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A New Spectrophotometric Method for the Determination of Itraconazole Based on the Oxidation Reaction

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ABSTRACT

The solubility of Itraconazole (Itcz) in various solvents such as distilled water, hydrochloric acid and sulphuric acid in presence of cationic and anionic surfactant i.e. cetyl trimethyl ammonium bromide (CTAB) and sodium lauryl sulphate (SLS) was examined. It has been found that SLS greatly enhanced the solubility of Itraconazole by 13 fold. A simple spectrophotometric method has been proposed for the determination of Itraconazole in pure and pharmaceutical formulation by ammonium metavanadate in presence of SLS. The method is based on the formation of wine red colored species on treating Itcz with ammonium metavanadate at CMC of SLS i.e. 0.0008M. The wine red species (due to reduced V(v)) exhibiting maximum absorbance at 385 nm.

Keywords: Itraconazole, sodium lauryl sulphate, solubility

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INTRODUCTION

Itraconazole a water insoluble oral triazole antifungal. It provides an effective oral treatment of several deep mycoses including asperigillosis and candidiasis[1,2]. It is a white to slightly yellowish powder and is insoluble in waster at all pH's in the range 1-12. Because of its poor aqueous solubility its absolute oral bioavailability[3] is only 55 percent. Surfactants SLS and CTAB were used for increasing the solubility of Itcz. It was found that by addition of V(v) ions to an acidic solution of Itcz, at first wine red color species was obtained which became darken brown with increase in time.

EXPERIMENTAL

A systronic model Uv-Vis recording spectrophotometer equipped with 10ml 11matched quartz cuvetts was used for all spectral measurements. All of chemical used in the study were of the highest purity available. Triply distilled water was used throughout. