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Review Paper

Analytical methods for determination of terbinafine hydrochloride in pharmaceuticals and biological materials ☆

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ABSTRACT

Terbinafine is a new powerful antifungal agent indicated for both oral and topical treatment of mycosessince. It is highly effective in the treatment of determatomycoses. The chemical and pharmaceutical analysis of the drug requires effective analytical methods for quality control and pharmacodynamic and pharmacokinetic studies. Ever since it was introduced as an effective antifungal agent, many methods have been developed and validated for its assay in pharmaceuticals and biological materials. This article reviews the various methods reported during the last 25 years.

Contents

1. Introduction

Terbinafine hydrochloride (TFH) (Fig. 1) is an allylamine derivative. Chemically, it is [(2E)-6,6-dimethylhept-2-en-4-yn-1-yl](methyl)(naphthalen-1-ylmethyl)amine hydrochloride. Its molecular weight

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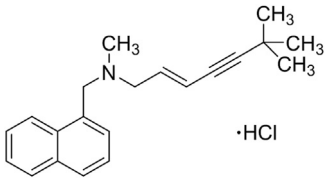

Fig. 1. Terbinafine hydrochloride.

is 327.89 corresponding to the molecular formula of $C_{21}H_{26}NCl$. It melts at 195–198 °C (changes in crystal structure begin at 150 °C). TFH is freely soluble in methanol and methylene chloride; soluble in ethanol; and slightly soluble in water [1]. Like all other allylamines, it inhibits ergosterol synthesis by inhibiting squalence epoxidase an enzyme that plays a role in fungal cell wall synthesis pathway [2]. In laymans' terms, it inhibits the growth of fungal and bacterial cell wall, leading to the death of the cell, as the contents of the cell are unprotected. Therefore, it is applied to the skin in the occurrence of dermatophytoses, pityriasis versicolor and cutaneous candidiasis [3], superficial fungal infections like seborrheic dermatitis, tineacapatis, and onychomycosis especially for its short-duration therapy [4]. Generally, TFH is the main chemical form of terbinafine for pharmaceutical purposes. It comes as a tablet for oral administration, and is usually taken once a day for 6 weeks for fingernail fungus treatment and once a day for 12 weeks for toenail fungus treatment. The cream and powder formulations of the drug are used for superficial skin infections such as jock itch (tineacrusis), athlete's foot (tineapedis) and ringworm. Terbinafine is highly lipophilic in nature and tends to accumulate in skin, nails and fatty tissues. Excessive terbinafine may cause some side effects such as allergic reactions (difficulty in breathing, throat closing, and swelling of hips, tongue, face and liver), rash, and changes in vision and blood problems [5].

Because of its therapeutical importance, quantitative determination of terbinafine in pharmaceuticals and human physiological fluids is of considerable significance in both quality control of preparations and chemical diagnosis. In the last approximately 25 years, several methods have been reported for the determination of terbinafine in pharmaceuticals and biological materials including body fluids. The current review surveys the methods developed to determine terbinafine in drug, drug products, body fluids and other biological materials.

2. Methods for pharmaceuticals

2.1. Pharmacopoeial methods

TFH is an official drug in European Pharmacopoeia [6], British Pharmacopoeia [7] and United States Pharmacopoeia [8]. European Pharmacopoeia and British Pharmacopoeia describe a titrimetric procedure in which 250 mg of TFH is dissolved in 50 mL of 96% ethanol, 5.0 mL of 0.01 mol/L HCl is added, and the unreacted HCl is titrated with 0.1 mol/L NaOH, and the end point is determined potentiometrically. The volume of NaOH added between the two inflection points corresponds to the amount of TFH.

In the method described in United States Pharmacopoeia, TFH assay was done by using high performance liquid chromatography (HPLC), in which C_{18} (150 mm × 3.0 mm, 5 μm) column was used as stationary phase and the mobile phase was composed of buffer (0.2% triethylamine in water, pH was adjusted to 7.5 with dilute acetic acid), acetonitrile and methanol with a gradient elution. Column temperature was set at 40 °C and the flow rate at 0.8 mL/min. Column effluent was monitored at 280 nm.

