SPECTROPHOTOMETRIC, POTENTIOMETRIC AND HPLC DETERMINATIONS OF KETOCONAZOLE IN SOLID PHARMACEUTICAL FORMULATIONS

M. Ilievska, G. Trendovska, B. Panzova, B. Bogdanov*

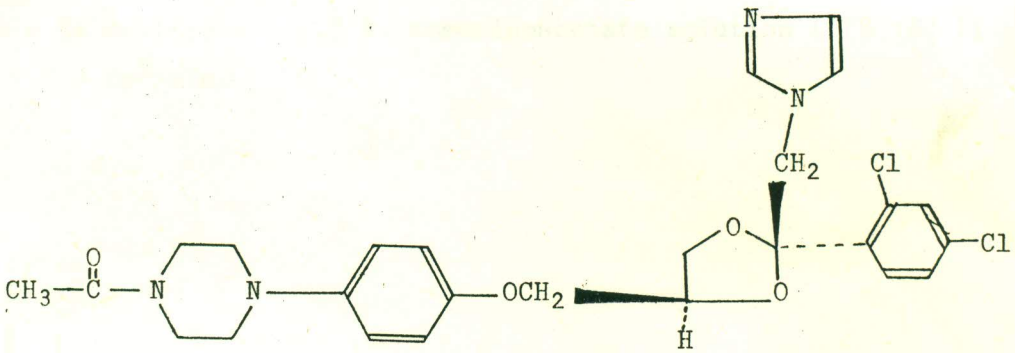
Alkaloid, Pharmaceutical Company, Skopje

*Institute of Chemistry, Faculty of Science, Skopje

Ketoconazole has been widely used as an antifungal drug. The determination of ketoconazole can be carried by spectrophotometric, potentiometric and HPLC methods. These three methods were compared and discussed with respect to their sensitivity, selectivity and ready-applicability in routine work for the determination of ketoconazole.

INTRODUCTION

Ketoconazole is an antifungal drug with complex structure:



Few data have hitherto been reported on the quantitative assay of this compound [1-3]. According to US pharmacopeia [1] ketoconazole is determined potentiometricaly, although for quantitative determination in dosage forms, the official method is HPLC. Pharmacopeia Jugoslavica [4] has not includied an official monograph yet. This deficiency stimulated us to compare the HPLC, spetrophotometric and potentiometric method of determination of ketoconazole and to point out the convenience of its introduction as a routine procedure for determination quality control of Oromycosal® formulation.

EXPERIMENTAL

Apsorption spectra and spectrophotometric determination were carried out on a "Gilford 250" and "LKB 4050" spectrophotometer, in 1 cm cuvettes. The concentration of ketoconazole stock solutions was 10^{-4} mol·dm^{-3} in 0.1 mol·dm^{-3} HCl. Solutions in range of investigated concentrations were obtained by dilution of stock solution and ranged from 0.003 to 0.02 mg·cm^{-3}. The absorbance was measured at 224 nm.

Potentiometric titrations were made using "Radimeter pH meter" with a glass and saturated (KCl) calomel electrode. The determined ketoconazole is dissolved in acetic acid. A solution of $HClO_4$ (0.1 mol·dm^{-3}) in acetic acid was used for titrations. The ketoconazole was determined from the titration curve using a graphic method. Each cm^3 of $HClO_4$ (0.1 mol·dm^{-3}) is equivalent to 0.02657 g of ketoconazole.

HPLC analysis of ketoconazole, in the presence of econazole as internal standard, was performed by "LKB system" using Ultrapac LiChrosorb RP 18, 5 µm column and 224 nm detection. The mobile phase consisted of a 0.2% diethilamin in methanole - 0.5 % ammoniumacetate solution (78 :22); flowrate = 0.9 cm^3/min.

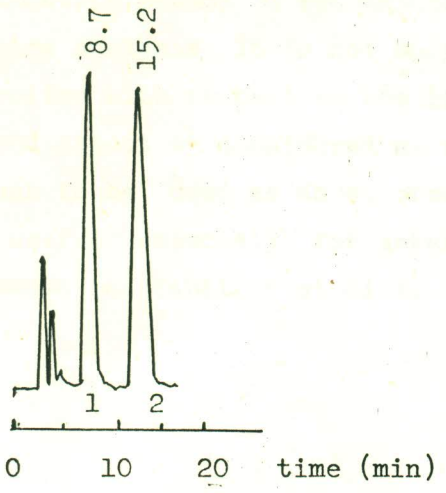


Fig. 1. Typical chromatogram of ketoconazole tablets.

Legende: 1. Ketoconazole
2. Econazole

RESULTS AND DISCUSSION

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

Table 1. Results of spectrophotometric (I), potentiometric (II) and HPLC (III) determination of ketoconazole

Method	Statistics			
	$\bar{X}$*	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

* mg/tab.; average of ten samples.

The described methods for quantitative determination of ketoconazole in Oromycosal® tablets are simple and accurate. They can be performed directly without removing the ingredients. The differences in assay values in all methods were not statistically significant. The spectrophotometric method is recomended for quantitative determination in routine analysis. It is not only satisfactorily reproducible, but also selective with respect to the ingredients. 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 especialy for determination of impurities and degradation products in stability studies.

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ИЗВОД

СПЕКТРОФОТОМЕТРИСКО, ПОТЕНЦИОМЕТРИСКО И HPLC КВАНТИТАТИВНО ОПРЕДЕЛУВАЊЕ НА КЕТОКОНАЗОЛ ВО ЦВРСТИ ФАРМАЦЕВТСКИ ОБЛИЦИ

М. Илиевска, Г. Трендовска, Б. Панзова, Б. Богданов*

Р. О. "Алкалоид" - Скопје, *Хемиски институт ПМФ - Скопје

Кетоконазолот е антифунгицидна супстанца, дериват на пиперазинот. Вршено е квантитативно определување на кетоконазол во цврсти фармацевтски облици употребувајки спектрофотометриски метод, потенциометриска титрација во неводена средина и HPLC метод. За секој метод определени се оптималните услови при кои се избегнува влијанието на ексципиентите врз одредувањето на концентрацијата на активната супстанца. Добиените резултати од трите методи меѓусебно се споредувани и дискутирани во поглед на точноста, репродуцибилноста и применливоста за рутинска контрола на квалитетот на OROMYCOSAL® препарати, производ на "Алкалоид" - Скопје.