DETERMINATION OF KETOCONAZOLE IN TABLETS BY USING THREE DIFFERENT METHODS

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ABSTRACT
Ketoconazole has been widely used as an antifungal drug that is formulated as tablets, cream and over-the-counter ketoconazole shampoo. The aim of this research was to study and to standardize an ultraviolet spectrophotometric (UVS) method, potentiometric and a high performance liquid chromatographic (HPLC) method for the determination of ketoconazole in commercially available Oromycosal® tablets. These three methods were compared and discussed with respect to their sensitivity, selectivity and ready-applicability in routine analytical work. Absorption spectra and spectrophotometric determinations were carried out on the UVS spectrophotometer. Investigated concentrations were in range from 0.003 to 0.02 mg?dm⁻³. The absorbance was measured at 224 nm. In potentiometric titrations glass and saturated (KCl) calomel electrode were used. HPLC analyses of ketoconazole were carried in the presence of econazole as internal standard. It can be concluded that the described methods are simple, fast and reliable for determination of ketoconazole in pharmaceutical preparations. The preparation of the samples is easy, the excipients do not interfere in the methods, so they can be used in routine quality control analysis.

INTRODUCTION
Ketoconazole is used to treat fungal infections. Ketoconazole is most often used to treat fungal infections that can spread to different parts of the body through the bloodstream such as yeast infections of the mouth, skin, urinary tract, and blood, and certain fungal infections that begin on the skin or in the lungs and can spread through the body. Ketoconazole is also used to treat fungal infections of the skin or nails that cannot be treated with other medications. It works by slowing the growth of fungi that cause infection. Ketoconazole (cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2(1H-imidazol-1-ytmethyl)-1,3-dioxolan-4-y]-methoxy]phenyl]piperazine) is in a class of antifungals called imidazoles with complex structure.

Figure 1. Chemical structure of ketoconazole

Source: The United States Pharmacopoeia 32th NF 27 (2009)

Objective

The aim of this research was to study and to standardize an ultraviolet spectrophotometric (UVS) method, potentiometric and a high performance liquid chromatographic (HPLC) method for the determination of ketoconazole and to point out the convenience of this introduction as a routine procedure for quality control of Oromycosal® tablets.

Materials and methods
Absorption spectra and spectrophotometric determination were carried out on a "Gilford 250" and "LKB 4050" spectrophotometer, in 1 cm cuvettes.
Potentiometric titrations were made using "Radiometer pH meter" with a glass and saturated (KCl) calomel electrode. HPLC analysis were performed by "LKB system" using Ultrapac LiChrosorb RP 18 (5 μm) column, with the mobile phase consisting of 0.2% diethilamin in methanol/0.5% ammonium acetate solution (78:22); flow rate = 0.9 cm³/min and UV detection at 224 nm.

Methanol was of HPLC grade and purchased from Merck (Darmstadt, Germany). Ketocinazole was purchased from Sigma (St. Louis, MO, USA). Econazole was also purchased from Sigma (St. Louis, MO, USA). Acetic acid and diethylamine were of analytical grade and from Sigma. Deionized water was produce using a Millipore Milli-Q apparatus (Milford, MA, USA). Oromycosal® tablets were taken from the market.

For spectrophotometric determination the concentration of ketoconazole stock solutions was $10^{-4}$ molˑdm⁻³ in 0.1 molˑdm⁻³ HCl. Solutions in range of investigated concentrations were obtained by diluting of stock in range from 0.003 to 0.02 mgˑdm⁻³. The absorbance was measured at 224 nm. For potentiometric determination samples are dissolved in acetic acid. A solution of HClO₄ (0.1 molˑdm⁻³) in acetic acid was used for titrations. Each cm³ of HClO₄ (0.1 molˑdm⁻³) is equivalent to 0.02657 g of ketoconazole.

For HPLC determination of ketoconazole, in the presence of econazole as internal standard the stock solution was prepared by dissolving of 50 mg ketoconazole (accurately weighted) and econazole (accurately weighted) in the 100 ml of mobile phase. The working standard solutions were prepared by diluting the stock solution with the mobile phase in a 10-ml volumetric flask. The concentrations of ketoconazole working standard solutions were 25, 50, 100, 150 and 200 μg/ml.

Results and discussion

The results obtained by these three methods are given in Table 1.

<table>
<thead>
<tr>
<th>Method</th>
<th>x̄</th>
<th>SD</th>
<th>r</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>196.86</td>
<td>1.28</td>
<td>I-II = 0.94</td>
<td>I-II = 1.54</td>
</tr>
<tr>
<td>II</td>
<td>198.32</td>
<td>1.59</td>
<td>I-III = 0.92</td>
<td>II-III = 1.71</td>
</tr>
<tr>
<td>III</td>
<td>197.28</td>
<td>2.08</td>
<td>I-III = 0.90</td>
<td>I-III = 2.64</td>
</tr>
</tbody>
</table>

The described methods for quantitative determination of ketoconazole in Oromycosal® tablets are simple and accurate. For determination of assay of ketoconazole in tablets this methods can be performed directly without removing the ingredients. The differences in assay values in all methods were not statistically significant.

Conclusions

The described methods are simple, fast and reliable for determination of ketoconazole in pharmaceutical preparations. The preparation of the samples is easy, the excipients do not interfere in the methods, so they can be used in routine quality control analysis.

The spectrophotometric method that is recommended for quantitative determination in routine analysis is not only satisfactorily reproducible, but also selective with respect to the ingredients. It can be compared favorably in respect to the sensitivity with the potentiometric and chromatographic methods. Although, the potentiometric method cannot be considered as selective, it is rapid and reproducible enough to be used as an alternative routine method. The HPLC method is useful especially for determination of impurities and degradation products in stability studies of ketoconazole in pharmaceutical preparations.

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References


