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Original Article

DEVELOPMENT AND *IN VITRO* EVALUATION OF PHYTOSOME OF TERBINAFINE HYDROCHLORIDE FOR ORAL DRUG DELIVERY

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ABSTRACT

Objective: The purpose of this study was to develop and *in vitro* evaluation phytosome of terbinafine HCL to enhance the bioavailability for oral route.

Methods: The novel phytosome of terbinafine hydrochloride (TFH) was formulated with the molar ratio (1:2) of drug and phospholipid by using solvent evaporation technique. The resulting TFH-PC was determined by means of particle size analyzer (PSA), percentage yield, microscopy, drug content, transmission electron microscopy (TEM). Substantial contact of terbinafine HCL with phospholipids was completed through Fourier transforms infrared spectroscopy (FTIR).

Results: The all relevant results of TFH-PC were showed that the percentage entrapment efficiency of formulation was found in 76% to 90%. *In vitro* release data were exhibited approximately 65% to 79% of the drug released from the TFH-PC formulation by using dialysis membrane technique. Therefore, Formulation (F3) was accomplished that phytosome contain the superior physical characters and compatibility with drug and phospholipids than to make it easy to overcome the competence of drug to pass the lipid-rich bio-membrane.

Conclusion: In present work, terbinafine loaded phytosome was formulated for increasing the oral bioavailability of selected drug. Hence, TER-HCL phytosome were effectively improved the absorption of drug in form of phospholipids complex.

Keywords: Terbinafine HCL phytosome (TFH-PC), Solvent evaporation method, FTIR, TEM

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INTRODUCTION

From the ancient time, various herbal drugs have been familiar to the development of the well creations in biological activities of phyto-pharmacological science with their superior advantages for various herbal remedies [1]. The phyto-chemical and phyto-herbal drugs are found in the nature of polar solvents (water). When it gives orally then they exhibit the reduce profile of drug. Although they cannot be penetrate through inactive form due to larger molecular mass and reduced lipid polymer profile [2]. A number of phyto-drug and its effectiveness to go beyond the lipid-rich genetic membrane and that cause the resulting reduce oral availability of drugs [3]. Phytocomplexes are formulated with adding of soya phospholipids and elected of drug. Subsequently, by taking place of physically and chemically character of the drug and phoshpolipid with spectroscopic analysis after it taking into consideration as a novel entities [4]. Phytosomal formulation are included as capacity to improve the movement of drug inside the body. This system can be typically utilize in the curing of severe and long term hepatic infection due to toxic metabolite or transitive sources and nature of degenerative substance. Thus, it may be too helpful in the treatment of inflammation of various chemical and compositions of other drugs [5]. The phytosomes are prepared through phospholipids molecules and connected to the tiny cell like division. As a result, phytosome has become the pioneer advancement towards the standardized herbal formulation for enhancement of absorption of poor boilable drug [6]. The leading of this phytosomal formulations were produced in 1989 by Italians researcher congregation. However, this technology was based on the herbal-chemical investigation of clear polyphones compounds with their potent bonding potency of phospholipids and whole plant tissue [7]. By this knowledge, it can raise the superior assistance for the delivery of medicament at the tissue site for well incorporation of drug and lipids [8].

Terbinafine hydrochloride is a synthetic allylamine antifungal agent. It's for the most part of BCS group IInd. Currently terbinafine hydrochloride is applied as an antifungal agents beside the treatment of fungal infection of toes and fingernails that is occur mostly from fungus substance onychomycosis. It is exhibit the *in vitro* activity adjacent to the largest part of the strain of other microbes such as *candida albicans.* Terbinafine hydrochloride is a novel effective antifungal substance that is little soluble in water. For that reason, it is the slow release rate with water but it is highly soluble in methanol. Consequently, drug concentration with the body fluids which is lesser than the Minimum Inhibitory Concentrations (MIC). There are various pharmaceutical and chemical study of the drug required the valuable analytical practice or method for better controlling of *in vitro* and *in vivo* profile. After that, numerous techniques have been established to confirm its evaluation in organic and natural materials for the better action of drug in treatment of fungal infection at body site [9, 10].

MATERIALS AND METHODS

Materials

For the development of phytosome, terbinafine hydrochloride was obtained from Macleod pharmaceuticals Pvt. Ltd, baddi, soya phosphatidylcholine (leciva-S25) was received from web life science pvt. ltd, and methanol was used the HPLC grade.

