Development, Characterization and Solubility Study of Solid Dispersion of Terbinafine Hydrochloride

Narendra Kumar, Jain AK, Akhilesh, Chhater Singh, Kshitij Agarwal, Nema RK

Institute of Pharmacy, Bundelkhand University, Jhansi (U.P.)
S.D. College of Pharmacy and Vocational Studies, Bhopa Road, Muzaffarnagar

ABSTRACT: The formulation of poorly water-soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programs have problem in water-solubility. Terbinafine hydrochloride is one of them. Terbinafine hydrochloride (slightly water soluble drug) when prepared as solid dispersion showed improved solubility and dissolution. So the main purpose of this investigation was to increase the solubility and dissolution rate of terbinafine hydrochloride by the preparation of its solid dispersion with polyethylene glycol 6000 (PEG 6000) using fusion methods. The study shows that the solubility of terbinafine hydrochloride was increases in the presence of polyethylene glycol 6000 upto 10 % of carrier (36.89µg/mL). The dissolution rate increases with increased amount of PEG 6000 in all the solid dispersion formulation. Fourier Transform Infrared spectra revealed no chemical incompatibility between drug and polyethylene glycol 6000. Powder X-Ray Diffraction (PXRD) explained the reduction in crystalinity of terbinafine hydrochloride. The study clearly shows that on addition of PEG-6000 to terbinafine hydrochloride improves its dissolution rate.

KEY WORDS: Terbinafine hydrochloride, Solid dispersion, polyethylene glycol 6000, fusion methods.

Introduction

The oral route still represents the preferred way of administration owing to its several advantages and high patient compliance compared to other routes. However, poorly water-soluble drugs, when administered orally, have been shown to be slowly and unpredictably absorbed since their bioavailability is largely dependent on the dissolution process in gastrointestinal tract (Valleri M et al., 2004). When a drug is administered orally in solid dosage form such as tablet, capsules, or suspension it must be released from the dosage form and dissolved in the gastrointestinal fluids before it can be absorbed. The bioavailability of many poorly water-soluble drugs is limited by their dissolution rates. Terbinafine hydrochloride (Sweetman CS et al., 2002; synthetic allylamine derivative has a broad spectrum of antifungal activity when used orally or topically) is a slightly water-soluble drug. There are many techniques that have commonly been used to improve the solubility and dissolution that may lead to increase the bioavailability of poorly water-soluble drugs; which includes the surfactants, micronization, and the formation of solid dispersion. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion) (Kushida I et al., 2002), solvent or the melting-solvent method. Chiou and Riegelman out lined 6 types of drug carrier interactions (Chiou WL et al., 1971) in solid state dispersions: simple eutectic mixtures, solid solution (Goldberg AH et al., 1966), glass solutions of suspension (Stupak EI et al., 1978), compound or complex formations between the drug and the carrier (Geneidi AS et al., 1978), amorphous precipitations of a drug in a crystalline carrier (Yamashia K et al., 2003). Polyethylene glycol 6000 is most commonly used as a carrier in the solid dispersion system. So the aim of the present work was to increase the solubility of terbinafine hydrochloride.

Material and Methods

Terbinafine hydrochloride sample was obtained from FDC Limited; Verna Industrial Estate Verna Goa. Polyethylene glycol 6000 was purchase from the market; all the chemicals were A.R. Grade.

Preparation of Solid Dispersions and Physical Mixture

Solid dispersions were prepared by fusion method (Fernandez M et al., 1992). The carrier and adding amounts of terbinafine hydrochloride corresponding to ratio 1:1, 2:1, 3: 1and 5:1 was accurately weighed. The carrier was melted at 60°C and the drug was incorporated with constant stirring. The mixture was cooled on ice bath after drying; it was placed in a dessicator under vacuum for 24 hrs. Then, solid dispersion formulation was pulverized using a porcelain mortar and pestle. The pulverized powder was classified using the sieves (size # 60and # 120 mesh) and the particle size fraction of 100-250 µm was used for the study (Table 1). Physical mixtures were prepared by mixing the appropriate amount of terbinafine hydrochloride and polyethylene glycol 6000 in pestle and mortar and passed through sieve # 60.
**Table 1** Coating composition, Preparation method, and drug content of Solid Dispersion.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Carrier Name</th>
<th>Product Name</th>
<th>Drug (mg)</th>
<th>Carrier (mg)</th>
<th>Ratio of drug to Carrier</th>
<th>Drug Content (%)</th>
<th>Preparation &amp; method</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Polyethylene Glycol 6000</td>
<td>A11</td>
<td>1500</td>
<td>1500</td>
<td>1:1</td>
<td>95.3±1.05</td>
<td>Fusion</td>
</tr>
<tr>
<td>II</td>
<td>Polyethylene Glycol 6000</td>
<td>A12</td>
<td>1000</td>
<td>2000</td>
<td>1:2</td>
<td>92±2.00</td>
<td>Fusion</td>
</tr>
<tr>
<td>III</td>
<td>Polyethylene Glycol 6000</td>
<td>A13</td>
<td>750</td>
<td>2250</td>
<td>1:3</td>
<td>85±0.56</td>
<td>Fusion</td>
</tr>
<tr>
<td>IV</td>
<td>Polyethylene Glycol 6000</td>
<td>A15</td>
<td>500</td>
<td>2500</td>
<td>1:5</td>
<td>80±1.56</td>
<td>Fusion</td>
</tr>
<tr>
<td>V</td>
<td>Polyethylene Glycol 6000</td>
<td>PMA13</td>
<td>500</td>
<td>1500</td>
<td>1:3</td>
<td>-</td>
<td>Physical Mixture</td>
</tr>
</tbody>
</table>

