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Preparation of Terbinafine Hydrochloride Cubosomes: Preformulation Studies

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Abstract
Cubosomes are self-assembled liquid crystalline particles that can be used for carrier potential of hydrophilic, lipophilic and amphiphilic drugs as compared to free drug directly to the particular site of action, thus allow drug targeting and the sustained or controlled release of conventional medicines. Terbinafine hydrochloride (TB-HCl) is a synthetic allylamine antifungal agent. The present research was aimed at preformulation characterization of TB-HCl. The drug was characterized for its micromeritic properties, DSC, XRD, FTIR etc. The standard plot indicates high linear correlation between concentration of drug and absorbance. This data further provide a basis for the development of topical cubosomal formulation.

Keywords
Differential Scanning Calorimetry, Micromeritics, Preformulation, Terbinafine Hydrochloride, X-Ray Diffractometry.

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INTRODUCTION
The objective of preformulation studies is to develop a portfolio of information about the drug substance to serve as a set of parameters against which detailed formulation design can be carried out. Preformulation investigations are designed to identify those physicochemical properties of drug substances and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product [1, 2]. Topical drug delivery is the term used for localized treatment of dermatological condition where the medicine has effects only in specific area, not throughout the body. Cubosomes are discrete, sub-micron, nano-structured particles of bicontinuous cubic liquid crystalline phase. Cubosomes possess the same microstructure as the parent cubic phase but have larger specific surface area and their dispersions have much lower viscosity in comparison to the bulk cubic phase. Cubosomes are nanoparticles, more accurately nanostructure particles of a liquid crystalline phase with cubic crystallographic symmetry formed by the self-assembly of amphiphilic or surfactant like molecules. However, the cubic phases possess a very high solid like viscosity, which is a unique property because of their intriguing bicontinuous structures which enclose two distinct regions of water separated by a controlled

bilayer of surfactant. As a result, the cubic phases can be fractured and dispersed to form particulate dispersions that are colloidally and/or thermodynamically stable for longer time. Cubosomes have a great potential in drug nanoformulations [3-6].

Cubosomes can be manufactured by two distinct methods [7]:

Top down Technique: It is the most widely used procedure in which bulk cubic phase is first produced and by application of high energy such as high pressure homogenization it is processed into cubosomes nanoparticles.

Bottom up Technique: It is more recently developed technique of cubosome formation, allowing cubosomes to form and crystallize from precursors on the molecular length scale.

Advantages of cubosomes [7]:

- High drug payloads due to high internal surface area and cubic crystalline structures.
- Relatively simple method of preparation
- Biodegradability of lipids
- Capability of encapsulating hydrophilic, hydrophobic and amphiphilic substances.
- Targeted release and controlled release of bioactive agents

Terbinafine is an allylamine which has a broad spectrum of antifungal activity in fungal infections of the hair and skin such as Pityriasis versicolor. It shows oral bioavailability of about 40% because of first pass hepatic metabolism. So Terbinafine is increasingly administered by topical route may increase the bioavailability. Terbinafine hydrochloride is highly lipophilic in nature and tends to accumulate in skin, nails, and fatty tissues. Like other allylamines, terbinafine inhibits ergosterol synthesis by inhibiting the fungal squalene monooxygenase (squalene 2, 3-epoxidase), an enzyme that is part of the fungal cell wall synthesis pathway. So terbinafine prevents conversion of squalene to lanosterol, ergosterol cannot be synthesized. This is thought to change cell membrane permeability, causing fungal cell lysis. It is an anti-fungal which diffuses rapidly into the skin from topical applications and effectively treats athlete's foot i.e. tinea pedis. Terbinafine hydrochloride interferes with the integrity and growth of the fungal cell wall by weakening the cell wall and eventually leading to fungal cell death. It is effective at low levels and diffuses rapidly into the skin to effectively cure tinea. [8, 9, 10].

MATERIALS AND METHODS

Materials:

Terbinafine Hydrochloride was purchased from Yarrow chemicals, Mumbai, India and Ethanol analytical grade was purchased from Himedia Mumbai, India.

