the genus Candida (e.g. Candida glabrata). As a cream or powder, it is used topically for superficial skin infections such as jock itch

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(tinea cruris), athlete's foot (tinea pedis), and other types of ringworm (tinea corporis). Tablets by mouth are often prescribed for the treatment of onychomycosis, a fungal nail infection, typically by a dermatophyte or Candida species.

Like other allylamines, terbinafine inhibits ergosterol synthesis by inhibiting squalene epoxidase, an enzyme that catalyzes the conversion of squalene to lanosterol. In fungi, lanosterol is then converted to ergosterol in humans, lanosterol becomes cholesterol. However, as fungi and animals diverged around 1.1 billion years ago - there is enough difference in this enzyme that terbinafine preferentially binds fungal squalene epoxidase, making it selective for inhibiting ergosterol production in fungi without significantly affecting cholesterol production in mammals. This is thought to fatally disrupt the fungal cell membrane.

2. Materials and methods

2.1. Materials

Terbinafine was obtained from Niksan Pharmaceuticals, Gujrat and Excipients - Sodium chloride, Methanol and Disodium hydrogen phosphate were obtained from Finar Pvt. Ltd., Ahemadabad, Cholesterol from Thomas baker (chemical), Mumbai., Ethanol from Changshu Yangquan Chemical, China., Potassium dihydrogen phosphate Molychem, Mumbai, and Soya lecithin from LobaCheim Pvt. Ltd., Mumbai.

2.2. Preformulation study

Melting point

In experimental settings, the melting point is really defined as the range of temperatures from which the first crystal begins to melt to which the last crystal just vanishes. Melting point equipment was used to determine melting point.

Solubility

Terbinafine HCl was tested for solubility in different polarity solvents. Studies on drug solubility are conducted in triplicate at 25°C by agitating extra drug in a stoppered volumetric flask containing 5 ml of solvent. The flasks were vortex combined for five minutes after sealing and then sonicated for 30 minutes. Mixtures were then allowed to shaken for 24 hours at 100 rpm with the help of water bath shaker. After 24 hrs samples were examined under UV spectroscopy.

Drug- Excipients compatibility study

The drug alone and optimized formulation was subjected to FTIR studies. For proposed study the samples were properly diluted with dried KBR and IR spectra were acquired in the range of 400-4000 cm^{-1} with resolution of 4 cm^{-1} using Shimadzu 8400S FT-IR.

Partition coefficient studies

The partition coefficient (oil/water) is a metric for a drug's lipophilicity and a sign of how evenly it is distributed during equilibrium between the organic and aqueous phases. A way to describe the drug's lipophilic/hydrophilic characteristics is by partition coefficient. At 37±0.5 °C, the partition coefficient of Terbinafine HCl was calculated by mixing 2.5 ml of octanol with 2.5 ml of water. After shaking, the system was left alone for 30 minutes. The amount of drug added to this solution was about 10 mg. And for about 24 hours, the above-formed mixture was not disturbed. Through the use of a separating funnel, two layers were separated, and the amount of Terbinafine HCl solubilized was calculated by measuring the absorbance at 282 nm in comparison to a reagent blank using a double beam UV/Vis spectrophotometer. Partition coefficient was determined as ratio of concentration of drug in octanol to the concentration of drug in water and the value were reported as log P.

$$\text{Log p} = \frac{concentration\ of\ drug\ in\ non\ aqueous\ phase}{concentration\ of\ drug\ in\ aqueous\ phase}$$

Quantitation of drug

Preparation of standard plot of Terbinafine HCl in methanol

A standard drug plot in methanol at an acceptable concentration range was created to determine the amount of Terbinafine HCl. By dissolving 10 mg of Terbinafine HCl in a 100 ml volumetric flask containing methanol, stock solutions of Terbinafine HCl with a concentration of 100µg/ml were created. Add the methanol, sonicate for one minute, and then increase the volume to the desired level. To achieve a concentration range of 4-36µg/ml, the stock solution

was further serially diluted in a 10 ml volumetric flask. Using a UV spectrophotometer, these were examined spectrophotometrically at 282 nm.

2.3. Preparation of Terbinafine HCl loaded proliposomes gel

The proliposomal gel formulations were made utilizing PC, cholesterol as the lipid component, according to the described meth with a small modification. PC and cholesterol were measured out accurately and placed in a glass vial with a wide opening that was dry and clean. Table 3 displays the ingredients in several proliposomal gel compositions. Following the addition of the drug, 400 L of 100% ethanol was added to the combination of the lipid component. The vials were then shaken intermittently for about 5 minutes while being warmed in a thermostatic water bath at 55–60°C to ensure that the components were evenly distributed. This was done to prevent the solvent from evaporating. To the resultant transparent solutions, 160 µL of double distilled water maintained at the same temperature was added while warming in the water bath till a clear or translucent solution was obtained, which upon cooling formed a yellowish translucent liquid or yellowish translucent gel or a white creamy proliposomal gel. The obtained gels were stored in the same closed glass vials in the dark until further characterization.