Methodology

Estimation of UV spectra of terbinafine hydrochloride

The UV Spectra of pure drug gets examined by UV spectrophotometer shimadzu. Stock solution of terbinafine HCL was made through dilute of 10 mg pure drug in 50 ml of methanol. After that, make the dilutions in the series 5-40 µg/ml with the methanol. Then the solutions of TER-HCL were examined through U. V. range at 224 nm with methanol as blank. Further UV curve was plotted and all outcomes were recorded and determined as well as [11].

Solubility studies

In this Study, the 50 mg amount of drug of terbinafine was dissolved in 3 ml of aqueous solvent of water and other solvent like methanol, chloroform, and buffer containing potassium dihydrogen phosphate 6.8 pH, acidic 1.5 pH. Later than the solution is filled in culture tube and that tightly blocked. All samples were kept at water bath shaker

for 24 h at room temperature. Afterward, each one was centrifuged at 15000 rpm for 15 min and supernatant was formed. It's scanned through UV at 224 nm [12].

Partition coefficient of drug

For measuring of drug lipid nature of selected drug, partition coefficient analysis technique used as n-octanol and water system, it is done by shake flask process. The requisite amount of terbinafine HCL was dissolved in 10 ml of water/n-octanol system and it is kept for 24 h then separated the two layers of water and n-octanol in each tube for centrifugation and then absorbance was taken at λ max 224 after making suitable dilution [13].

Drug-excipient interaction study by FT-IR

FT-IR used as device to make the contact among drug and phospholipids. For this process, drug and excipient were taken in ratio of 1:2. The both sample were examined through FT-IR underneath the array of 400-4000 cm^{-1}. After that, obtained spectrum of actual drug and excipient were checked in the least incongruity and physical changes also [14].

Preparations of terbinafine hydrochloride phytosome

The phytosome of terbinafine HCL and soya lecithin were developed with the solvent evaporation method. The precise amount of drug and phospholipid was taken in 250 ml RBF (round bottom Flask) with each molar part of drug and phospholipid ratio (1:2). After that TER-PC were refluxed at temp range of 40 °C for 2 h with the methanol. At that time the apparent solution of drug and phospholipids were dried up at 60 °C by way of vacuum evaporator to get rid of unwounded particle from clear the solvents for getting better formation terbinafine-phospholipid complex. The formulated solution of TER-PC was placed in the desiccators for overnight. After overnight, than the solution become hydrate with phosphate buffer containing pH 6.8 with constant stirring to obtain the phytosome complex, after that phytosome was kept in amber color glass bottle and stored in the cool place at room temp [15].

Table 1: Composition of various phytosome formulations containing terbinafine hydrochloride and phospholipid

S. No.	Formulation code	Drug: soya lecithin (Molar ratio)	Methanol (ml)
1	F1	1:1	10
2	F2	1:1.5	10
3	F3	1:2	10
4	F4	1:2.5	10
5	F5	1:3	10
6	F6	1:4	10

*Value is expressed as for the experiment (mean±SD, n=3)

Evaluation of prepared phytosome

Microscopic view

For the microscopic evaluation of phytosome, primarily the drop of TER-PC was placed on top of the glass slide and it enclosed with a wrap slip in microscopy. Subsequently, Microscopic image of the complex was revealed at 40 angles with superior configuration of phytosome [16].

Particle size analysis

The particle size study of prepared formulation was done by Malvern zetasizer at 25 °C by applying laser light dispersion system. Although, this technique is primed with argon laser based procedure as well as it is widely use to assessment of particle size and distribution. The 100 mg of phytosome was grind and mixed in 10 ml of distill water prior to study [17].

Determination of drug content

Drug content of phytosome was performed as a result of suspending the exactly mass of 100 mg complex with 10 ml methanol. After making appropriate dilutions range for absorbance. It was estimated with UV Spectroscopy at 224 nm and drug content was established on the basis of definite absorbance [18].

Entrapment efficiency

The entrapment efficiency of phytosome was determined by using cooling centrifuged systems at 15000 rpm for 15 min at 4 °C. The entrapment ability of the drug with phospholipids complex was assessed through the UV spectroscopy. And the percentage entrapment efficiency was fig. out by specified formulas [19].

$$\%EE = \frac{Amount\ of\ drug\ added - Amount\ of\ drug\ unentraped}{Amount\ of\ drug\ added} X100$$

FT-IR spectroscopy

The establishment of the phytosome complex was validated through FT-IR spectroscopy by means of modulating the complex with the range of the particular components and their physical mixtures. FT-IR spectroscopy was considered as useful tool for managing the dependability of phytosomal drug whereas micro-dispersion in water or else behind incorporation of generally pure drug [20].

