

# 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 0.02mg?dm<sup>-3</sup>. 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.

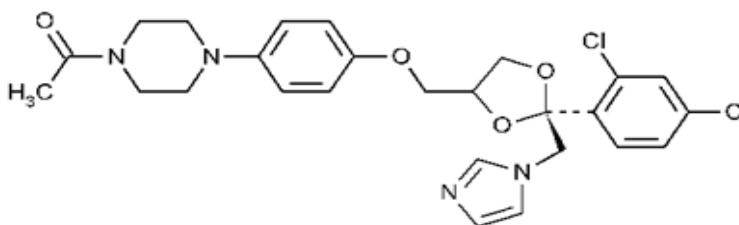
## UDC CLASSIFICATION & KEYWORDS

■ 681.2-5 ■ Assay ■ Ketoconazole ■ Tablets■

## 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-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine) is in a class of antifungals called imidazoles with complex structure

Figure 1. Chemical structure of ketoconazole



Piperazine,1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-,cis-(±)-cis-1-Acetyl-4-[p-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine [65277-42-1].

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

## Objective

Few data have been reported on the quantitative assay of this compound (European Pharmacopoeia 2008) as pure substance and in pharmaceutical formulations such as tablets, cream and over-the-counter ketoconazole shampoo (Heyden YV, Nguyet ANM, Detaevernier MR, Massart DL and Vercammen JP 2002, Arranz P, Arranz A, Moreda JM, Cid A, Arranz JF 2003, Staub I, Bergold AM 2004, Vander Heyde Y, Nguyen Minh Nguyet A, Detaevenier M R, Massart D L, Plaizier-Vercammen J. 2002, El-Shabouri SR, Emara KM, Kashaba PY, Mohamed AM. 1998). According to US Pharmacopoeia ketoconazole is determined as pure substance by potentiometric method, although for quantitative determination in dosage forms, the official method is HPLC (The United States Pharmacopoeia 32th NF 27 2009).

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  $\mu\text{m}$ ) column, with the mobile phase consisting of 0.2% diethylamin in methanole/0.5% ammonium acetate solution (78:22); flow rate = 0.9  $\text{cm}^3/\text{min}$  and UV detection at 224 nm.

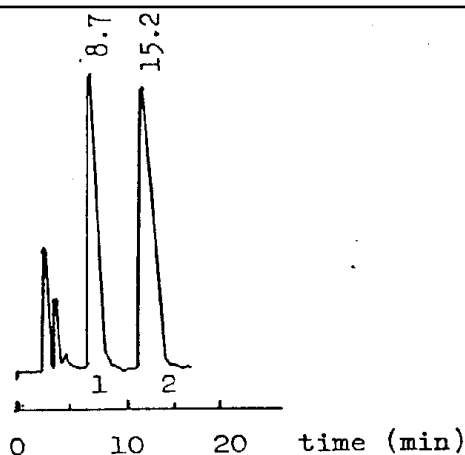
Methanole was of HPLC grade and purchased from Merck (Darmstadt, Germany). Ketocinazole was purchased from Sigma (St. Louis, MO, USA). Econazole was also purchased from Sigma (St. Louis, MO, USA). Acetic acid and diethylamine were of analytical grade and from Sigma. Deionized water was produce using 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  $10^{-4} \text{ mol dm}^{-3}$  in 0.1  $\text{mol dm}^{-3}$  HCl. Solutions in range of investigated concentrations were obtained by diluting of stock in range from 0.003 to 0.02  $\text{mg dm}^{-3}$ . The absorbance was measured at 224 nm. For potentiometric determination samples are dissolved in acetic acid. A solution of  $\text{HClO}_4$  (0.1  $\text{mol dm}^{-3}$ ) in acetic acid was used for titrations. Each  $\text{cm}^3$  of  $\text{HClO}_4$  (0.1  $\text{mol dm}^{-3}$ ) 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  $\mu\text{g/ml}$ .

Figure 2. Typical chromatogram of ketoconazole in tablets



Source: Author. Ketoconazole is presented as peak 1. Econazole is presented as peak 2.

## Results and discussion

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

Table 1. Results for content of ketoconazole in tablets by spectrophotometric (I), potentiometric (II) and HPLC (III) methods

Method	Statistic			
	$\bar{x}$	SD	r	F
I	196,86	1,28	I-II = 0.94	I-II = 1.54
II	198,32	1,59	II-III = 0.92	II-III = 1.71
III	197,28	2,08	I-III = 0.90	I-III = 2.64

Source: Author. Data for content of ketoconazole are presented in  $\text{mg/tablet}$  as the mean value on ten samples

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.

## References

- Arranz P, Arranz A, Moreda JM, Cid A, Arranz JF. Stripping voltammetric and polarographic techniques for the determination of anti-fungal ketoconazole on the mercury electrode, (2003) *J. Pharm.Biom. Anal.*, New York, 33, 589-596
- El-Shabouri SR, Emara KM, Kashaba PY, Mohamed AM. Charge-transfer complexation for spectrophotometric assay of certain Imidazole antifungal drugs (1998) *Anal. Lett*, New York, 31, 1367-1385
- European Pharmacopoeia (2008) 6th Ed., Ketoconazole 01/2008:0921 corrected 6.0, European Pharmacopoeia Commission, 2216-2218
- Heyden YV, Nguyet ANM, Detaevenier MR, Massart DL and Vercammen JP. Simultaneous determination of ketoconazole and formaldehyde in a shampoo: liquid chromatography method development and validation, (2002) *J. Chromatogr. A* 958, 191-201
- Staub I, Bergold AM. Determination of Ketoconazole in Shampoo by High Performance Liquid Chromatography (2004) *Acta Farm. Bonaerense* 23 (3), 387-390
- The United States Pharmacopoeia 32th NF 27 (2009), Ketoconazole, Ed. Rockville: United States Pharmacopeial Convention, 2737-2738
- Vander Heyde Y, Nguyen Minh Nguyet A, Detaevenier M R, Massart D L, Plaizier-Vercammen J. Simultaneous determination of ketoconazole and formaldehyde in a shampoo: liquid chromatography method development and validation (2002) *Journal of Chromatography A* 958 (1-2), 191-201