**Fig.1** Solubility Diagram of Terbinafine HCl in water at 27°C in presence of carrier (Polyethylene Glycol 6000).

**Estimation of Terbinafine Hydrochloride**

Terbinafine hydrochloride (El-Sahraty HNY et al., 2002) was estimated at 283.2 nm using UV spectrophotometer (Shimadzu-1700). Standard curve for the estimation was prepared in 20% v/v methanolic citrate buffer pH 3.0 in the concentration of 5-40 µg/ml. In this concentration range good linearity was observed with correlation coefficient (R2)=0.9999. The graph obeyed the Beer-Lambert’s law in the selected concentration range.

**Phase Solubility Study**

Solubility studies were performed according to the Higuchi (Higuchi T et al., 1965) and Connors method.

An excess amount of terbinafine hydrochloride was placed in to 50-ml flasks containing different concentrations of polyethylene glycol 6000 in 25-ml distilled water. All flasks were closed with stopper and covered with cellophane membrane to avoid solvent lose. The flasks were placed in the incubator shaker for 72 hours, after 72 hours the content of each flasks were then filtered through whatman filter paper; the diluted were filtrates was and assayed spectrophotometrically (Shimadzu 1700 UV spectrophotometer) for terbinafine hydrochloride content at 283.2 nm. All solubility measurements were performed in triplicate (Fig.1).

**Drug Loading**

The dispersion system equivalent to 25.0 mg of terbinafine hydrochloride was added in 25 ml volumetric flask and dissolved in citrate buffer (pH=3.0). The volume was made up to the mark with citrate buffer (pH=3.0) and filtered. One ml of filtrate was further diluted to 10.0 ml with citrate buffer (pH=3.0) and absorbance was recorded at 283.2 nm. The amount of drug in each dispersion system was determined spectrophotometrically (**Table 1**).
In-Vitro Drug Release

In-vitro release rate of terbinafine hydrochloride solid dispersion of different samples were determined using single station USP dissolution test apparatus. The dissolution medium consisted of citrate buffer of pH 3.0 was used. Samples of drug, solid dispersion equivalent with 100 mg of drug was spread onto the surface of 900 ml of preheated dissolution medium at 37°C. Aliquots of 2ml were withdrawn at regular intervals of time i.e. 5,10,15,20, up to 120 min and the same is replaced with fresh dissolution medium each time. The samples obtained were filtered through whatman filter paper no. 1. Then the absorbance was measured at 283.2nm.

Fourier Transform Infrared Spectroscopy

FT-IR spectra (500-4000cm⁻¹) were obtained on a Nicolet Avatar 37- DTGS FT-IR spectrophotometer (Nicolet) with a resolution of 4 cm⁻¹. KBr pellets were prepared by gently mixing of 1 mg sample with 200 mg potassium bromide.

Differential Scanning Calorimetry

Differential scanning calorimetric measurements were carried out by using a thermal analysis instrument (USA-2910-MDS DSC) equipped with a liquid nitrogen sub ambient accessory. 2-6 mg Samples were accurately weighed in aluminum pans, thematically sealed and subsequently scanned at 1°C/min under nitrogen gas purge.

X-ray Diffraction

Diffraction patterns were obtained at room temperature on a Philips PW 1710 Diffractometer (Philips, Holland).

Solubility Studies

The Solubility of terbinafine hydrochloride in distilled water at 27°C was found to be 5.32µg/mL. The influence of polyethylene glycol 6000 upon the solubility of terbinafine hydrochloride is presented in Fig-1. The figure shows that the solubility of Terbinafine Hydrochloride was increased in the presence of polyethylene glycol 6000 upto 10% of carrier (36.89µg/mL), which may be due to the wettability action of polyethylene glycol 6000.