Transmission electron microscopy (TEM)

Morphological inspection of phytosome of terbinafine HCL in powder and several selected terbinafine HCL-PC complex formulations were examined with TEM. Phytosome formulation was diluted with a 0.01 % and shake for 10 min. A drop of the phospholipid complex was kept on top of a carbon-coated copper grid, avoiding a thin coating. The film of the PC was air-dried and then imaged [21].

***In vitro* release profiles**

The release studies of terbinafine HCL phytosome were evaluated by a dialysis technique using a dialysis membrane (molecular weight cutoff of 3500 Da). The release studies were performed in PB solution (pH 6.8). A total 3 ml of phytosome containing drug sample were transferred into a dialysis membrane and then immersed into 50 ml of PB at room temp with gentle shaking. Subsequently, According to the predesigned time intervals, 3 ml sample of the release medium was withdrawn and subsequently, 3 ml sample of the fresh medium was placed in to the release medium. The accumulative drug release of the phytosome was determined as a percentage of the drug released [22].

Drug release kinetic studies

In the current study, the *in vitro* release studies of the formulation was analyzed by this process, the data of the prepared formulation was placed in different equations and determine the kinetics model and percentage release of optimized formulation of phytosome. Thus, The kinetic models were used for determine the percent release of drug as well as by Zero-order equation, First-order, Higuchi's model and Korsmeyer-Peppas equation.

RESULTS AND DISCUSSION

Results of preformulation study of drug

Organoleptic properties of drug terbinafine hydrochloride found to be as per USP monograph. The organoleptic properties of terbinafine hydrochloride were found to the given below table 2.

Table 2: Organoleptic properties of terbinafine hydrochloride

S. No.	Properties	Inferences
1.	Colour	White
2.	Odour	Odourless
3.	Appearance	Fully Powder
4.	Taste	Bitter

*Value is expressed as for the experiment (mean±SD, n=3)

Melting point

Table 3: Melting point of terbinafine hydrochloride

Drug	Observed melting point	Reference melting point
Terbinafine hydrochloride	196-200 °C	195-198 °C

*Value is expressed as for the experiment (mean±SD, n=3), The melting point of terbinafine hydrochloride was found to be in range 196±200 °C which is of the pure drug. Hence, the drug sample was free from all type of impurities [23].

U V spectroscopy determination of absorption maxima in methanol

Absorption maxima of terbinafine HCL were found to be at 224 nm similar to literature as shown in fig. 1.