Drug Profile [11]

Chemical structure and 3D structure of Terbinafine hydrochloride is shown in figure: 1 [https://pubchem.ncbi.nlm.nih.gov]

Physicochemical properties of Drug is given in table: 1

Pre-formulation studies [12-16]

Micromeritic properties

a) Bulk Density:

Bulk Density was determined by pouring the powder into graduated cylinder. The bulk volume (Vb) and weight of powder (M) was recorded and the bulk density was calculated by following formula.

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Bulk volume}}$$

b) Tapped Density:

The cylinder containing powder was tapped for fixed time. The minimum volume (Vt) occupied in the cylinder after tapping and weight (M) of blend was measured. Tapped density was calculated by using formula

$$\text{Tapped density} = \frac{\text{Mass}}{\text{Tapped volume}}$$

c) Compressibility Index:

An indirect method of measuring powder flow from densities was developed by Carr.

Carr's index of the powder was calculated according to equation:

$$\text{Carr's index} = \frac{\text{tapped density-bulk density}}{\text{tapped density}} \times 100$$

d) Hausner's Ratio:

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

e) Angle of Repose:

Angle of repose was determined by using fixed funnel method. The powder was allowed to flow freely through funnel on to the surface. The diameter of powder heap was measured and angle of repose was calculated by following formula.

$$\theta = \tan^{-1} h/r$$

Where h-height of pile of powder
r= radius of the powder pile

Melting point:

Melting point of TB-HCl was determined with the help of capillary melting point apparatus.

UV visible spectroscopy [17]

a) Determination of λ max

Accurately weighed amount (10mg) of TB-HCl was transferred in to 10 ml volumetric flask and volume was made up to 10 ml with solvent. From this solution, 1 ml was withdrawn and added to the 10 ml volumetric flask and diluted up to 10 ml with solvent. Finally, sample was scanned in the range of 200-400 nm. The wavelength of the maximum absorption was noted, and UV spectrum was recorded.

b) Calibration Curve of Terbinafine hydrochloride:

Preparation of calibration curve in ethanol: Accurately weighed amount (10mg) of TB-HCl was added to 10 ml volumetric flask and the volume was made up to 10 ml with ethanol (1000 µg/ml). From this solution 1 ml was withdrawn and added into 10 ml volumetric flask and volume was made to 10 ml with ethanol (100µg/ml). This solution was used as stock solution. Standard solutions were prepared in the concentration range of 2-10µg/ml by suitable dilutions of the stock solution in ethanol and absorbance was taken at 223 nm by UV Spectroscopy (Shimadzu).

Preparation of calibration curve in pH 6.4 buffer: Accurately weighed amount (10mg) of TB-Hcl was added to a volumetric flask and the volume was made up to 10 ml with phosphate buffer (pH 6.4). From this solution 1 ml was withdrawn and added into 10 ml volumetric flask and volume was made to 10 ml with pH 6.4 buffer (100µg/ml). This solution was used as stock solution. Standard solutions were prepared in the concentration range of 2-10µg/ml by suitable dilutions of the stock solution in pH 6.4 buffer and absorbance was taken at 223 nm by UV Spectroscopy.

FTIR Spectroscopy [18]

FTIR spectrum of drug and excipients sample was recorded for its identification. The spectrum of sample was recorded over the wave number 4000 to 400 cm^{-1} in an FTIR spectrophotometer. The identified peaks were compared with the principle peaks of reported IR spectrum and the sample was identified.

X-Ray Diffractometry (XRD)

The physical nature of the drug was identified by using X-Ray Diffractometry studies. The pure drug sample was analyzed by using Brooker D2 Phaser powder X-Ray Diffractometer.

Differential Scanning Calorimetry (DSC) [19]

Thermogram of pure TB-Hcl were taken for DSC study. An empty aluminum pan was used as a reference. DSC measurements were performed at a heating rate of 5^oC/min from 50 to 400^oC using aluminium sealed pan. The sample size was 4.5 mg of pure drug for measurements. During the measurement, the sample cell was purged with nitrogen gas at 40 ml/min.