Table 1 Composition of Proliposomal gel containing Terbinafine HCl

S.No.	Formulation code	Terbinafine HCl (%w/w)	Phospholipid: Cholesterol ratio (molar ratio)	Amount of phospholipid (mg)	Amount of cholesterol (mg)	Amount of ethanol (µl)	Amount of water (µl)
1	PG1	1	0.01:0.01	75.8	38.6	800	200
2	PG2	1	0.02:0.01	151.6	38.6	800	200
3	PG3	1	0.03:0.01	227.4	38.6	800	200
5	PG4	1	0.04:0.01	303.2	38.6	800	200
6	PG5	1	0.03:0.02	227.4	77.2	800	200
7	PG6	1	0.03:0.03	227.4	115.8	800	200

2.4. *In vitro* characterization of Terbinafine HCl loaded proliposome gel

Yield of Proliposme gel

Yield of prepared proliposomal gel was determined by given below equation

$$Percentage\ yield = \frac{Practicle\ amount\ of\ proliposomal\ gel}{Theoritical\ mass} \times 100$$

Encapsulation and Loading Efficacy of Terbinafine HCl

The proliposomal gels were hydrated with 10 ml water and bath sonicated for 3 min. The resulting dispersion was used for the centrifugal test to determine the degree of entrapment. Unentrapped free drug from the produced liposomal dispersion was removed by adding 2 ml of the dispersion to a centrifuge tube, centrifuging the samples at 15000 rpm for 30 minutes, filtering the sample through a 0.22 micron filter, and analysing the sample using a UV spectrophotometer.

Viscosity and Rheological properties

The rheological analysis of the experimental gels was performed using a Brookfield viscometer pro D II + apparatus, equipped with standard spindle LV1 with 61 marking. Viscosity of all investigate formulation was determined at 100rpm and optimized concentration was selected.

Particle Size, Polydispersity and Zeta Potential Determination

Using the Zetasizer Nano ZS90, photon correlation spectroscopy was used to calculate the average size of liposomes. Each sample was properly diluted before size analysis was carried out at 25°C and a 90° angle of detection. The device provided data on the liposomes' size and polydispersity index (PI). Size and polydispersity index (PI) of liposomes were

obtained from the instrument. Surface charge (zeta potential) of the liposomes was also measured by using Zetasizer Nano ZS90 (Malvern Instruments).

In vitro drug release study

Franz diffusion cells that had been constructed carried out the release of Terbinafine from proliposomal formulations and Terbinafine powder (control) with an effective diffusion area of 4.153 cm^2. The donor compartment-facing side of the dialysis membrane was positioned between the diffusion cell's compartments and heated to room temperature. About 1g of the proliposomal gel equivalent to the 1%w/w of Terbinafine HCl was applied to the skin surface in the donor compartment, which was covered by parafilm, after the dialysis membrane had time to equilibrate. A 15ml phosphate buffer solution with a pH of 6.8 was added to the receptor compartment of the cell. The solution in the receptor compartment was kept at 37°C throughout the tests, and it was agitated at 100 rpm. The amount of drug release was determined by removing 1ml aliquots of sample at appropriate time intervals up to 24 h the volume was replenished with an equal volume of phosphate buffer to maintain sink conditions. At the end of the study, the samples were suitably diluted and the amount of drug was determined spectrophotometrically at 282 nm.

Drug release kinetics

Several kinetic models, such as the zero order plot, first order plot, and higuchi plot, were used to study the release kinetic.

Data from in vitro drug release studies were plotted in different kinetic models to study the release kinetics of the optimised formulation. These models included the Higuchi model, which plots the percentage of drug released against the square root of time, and the zero order model, which plots the amount of drug releases against time. The correlation coefficient value being close to 1 supported the best fit model.

Zero Order Model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$Q_0 - Q_t = K_0 t$ (1)

Rearrangement of equation (1) yields:

$Q_t = Q_0 + K_0 t$ (2)

Where Q_t is the amount of drug dissolved in time t,

Q0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time. Data from in vitro drug release studies were shown as the amount of drug released vs time to analyse the release kinetics.

First Order Model

The absorption and/or elimination of some drugs have also been described using this approach, despite the fact that it is challenging to grasp this mechanism on a theoretical foundation. The release of the drug which followed first order kinetics can be expressed by the equation:

$\log C = \log C_0 - K_t / 2.303$

Where C0 is the initial concentration of drug, k is the first order rate constant, and t is the time. The data obtained are plotted as log percentage of drug remaining vs. time which would yield a straight line with a slope of -K/2.303.

Application: The absorption and/or elimination of some drugs have also been described using this approach, despite the fact that it is challenging to grasp this mechanism on a theoretical foundation.

Higuchi's Model

Graph was plotted between percentages of drug released Vs square root of time.

$Q=K^{1/2}$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence drug release rate is proportional to the reciprocal of the square root of time.

Application: This relationship can be used to describe how a drug dissolves when it is included in a variety of pharmaceutical dosage forms with modified release, such as some transdermal systems and matrix tablets that contain water soluble drug.

3. Result and discussion

3.1. Melting point

Terbinafine HCl bulk powder form was found to have a melting point that ranged from 197.67±1.15°C -198.67±1.52°C.

3.2. Partition coefficient determination

The lipophilic nature of the drug in bulk API form was described by the partition coefficient of Terbinafine HCl in the n-octanol-water system, which was determined to be 3.22± 0.013. The observed value was also found to be extremely near to the reference value 3.31.

3.3. UV Scan of Terbinafine HCl

The drug Terbinafine HCl has the following maximum rates of absorption in methanol.

Table 2 Absorption maxima of Terbinafine HCl drug in methanol

Solvent	Absorption maxima
In methanol	282nm

3.4. Preparation of standard curve of Terbinafine HCl drug in methanol

The standard calibration curve's absorbance information is provided in the A calibration curve was created using the absorbance of Terbinafine HCl at various concentrations. The straight line calibration equation was found to be y = 0.0311x+0.0089 with a correlation coefficient of 0.999 this equation was utilised to calculate the concentration of unknown samples.