In-Vitro Dissolution Studies

Terbinafine hydrochloride release from the solid dispersion alone was studied in citrate buffer (pH 3.0) up to 2 hrs. The average percentage release of the pure terbinafine hydrochloride was found to be 64% in 2 hrs. In the solid dispersion formulation using PEG 6000 as carrier the dissolution rate increases with increased amount of PEG 6000. The best results among solid dispersions with PEG6000 were obtained from the formulation A13 (Fig 2). The increased dissolution rate may be due to the higher solubility of PEG in dissolution medium and better wettability of terbinafine hydrochloride in the formulation. On further increasing the amount of PEG 6000 (A15) the dissolution rate slightly decreased that may be due to the higher amounts of carrier itself takes time to dissolve (Fig. 2).

![Fig. 2 Release profile of Terbinafine HCl from different Terbinafine HCl-Polyethylene glycol 6000 solid dispersions in citrate buffer (pH 3) at 37°C.](image-url)
Fourier Transform Infrared Spectroscopy

FT-IR studies were performed to detect the possible interactions between the terbinafine hydrochloride and PEG 6000 in the solid dispersion leading to crystalline state with PEG 6000. The characteristic peaks of terbinafine hydrochloride, PEG 6000, physical mixtures and their formulations are given in Table 2. Comparing the spectra of physical mixtures with those of solid dispersions prepared by using different methods revealed that there were no differences in the positions of the absorption bands, hence providing evidence for the absence of any chemical incompatibility between PEG 6000 with terbinafine hydrochloride under investigation. The absence of any significant change in the IR spectral pattern of drug-polymer physical mixture indicated the absence of any interaction between the drug and the polymer.

Powder X-ray Diffraction Study

The diffraction spectra of terbinafine HCl and PEG 6000 show numerous distinct peaks indicating that both are present in a highly crystalline state (Fig. 3A, 3B). The PXRD pattern of solid dispersion of sample A13 (Fig. 3C) exhibits all the characteristic diffraction peaks of PEG 6000 and crystalline terbinafine hydrochloride, but of lower intensity. This study reveals that some terbinafine hydrochloride still exists in the crystalline state in the solid dispersions and at this concentration (25%), the proportion of the drug may equal or exceed its solid solubility. Comparison of the ratios of the intensities of the lines of solid dispersion formulations with the corresponding to physical mixtures reveals that the crystallinity of terbinafine hydrochloride is reduced in PEG 6000 and terbinafine hydrochloride formulations (Fig. 3). The reduction in crystallinity appears in all the solid dispersions independently where the solid dispersion preparation method used. Thus it was proved that by formulating solid dispersion of terbinafine hydrochloride with PEG 6000 decreases the crystallinity of drug, hence increases the aqueous solubility.

Conclusion

The study clearly shows that on addition of PEG-6000 to terbinafine hydrochloride improves its dissolution rate. Mechanisms involved are solubilization and improved wetting of the drug in the polyethylene glycol rich microenvironment formed at the surface of drug crystals after dissolution rate compared with physical mixtures. No solid solution formation and no hydrogen bonding interaction between PEG6000 with terbinafine hydrochloride could be detected. The aqueous solubility of drug was increases due to the crystallinity of drug reduces in solid dispersion formulation with polymers i.e. PEG6000.

Table 2 FT-IR Peaks of Pure Terbinafine HCl, Polyethylene glycol 6000, Solid dispersion of Terbinafine HCl and Polyethylene glycol 6000.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Description</th>
<th>Characteristic peaks (Cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Terbinafine HCl</td>
<td>3040.94, 2968.26, 2863.67, 2444.93, 2223.76, 1262.32, 958.83 and 777.13</td>
</tr>
<tr>
<td>2</td>
<td>Polyethylene glycol 6000</td>
<td>1413.18, 1280.97, 1060.13 and 3445.20 (broad band)</td>
</tr>
<tr>
<td>3</td>
<td>Terbinafine HCl and Polyethylene glycol 6000</td>
<td>3041.94, 2968.26, 2863.67, 2445.20, 2223.26, 1262.32, 958.83, 777.13 1413.18, 1280.97, 1060.13 and 3446.20</td>
</tr>
</tbody>
</table>
Fig. 3  PXRD of A. Pure Terbinafine HCl, B. Polyethylene glycol 6000, C. Solid dispersion of Terbinafine HCl & Polyethylene glycol 6000 and D. Physical mixture of Terbinafine HCl & Polyethylene glycol 6000.

References