RESULTS AND DISCUSSIONS

Micromeritic properties

The micromeritic properties of the drug powder are given in Table: 2

Melting Point

The melting point of the pure drug Terbinafine hydrochloride was found in the range of 195°C-198°C. The melting point was found to be similar as given in literature. While comparing the melting point of drug with the standard, no significant difference were observed this indicated the purity of the drug.

UV Spectroscopy Analysis

a) Determination of λ max of TB-Hcl by UV spectroscopic method

The maximum absorption value of pure drug, Terbinafine hydrochloride was found to be 223nm wavelength. The observed λ max value of drug was found to be similar as given in literature. Hence the drug was considered to be pure. The UV spectrum of Terbinafine hydrochloride was showed in figure 2.

b) Calibration Curve of Terbinafine hydrochloride in ethanol and in pH 6.4 buffer

Standard graph of TB-HCl in ethanol and phosphate buffer (pH6.4) was plotted. Linearity was observed and good correlation was obtained with R^2 value of 0.9978 & 0.9975 for ethanol & phosphate buffer respectively (table 3 and figure 3, 4)

FTIR Spectroscopy

The FTIR spectrum of the drug, Terbinafine hydrochloride, was obtained using FTIR spectrophotometer. The spectrum is shown in figure 5.

X-Ray Diffractometry (XRD)

The X-Ray diffraction patterns of pure Terbinafine hydrochloride were illustrated in Figure 6. For the crystalline nature of drug powder the sharp intensity peaks were observed around20°, 22° and 25°. The characteristic peaks of TB-HCl appeared at a diffraction angle of $24.16^0$and maximum intensity of 1543 and several sharp diffraction peaks suggesting that the drug is present in crystalline form.

Differential Scanning Calorimetry (DSC)

DSC curves obtained for pure TB-HCl (4.5mg) is shown in figure 7. Pure Terbinafine hydrochloride showed a sharp melting endotherm at (212.59°C).

Table 1: Physicochemical properties of Terbinafine hydrochloride

Chemical Name	(2E)-N,6,6-trimethyl-N-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine hydrochloride
Chemical Group	Allylamine class
CAS Registry Number	78628-80-5
Molecular Weight	327.9
Molecular Formula	$C_{21}H_{25}N.HCl$
Melting Point	195°C-198°C
Description	White Crystalline powder, odourless
pKa	8.94
Solubility	Very slightly or slightly soluble in water, freely soluble in anhydrous ethanol and in methanol, slightly soluble in acetone

Table 2: Micromeritic properties of the drug

Sr no.	Parameters	Observations
1.	Bulk Density	0.3 gm/ml.
2.	Tapped Density	0.508 gm/ml
3.	Carr's index	41%
4.	Hausner's ratio	1.695
5.	Angle Of Repose	35.1°

Table 3: Calibration curve of Terbinafine hydrochloride in ethanol

Concentration (µg/ml)	Absorbance	
	In ethanol	In pH 6.4
2	0.1782	0.126
4	0.3698	0.254
6	0.5198	0.398
8	0.7151	0.515
10	0.8561	0.678