Table 3 Absorbance of different dilutions of drug at 282nm in methanol

Con.(µg/ml)	Absorbance
0	0±0
4	0.131±0.004
8	0.260±0.002
12	0.386±0.003
16	0.505±0.001
20	0.639±0.003
24	0.772±0.002
28	0.873±0.005
32	0.990±0.004

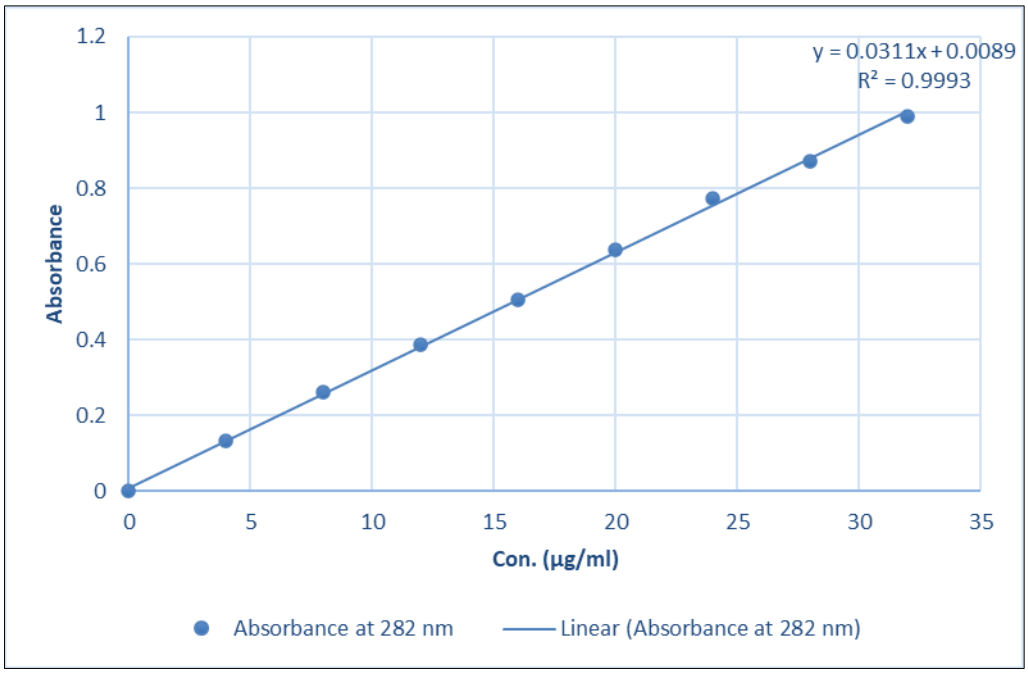

Figure 1 Standard calibration curve of Terbinafine HCl

3.5. Solubility study

Solubility of Terbinafine HCl in different solvents is as follows:

Table 4 Solubility of Terbinafine HCl in different solvents

S. No.	Name of solvent	Amount in mg/ml
1	Water	0.639±0.008
2	Propylene Glycol	1.887±0.024
3	pH 7.4 phosphate buffer	4.931±0.020
4	Methanol	64.019±0850
5	Dichloromethane	99.603±1.033

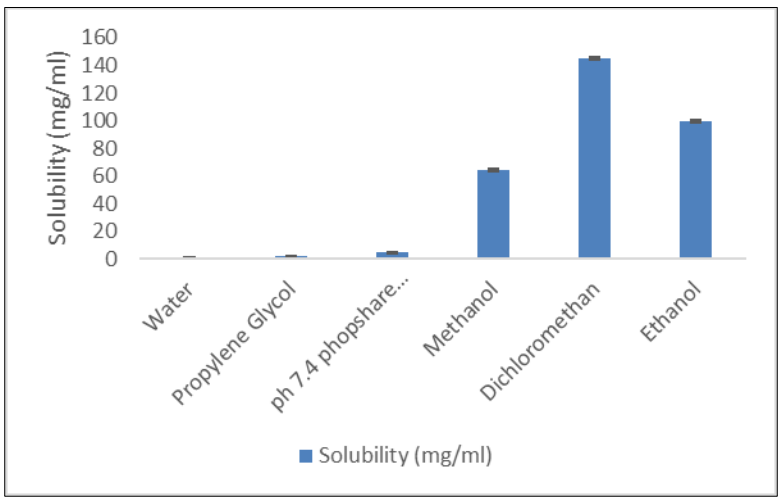

Figure 2 Solubility of Terbinafine HCl if different solvents

Table 4 demonstrated that Terbinafine HCl displayed good solubility in dichloromethane followed by methanol. But it remains insoluble in water and buffer solution.

3.6. FT-IR of Drug and formulation

Overlay FTIR spectrum of pure drug Terbinafine HCl and optimized formulation was shown in figure 3.