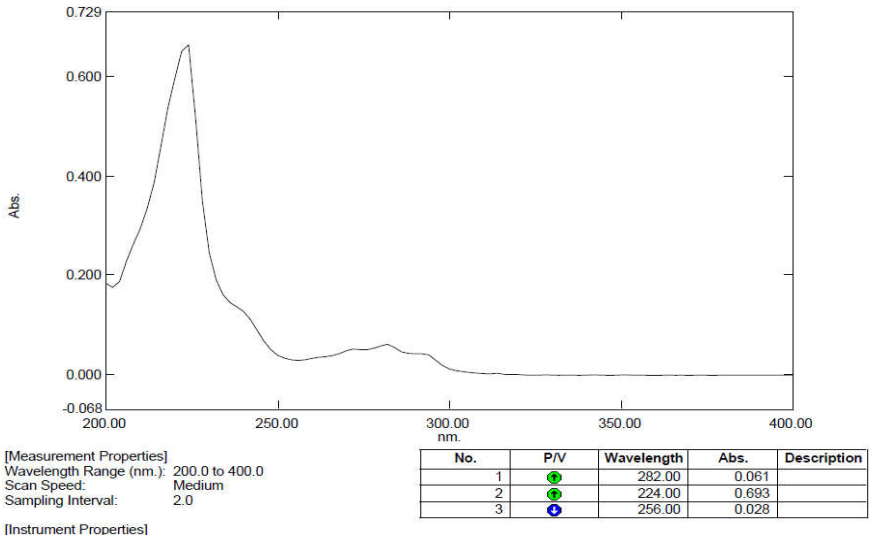

Fig. 1: UV spectrum of terbinafine HCL

Preparation of standard curve of terbinafine hydrochloride in methanol

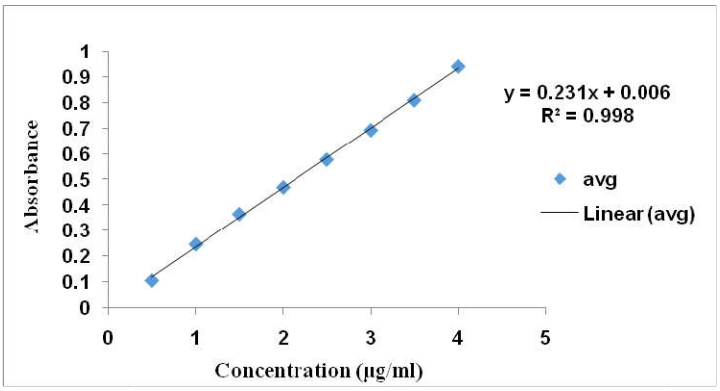

Fig. 2: Graph of standard calibration curve of terbinafine HCL in methanol, *Value is expressed as for the experiment (mean±SD, n=3)

The calibration curve for terbinafine hydrochloride was obtained by using the 5 to 4 µg/ml concentration of terbinafine hydrochloride in methanol. The absorbance was measured at 224 nm. The calibration curve of terbinafine hydrochloride as shows in graph indicated the regression equation Y= 0.231x+0.006 and R^2value 0.998, which shows good linearity as shown in fig. 2.

Solubility studies

The excess amount of terbinafine hydrochloride was dissolved separately in the below solvents and shake constantly for 24 h in the mechanical shaker at 25±2 °C. Solutions of drug, later than 24 h, sample were taken and absorbance of sample was recorded using UV spectrometer at range of 224 nm [24].

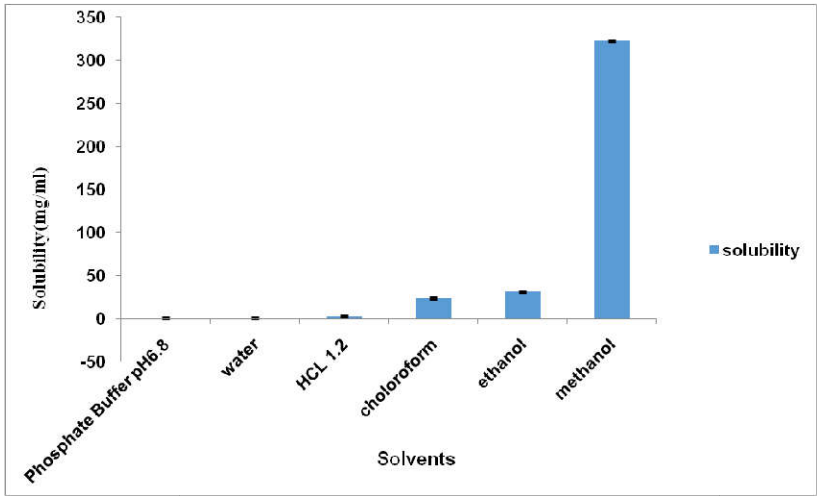

Fig. 3: Solubility study of drug in different solvents, (mean±SD, n=3)

Terbinafine hydrochloride was found to be highly soluble in methanol ranging 323.08±6.612 and sparingly soluble in ethanol, chloroform, buffer, slightly soluble in water. Solubility of terbinafine hydrochloride was determined with different solvents as shown in fig. 3.

Partition coefficient determination

ble 4: Partition coefficient determination of terbinafine hydrochloride

Partition coefficient of drug	Solvent system	Log P value (mean±SD)
Terbinafine hydrochloride	Water: n-octanol	1.3765±0.0008

*Value is expressed as for the experiment (mean±SD, n=3)

The partition coefficient of terbinafine HCL in n-octanol: water was found to be 1.3765±0.0008; this indicates that the drug is lipophilic in nature.

FT-IR of terbinafine hydrochloride and excipient

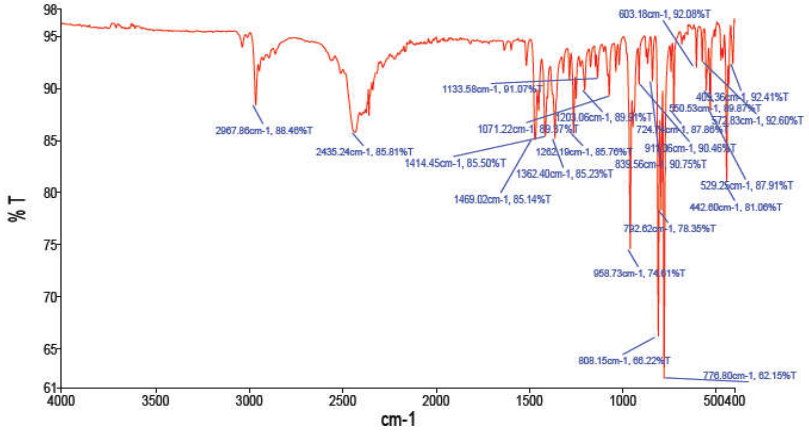

Fig. 4: FT-IR spectra of pure terbinafine hydrochloride, (mean±SD, n=3)

The FT-IR spectra of terbinafine HCL were shown in the fig. 4. These are all observed principal peaks 2967.86 cm^{-1}(OH stretching). This observation of terbinafine hydrochloride confirmed the purity and integrity below in IR spectra [25].