2.2. Titrimetric method

Other than the official methods [6,7], a titrimetric method in which TFH in anhydrous acetic acid medium was titrated with 0.05 mol/L acetous perchloric acid using crystal violet indicator has been described [9]. The method was applied to bulk drug and tablets with recoveries of 100.41% and 101.81%, respectively, and a coefficient of variation of 1.64.

2.3. UV-spectrophotometric methods

In the same article [9], an UV-spectrophotometric method was described for the determination of TFH in raw materials, tablets and creams. The calibration graph was linear over the concentration range of 0.8–2.8 μg/mL (r=0.9997) with a recovery close to 100% from the formulations and a coefficient of variation of about 10. Absorbance measurement of a methanolic solution of the drug at 223 nm has facilitated its determination in a concentration range of 1–3.5 μg/mL (r^2=0.999) with limit of detection (LOD) and limit of quantification (LOQ) values of 0.11 and 0.33 μg/mL, respectively. The method was applied to Fintrix coated 250 mg tablets with an accuracy of 0.08% (relative error, RE) [10]. In a similar method [11], absorbance of drug solution in methanol was measured at 282 nm and the method was applied to Tebif 250 mg tablets with an accuracy of 0.02% (RE). Beer's law was obeyed over a concentration range of 8–24 μg/mL with an LOD of 0.35 μg/mL and an LOQ of 0.81 μg/mL. Intra- and inter-day precisions were < 0.5% (relative standard deviation, RSD).

Two UV-spectrophotometric methods which are stability-indicating [12] and based on the absorbance measurement of drug in 0.1 mol/L HCl at 222 nm (method A) and in 0.1 mol/L acetic acid at 282 nm (method B) were described for bulk drug and tablets. Beer's law was obeyed over the concentration ranges of 0.2–4.0 μg/mL and 2.0–50 μg/mL for method A and method B, respectively, with corresponding molar absorptivities of 8.72×10^4 and 7.97×10^3 L/mol/cm. The methods were applied to the determination of TFH in tablets with a good accuracy (RE ≤ 1.26%) and precision (RSD ≤ 0.32%) and without detectable interference from tablet excipients. The drug was subjected to acidic, basic, hydrolytic, oxidative, thermal and photo degradation and used to assess the stability-indicating power of the methods. In both the methods, the drug was found to undergo slight degradation under base-induced stress conditions, substantial degradation under an oxidative stress condition, and non-degradation under other stress conditions. Another UV-spectrophotometric method employing 0.1 mol/L HCl as the medium and 223 nm as the wavelength of maximum absorbance was also reported [13]. The calibration graph was linear over a concentration range of 1–3.5 μg/mL (r^2=0.995), and LOD and LOQ values were 0.086 and 0.260 μg/mL, respectively. The method, when applied to coated tablets, was found to be accurate (RE < 1%) and precise (RSD around 2%). Absorbance of an aqueous solution of the drug was measured at 283 nm serving as the basis of the method for TFH in bulk and tablet forms. The method was valid over the concentration range of 5–30 μg/mL with LOD and LOQ values of 0.42 and 1.30 μg/mL, respectively. The method was applied to eye drops and the results were found to be satisfactory with an RE of 0.81% and an RSD of 1.34%. The method was also demonstrated to be rugged [14].

Two UV-spectrophotometric methods developed for the quantification of TFH in the presence of its degradation products [15] make use of the first spectral derivation (1D) and the first derivative of the ratio spectra (1DD) of the drug and its photodegradates at different selected wavelengths. Good linearity was observed in the range of 10–100 mg/mL with an LOD of 1.11 mg/mL and an LOQ of 3.36 mg/mL. The methods reported show good accuracy and precision.