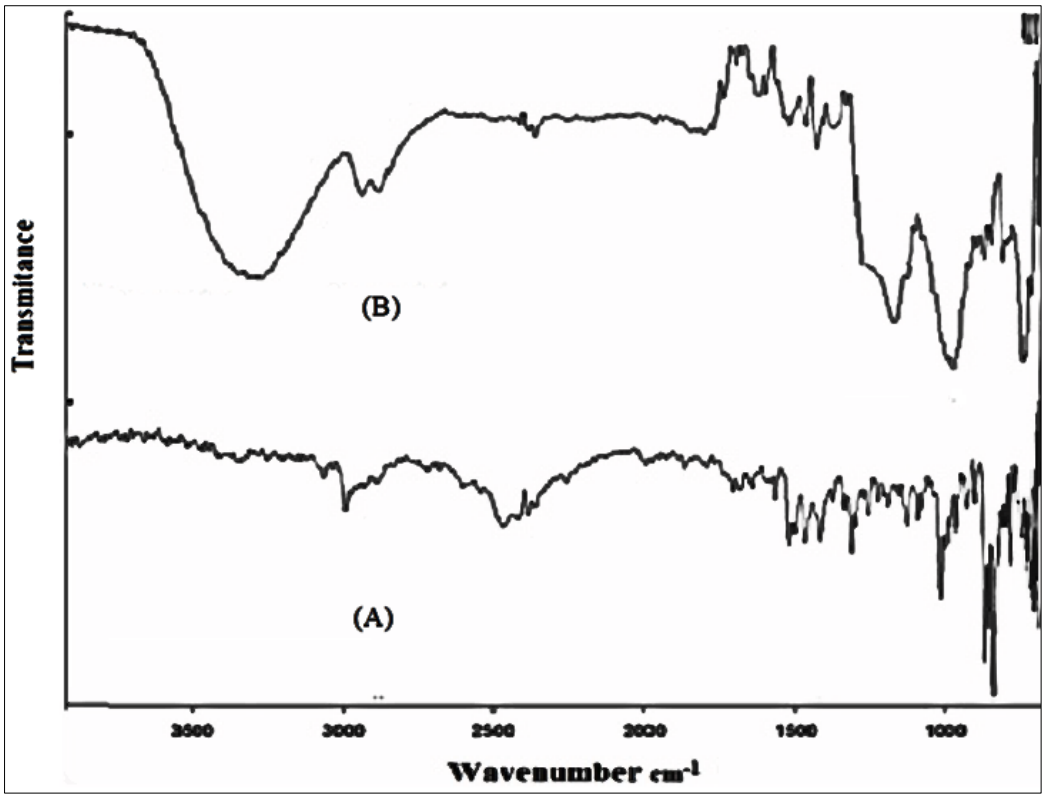

Figure 3 Overlay FT-IR of A) Terbinafine hydrochloride and B) optimized formulation

In FTIR spectrum of Terbinafine HCl, band at 2245.85cm^{-1} is assigned to the C ≡ C stretching bands. The bands a 1528, 3054.9cm^{-1} corresponds to aromatic C=C and C-H bending modes. The C-N bending is seen at 1119.85 cm^{-1}. In optimized formulation characteristics peak was slightly shift with reduced intensity. This study confirms that drug was encapsulated in phospholipid matrix.

3.7. Preparation of Terbinafine HCl containing proliposome

Proliposomes of Terbinafine HCl were prepared by modified coacervation phase separation method by varying the concentrations of PC to cholesterol. At low concentration of cholesterol with PC alone the formulation was flowable yellowish liquid with poor stability and low entrapment efficiency. To improve the stability and entrapment efficiency of formulations, cholesterol, a structural lipid, was employed at varying concentrations. The appropriate ratio of PC and cholesterol is the prime factor in maintaining the integrity of proliposomes. As reported earlier in our previous report the alteration in concentrations of PC and cholesterol leads to disruption and leakage of drug from vesicles before union of vesicles with the skin.

3.8. In vitro characterization Terbinafine HCl containing proliposomal gel

Visual Appearance

Visual appearance of all prepared formulation was shown in table 5.

Table 5 Visual appearance of all prepared formulation

S.No.	Formulation code	Visual appearance
1	PG1	Non uniform, Yellowish liquid
2	PG2	Non uniform, Translucent gel
3	PG3	Uniform, Homogenous, white creamy gel
4	PG4	Uniform, Homogenous, white creamy gel
5	PG5	Uniform, Homogenous, white creamy gel
6	PG6	Uniform, Homogenous, white creamy gel

Except for formulations PG1 and PG2, which were yellowish liquid and gel that was unstable, all created formulations were consistent, homogenous, and white creamy gel.

Determination of pH of all prepared formulation

pH of all prepared formulation was shown in table 6.

Table 6 pH of all prepared formulation

S.No.	Formulation code	pH
1	PG1	6.387±0.021
2	PG2	6.236±0.035
3	PG3	6.509±0.025
4	PG4	6.470±0.36
5	PG5	6.370±0.30
6	PG6	6.311±0.10

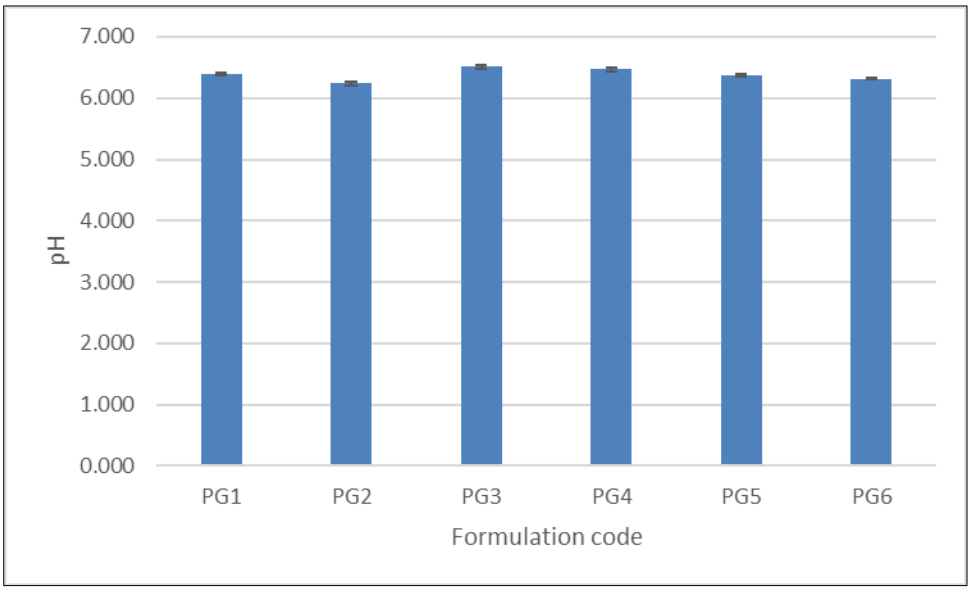

Figure 4 pH of all prepared formulation

The pH of every manufactured formulation was found to be in the range of 6.237±0.035 to 6.507±0.0255, which is near to the pH of the skin.

Percentage yield

Percentage yield of prepared formulation was shown in table 7.