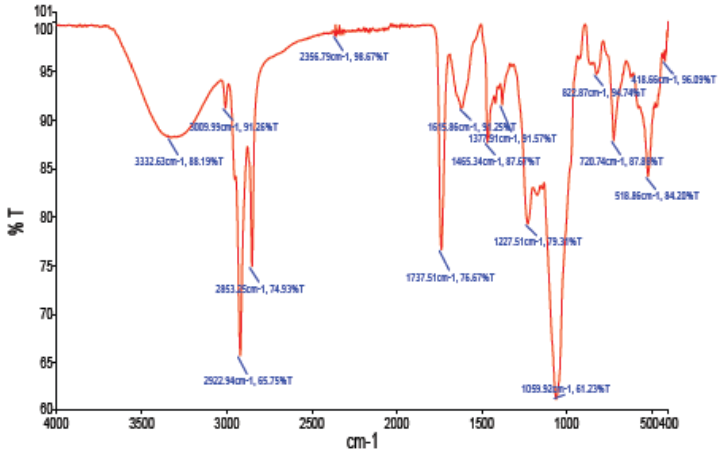

Fig. 5: FT-IR spectrum of soya lecithin, (mean±SD, n=3)

The FTIR spectra of soya lecithin were shown in the fig. 5. IR absorption peaks of soya lecithin at 3332.63 cm^{-1}(C–H stretching band of long fatty acid chain). This observation confirmed the purity and integrity of the lecithin.

FT-IR of pure drug and physical mixtures

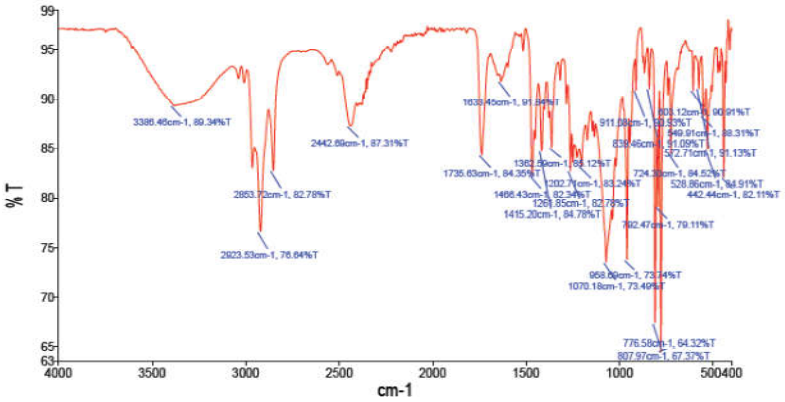

Fig. 6: FT-IR spectra of terbinafine hydrochloride and soya lecithin, (mean±SD, n=3)

All peaks of this mixture were manifested that resultant peaks of drug are existent in the beyond spectrum with excipient peaks. Therefore, no interaction was marked in this physical mixture fig. 6.

Characterization of phytosome formulation

Appearance of phytosome

Fig. 7: Terbinafine-phospholipid complex phytosome, (mean±SD, n=3)

From the above fig. 7**.** We observe the milky white appearance.

Photomicroscopic study

The photomicrograph of terbinafine phytosome formulation manifested that particles present in uniform shape without any aggregation.

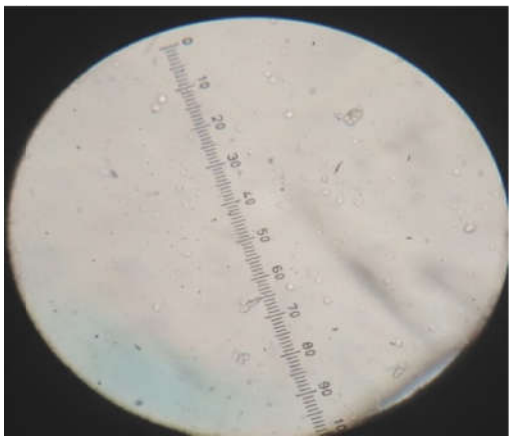

Fig. 8: Photomicrograph of terbinafine loaded phytosome, (mean±SD, n=3)