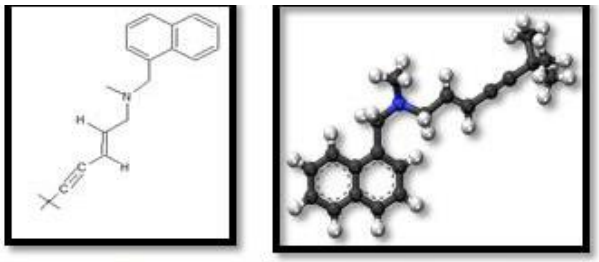

Figure1: Chemical structure and 3D structure of Terbinafine hydrochloride

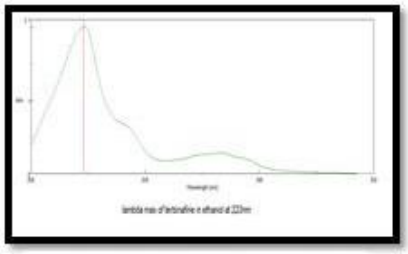

Figure2 : UV spectrum of Terbinafine hydrochloride in ethanol

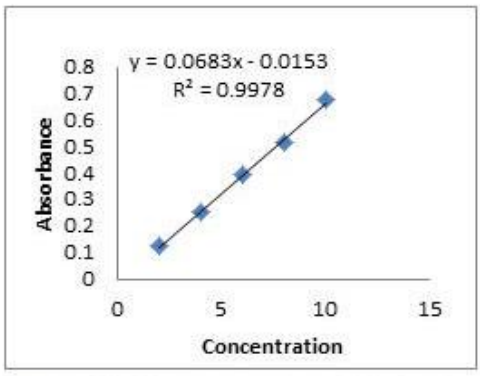

Figure3: Calibration curve of TB-HCl in ethanol

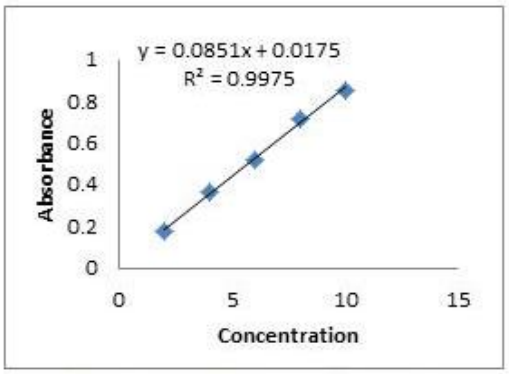

Figure 4: Calibration curve of TB-HCl in pH 6.4 buffer

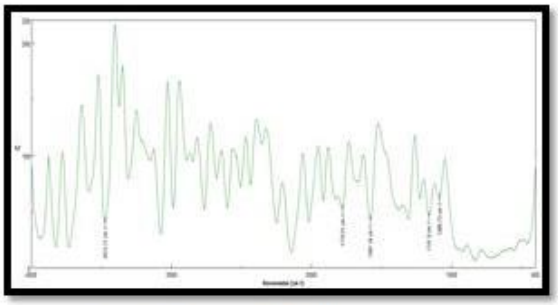

Figure 5: IR spectra of TB-HCl

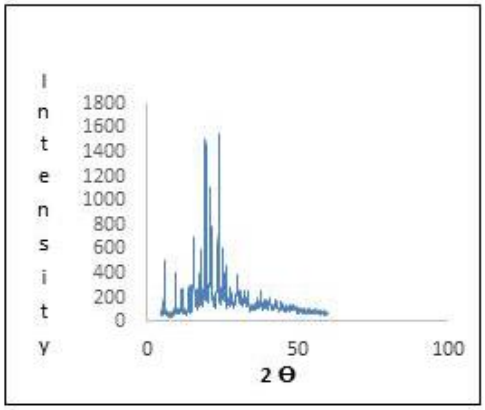

Figure 6: XRD of pure TB-HCl

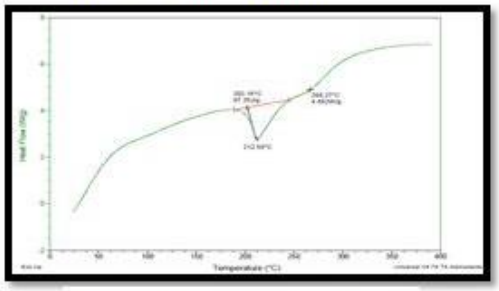

Figure 7: DSC thermogram of TB-HCl

CONCLUSION

Preformulation studies have played a significant role in anticipating formulation problems and identifying procedures to rectify and develop a safe, effective and stable formulation. This research article provides details of preformulation studies of Terbinafine Hydrochloride which would be helpful to use as a drug candidate.

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