Table 7 Percentage yield of all prepared formulation.

S.No.	Formulation code	Percentage yield
1	PG1	95.52±0.11
2	PG2	99.01±0.27
3	PG3	98.28±0.20
4	PG4	98.07±0.39
5	PG5	98.56±0.35
6	PG6	97.31±0.34

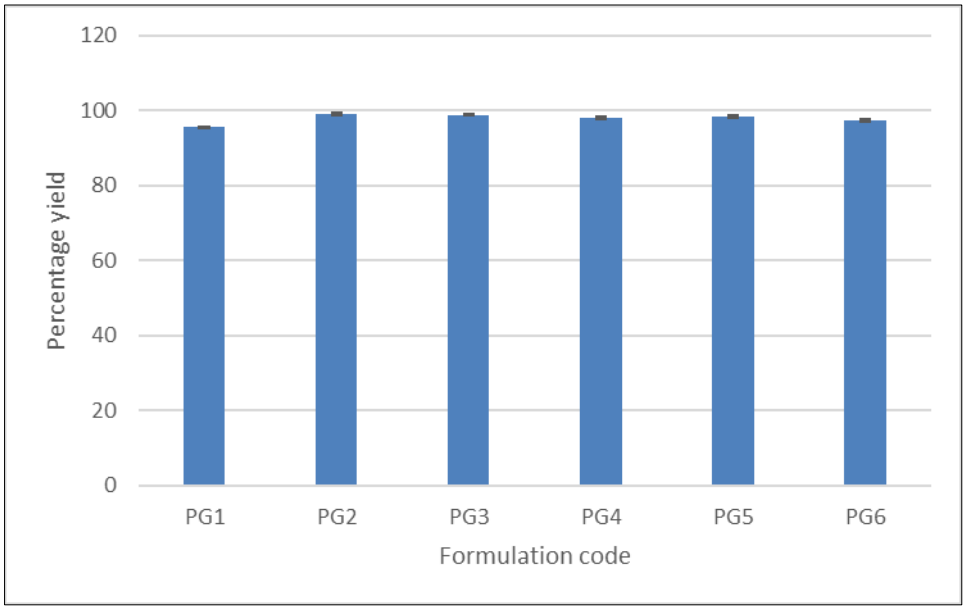

Figure 5 Percentage yield of all prepared formulation

Figure 5 showed that the range of the percentage yield for the entire formulation preparation was determined to be between 95.52±0.11 to 98.82±0.20.

Percentage Encapsulation of Terbinafine HCl loaded proliposome gel

Percentage Encapsulation of all prepared Terbinafine HCl loaded proliposome gel was as given below table 8.

Table 8 Percentage Encapsulation Efficacy of all prepared Terbinafine HCl loaded proliposome gel

Formulation Code	% Entrapment efficiency
PG1	77.203±0.322
PG2	87.492±0.851
PG3	97.138±0.643

PG4	95.423±0.743
PG5	98.424±0.647
PG6	96.388±0.669

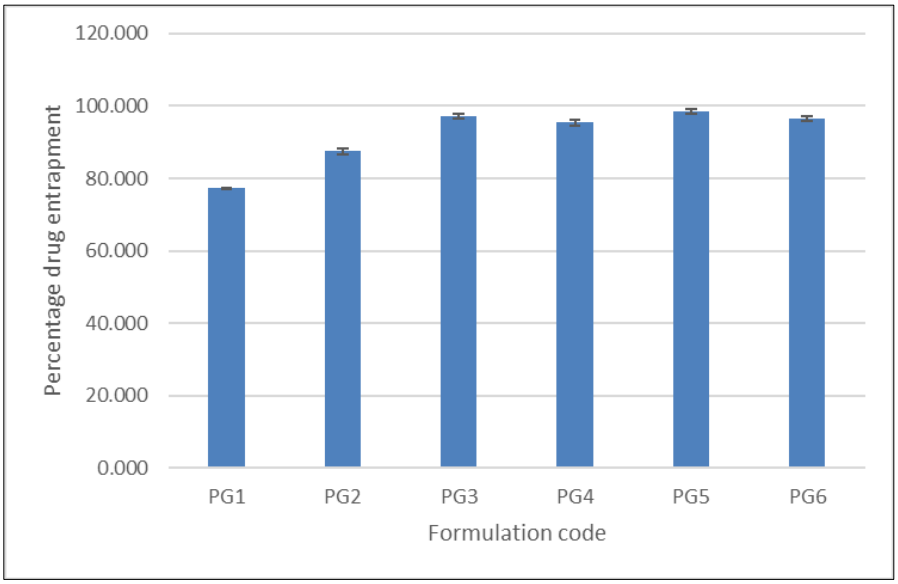

Figure 6 Percentage Encapsulation Efficacy of all prepared proliposomal gel formulation

Percentage Encapsulation The produced formulations were found to have an efficacy ranging from 77.203±0.322 to 98.424±0.6433. When the concentration of lecithin increases, the proliposome formulation's entrapment efficiency increases from 77% to 98%. More room would be available for the drug's accommodation with an increase in soy lecithin. Similarly on increasing amount of the cholesterol, the percentage drug entrapment increase. This could be due to the increased bilayer hydrophobicity and reduced permeability of the bilayer, leading to the effective intercalation of hydrophobic drug within the hydrophobic core of the bilayer with an enhanced drug pay load. Maximum percentage drug encapsulation efficiency was found to be for formulation P5 98.424±0.643.

Viscosity analysis

Viscosity of all prepared formulation were shown in table 9.