Particle size analysis

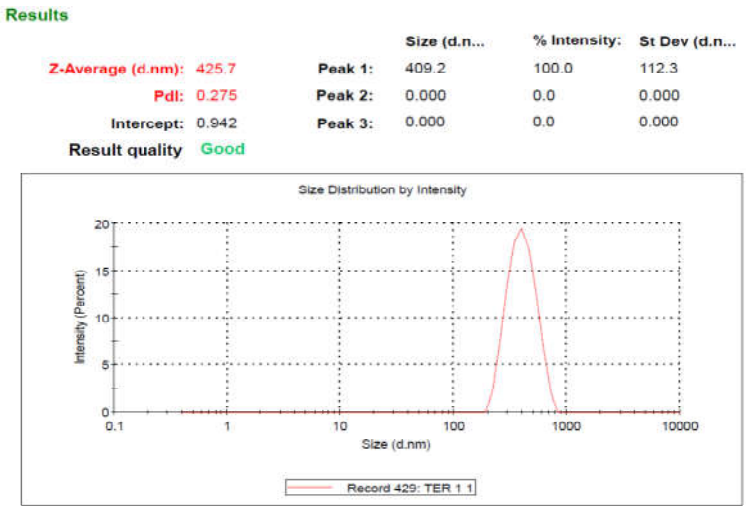

Fig. 9: Particle size distribution of phytosome formulation F3, (mean±SD, n=3)

The Particle size with polydispersity index of formulation (F3) was 425±112.3 nm with PDI 0.275±0.000 in fig. 9. Hence, the particle size of formulation was showed the high loading entrapment efficiency of the phytosome.

Determination of drug content

Table 5: % Drug content of phytosome formulation

S. No.	Formulation code	% Drug content
1	F1	100.378±0.826
2	F2	96.320±1.630
3	F3	101.461±2.710
4	F4	99.025±0.715
5	F5	91.179±2.042
6	F6	99.837±1.388

*Value is expressed as for the experiment (mean±SD, n=3)

The drug content of phytosome formulation was obtained in the range of 91.179±2.042 to 101.461±2.710 respectively. The percentage drug content of all formulations was found to be satisfactory. Hence, the process adopted for the phytosome formulations was found to be suitable. It is depicted above table 5.

Entrapment efficiency

Table 6: Different ratio of drug and phospholipid for phytosome formulation

F. Code	Drug: soya lecithin (Molar ration)	%EE
F1	1:1	76.3203±0.321
F2	1:1.5	83.1168±1.212
F3	1:2	88.0519±0.212
F4	1:2.5	90.6514±0.191
F5	1:3	80.735±0.090
F6	1:4	75.584±0.231

*Value is expressed as for the experiment (mean±SD, n=3)

The % drug entrapment efficiency of phytosome formulation was found to be 75.584±0.231 to 90.6514±0.191 which is represented in table 6. Hence, it is shown the better entrapment efficiency with drug and phytosome.

FT-IR spectroscopy of phytosome formulation

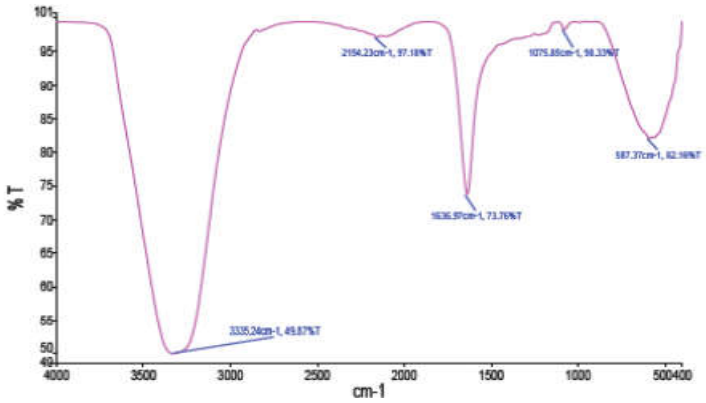

Fig. 10: FT-IR of final formulation F3, (mean±SD, n=3)

The FTIR spectra of final formulation (F3) represent that characteristic peak of terbinfine hydrochloride was not appeared in the phytosome spectra that which indicates that drug was completely encapsulate in the phytosome fig. 10.