Table 9 Viscosity of all prepared formulation

Formulation code	**Viscosity (cp) at 100 rpm**
PG1	1592.667±1.055
PG2	1877.000±1.646
PG3	2013.333±1.082
PG4	2158.333±1.528
PG5	2204.333±1.517
PG6	2296.667±1.155

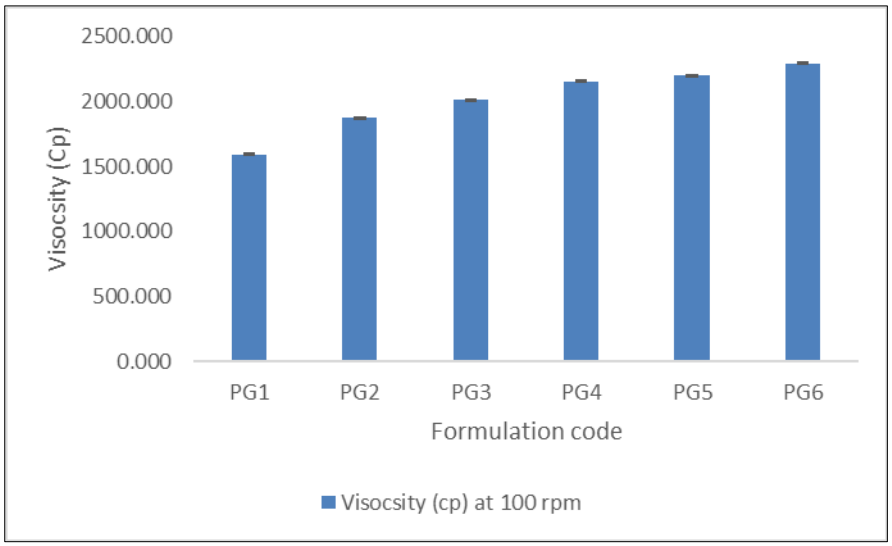

Figure 7 Viscosity of all prepared gel formulations

Viscosity of all prepared formulation were observed to be within the range.

On the basis of in vitro characterization parameters PG5 formulation was selected for further evaluation

Particle Size, Polydispersity and Zeta Potential Determination.

The particle size analysis of PG5 and revealed that the average particle size measured by laser light scattering method is around 314.25 nm as shown in table 10.

Table 10 Particle Size, Polydispersity and Zeta Potential Determination

S. No	Formulation code	Particle size (nm)	PDI	Zeta Potential(mv)
1	PG5	314.25	0.157	-21.63

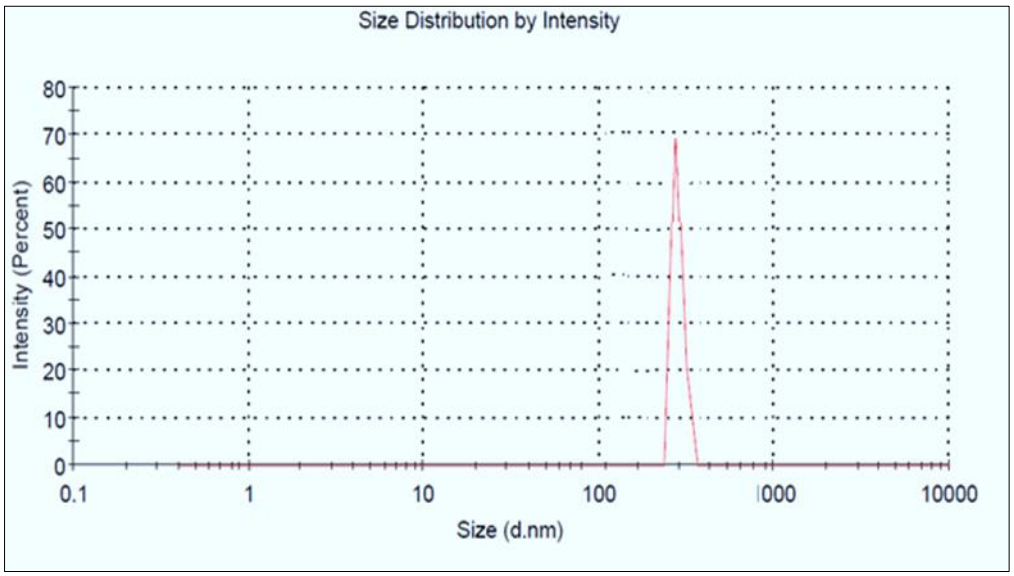

Figure 8 Particle size distribution of formulation PG5

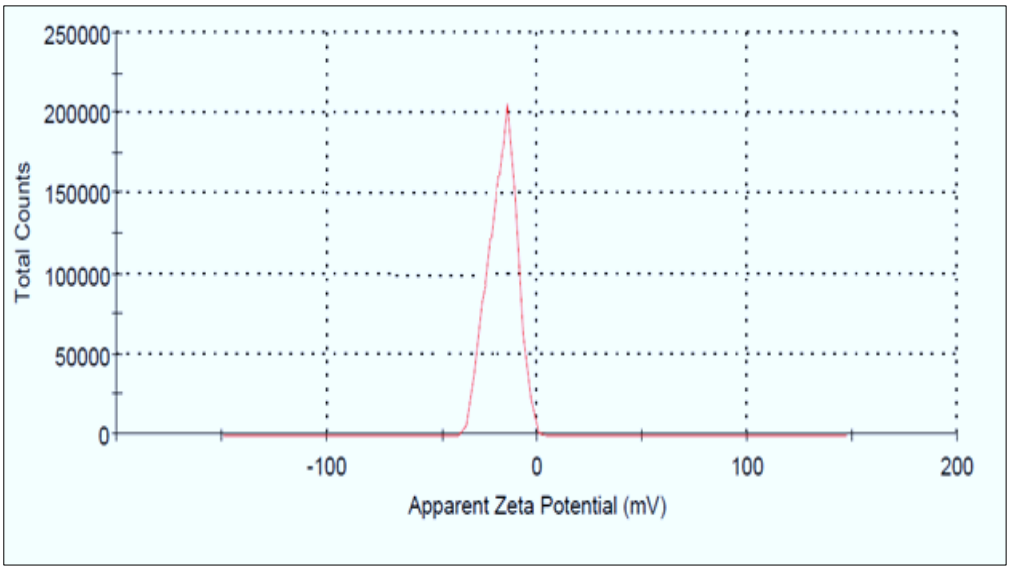

Figure 9 Zeta Potential of formulation PG5

In vitro drug release study

Comparison of In-vitro drug release study of aqueous drug suspension of Terbinafine HCl and Terbinafine HCl loaded proliposomal gel formulation PG5 was as given below table 11.

Table 11 Comparison of In-vitro drug release study of aqueous drug suspension of Terbinafine HCl and Terbinafine HCl loaded proliposomal gel formulation PG5

S.No.	Time (hr)	% Drug release of Pure drug Suspension	% Drug release of Formulation PG5
1	0	0±0	0±0
2	0.5	9.434±0.34	9.965±0.307
3	1	10.534 ±0.102	15.752±0.171
4	2	12.207±0.136	26.797±0.307
5	4	13.799±0.068	42.834±0.136
6	6	14.643±0.171	63.473±0.705
7	8	16.476±.0.102	82.524±0.364
8	10	17.006±0.104	89.277±0.046
9	12	17.272±0.136	95.547±0.682
10	24	17.923±0.105	94.341±0.341

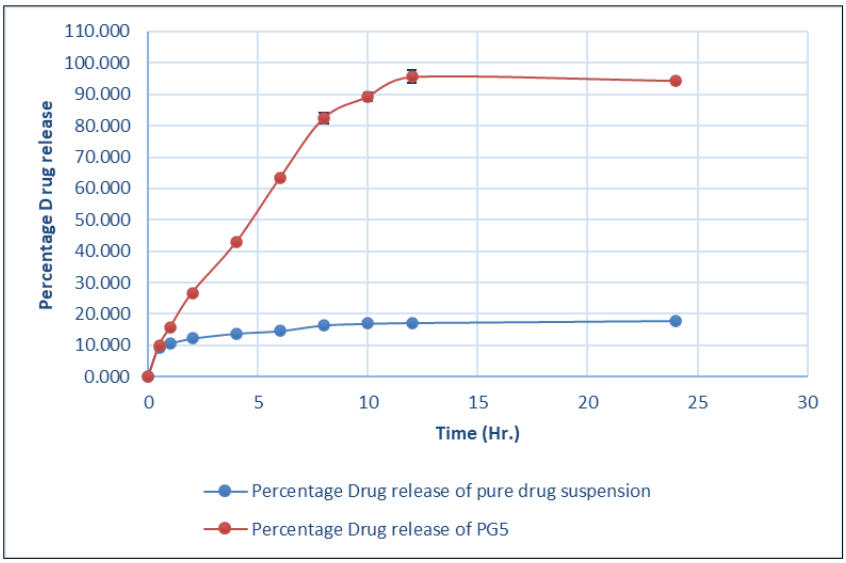

Figure 10 Comparison of In-vitro drug release study of aqueous drug suspension of Terbinafine HCl and Terbinafine HCl loaded proliposomal gel formulation PG5

Artificial cellophane membrane was utilised to study the in vitro release behaviour and the impact of composition on liposome stability. This depicts the percentage of drug release from formulations of prolioposomal gel and drug aqueous suspension. The fact that Terbinafine HCl was released from the control means that the drug's aqueous suspension was roughly 17.923±0.105% within 24 hours, which amply demonstrates the drug's low levels of permeation and solubilization. Proliposome formulations showed a typical biphasic release pattern with an initial quick burst release lasting for two hours and then a sustained release lasting for twenty-four hours. The rapid drug release may have been facilitated by the strong concentration gradient present at the early time points as well as by the quicker release of unentrapped drug from the proliposome formulations. The percentage drug release was found to be 95.547±0.682 for formulation PG5.