Transmission electron microscopy (TEM)

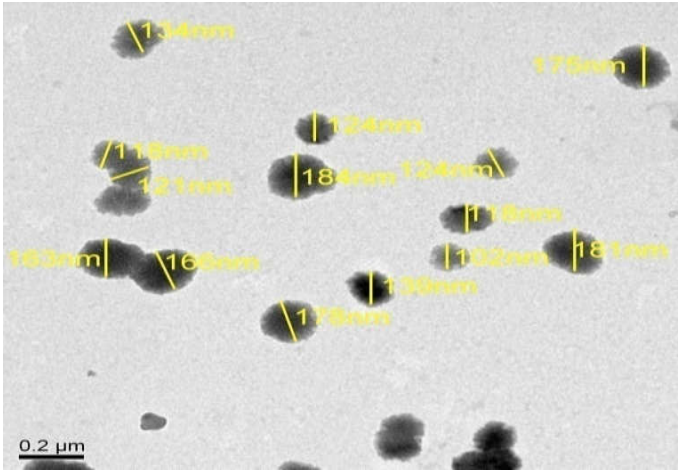

Fig. 11: TEM image of selected formulation F3 (mean±SD, n=3)

TEM image of TER-PC was established that the drug is completely encapsulated with the phytosome. The prepared formulation of terbinafine hydrochloride was exhibiting the effective results of physical entrapment of drug with Phospholipids molecules. Hence, it reveals the formation of phytosome in form of uniform micellar shape with selected drug fig. 11.

***In vitro* drug release profile**

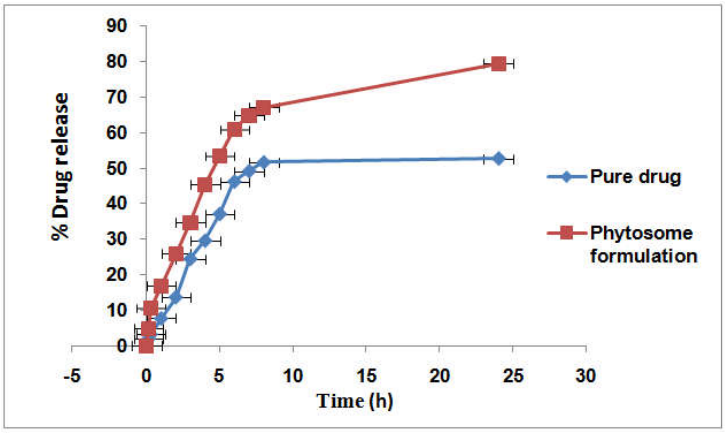

Fig. 12: Drug release profile of selected phytosome formulation F3 (mean±SD, n=3)

The percentage of drug release from the formulation (F3) was determined and cumulative % drug release compared with terbinafine hydrochloride phytosome formulations (F3). It was observed that the formulation (F3) has highest drug release as 79.437±0.572%. This is shown in fig. 12.

***In vitro* drug release kinetic**

In vitro drug release kinetic study data of formulation F3 was given below, (mean±SD, n=3).