Drug release Kinetic study

Zero order release

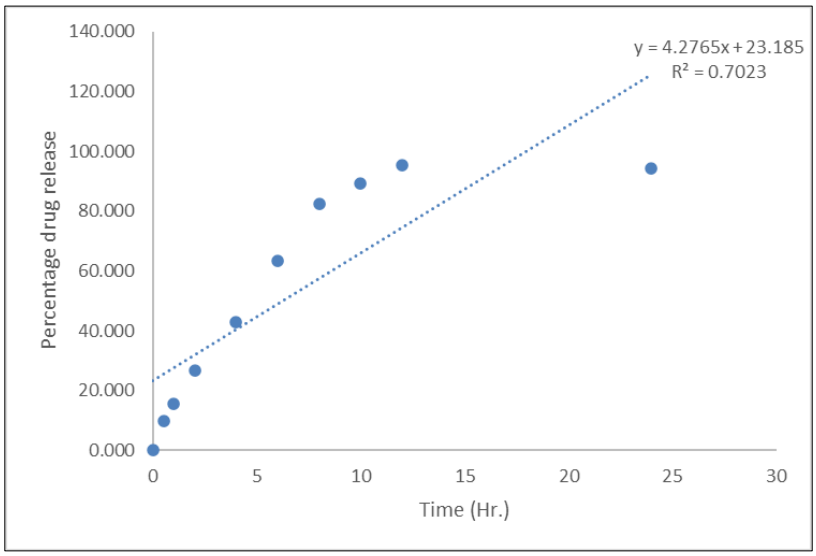

Figure 11 Zero order Drug Release of PG5 formulation

First Order

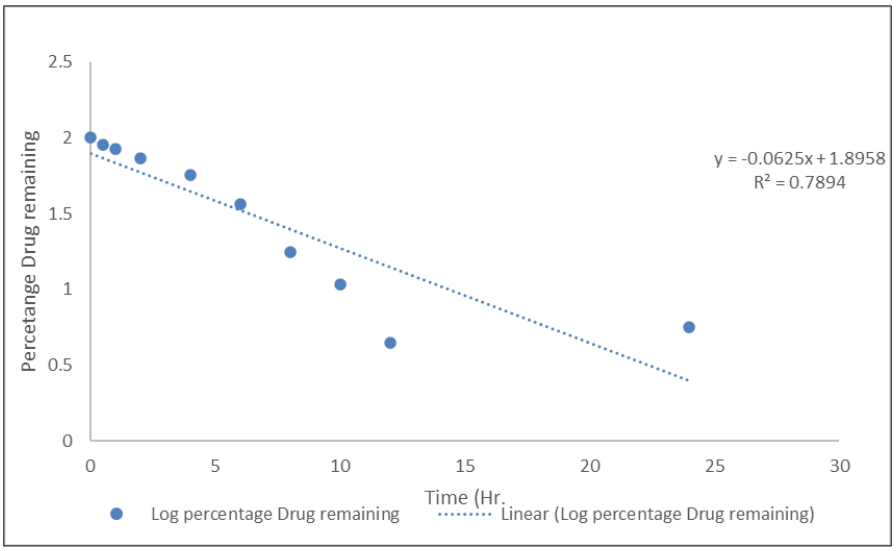

Figure 12 First order Drug Release of PG5 formulation

Higuchi Model

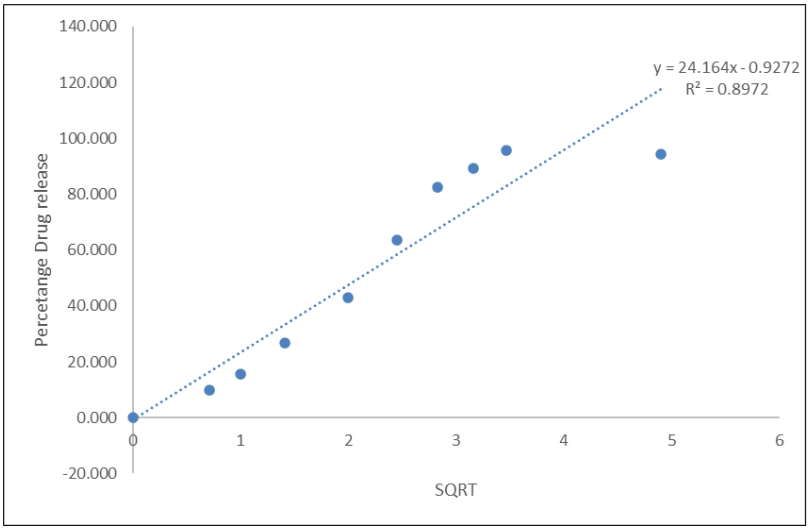

Figure 13 Higuchi model Drug Release of PG5 formulation

The data obtained for in vitro release were fitted into equation for the zero order, first order and higuchi. The calculated regression coefficients for zero order, first order and higuchi models. it was found that the in vitro drug release of formulation PG5 formulation was best explained by higuchi model as the plot showed the highest linearity, The value of R^2 found to be highest for the higuchi model.

4. Conclusion

Terbinafine HCl bulk powder form was found to have a melting point that ranged from 197.67±1.15°C -198.67±1.52°C. The lipophilic nature of the drug in bulk API form was described by the partition coefficient of Terbinafine HCl in the n-octanol-water system, which was determined to be 3.22± 0.013. The observed value was also found to be extremely near to the reference value 3.31. The standard calibration curve's absorbance information is provided in the A calibration curve was created using the absorbance of Terbinafine HCl at various concentrations. The straight line calibration equation was found to be y = 0.0311x+0.0089 with a correlation coefficient of 0.999 this equation was utilised to calculate the concentration of unknown samples. Terbinafine HCl displayed good solubility in dichloromethane followed by methanol. But it remains insoluble in water and buffer solution. Proliposomes gel of

Terbinafine hydrochloride were prepared by modified coacervation phase separation method by varying the concentrations of PC to cholesterol. Except for formulations PG1 and PG2, which were yellowish liquid and gel that was unstable, all created formulations were consistent, homogenous, and white creamy gel. The pH of every manufactured formulation was found to be in the range of 6.237±0.035 to 6.507±0.0255, which is near to the pH of the skin. The range of the percentage yield for the entire formulation preparation was determined to be between 95.52±0.11 to 98.82±0.20. Percentage Encapsulation The produced formulations were found to have an efficacy ranging from 77.203±0.322 to 98.424±0.6433. Maximum percentage drug encapsulation efficiency was found to be for formulation P5 98.424±0.643. Viscosity of all prepared formulation were observed to be within the range. On the basis of in vitro characterization parameters PG5 formulation was selected for further evaluation The particle size analysis of PG5 and revealed that the average particle size measured by laser light scattering method is around 314.25 nm as shown in table 12. The fact that Terbinafine HCl was released from the control means that the drug's aqueous suspension was roughly 17.923±0.105% within 24 hours, which amply demonstrates the drug's low levels of permeation and solubilization. Proliposome formulations showed a typical biphasic release pattern with an initial quick burst release lasting for two hours and then a sustained release lasting for twenty-four hours. The rapid drug release may have been facilitated by the strong concentration gradient present at the early time points as well as by the quicker release of unentrapped drug from the proliposome formulations. The percentage drug release was found to be 95.547±0.682 for formulation PG5. The calculated regression coefficients for zero order, first order and higuchi models. it was found that the in vitro drug release of formulation PG5 formulation was best explained by higuchi model as the plot showed the highest linearity, The value of R^2 found to be highest for the higuchi model.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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