Zero order

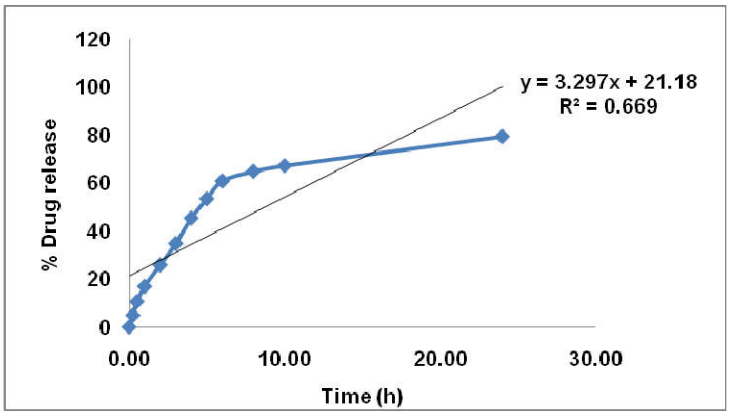

Fig. 13: Zero order graph of formulation F3

First order

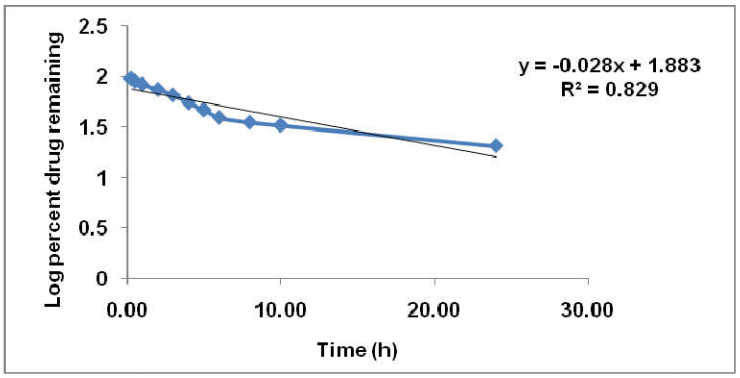

Fig. 14: First order graph of formulation F3

Higuchi model

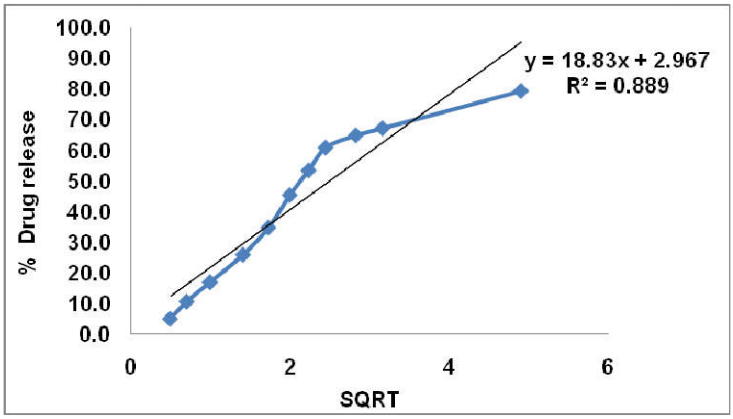

Fig. 15: Higuchi order graph of formulation F3

Korsmeyer peppas model

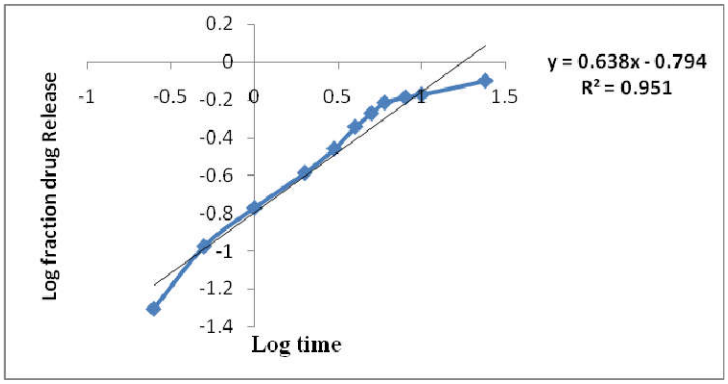

Fig. 16: Korsmeyer peppas order graph of formulation F3

Table 7: Kinetic equation parameter of F3 formulation

Formulation name	Zero order		First order		Higuchi		Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
TER-PC	0.669	3.297	0.829	-0.028	0.889	18.83	0.951	0.638

*Value is expressed as for the experiment (mean±SD, n=3)

Mathematical models of kinetic release are commonly used to predict the release process of the prepare formulation and compare the release profile. For the optimized formulation, the % drug release vs time (zero order), log percent drug remaining vs time (first order), log per cent drug release vs square root of time (Higuchi plot), and log of log % drug release vs. log time (Korsmeyer and Peppas Exponential Equation) were plotted. In each case, R^2 value was calculated from the graph and reported in table 7. Fig. 13, to fig. 16. Considering the determination coefficients, Korseymer peppas model was found (R^2=0.951) to fit the release data best. Hence, that the drug was released from terbinafine phytosome by a controlled mechanism.

CONCLUSION

The main goal of these oral formulations to provide the delivery of medicament or drug at the body site and tissue and to attain the desired plasma profile of drug intended for a definite period of time. However, shortened release of drug may cause the shorter residence instances and lower bioavailability of dosage form in the gastrointestinal tract. For avoiding such difficulties related to the drug, thus phytosome drug delivery system was effectively developed that exhibit the prohibited release of formulation and functionally overcome the lower bioavailability problems related to terbinafine hydrochloride. For optimized formulation, *in vitro* release was done in dihydrogen phosphate buffer (PB) containing pH 6.8 by means of dialysis membrane techniques. In addition, selected formulation (F3) vindicated the expected release approximately 80% designed for complete phase of time for 24 (h). Further, release kinetics of drug was followed the koresmeyer peppas modal for controlled formulation.

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Nil

AUTHORS CONTRIBUTIONS

Both authors are equally contributed.

CONFLICTS OF INTERESTS

Authors declare no conflicts of interest.

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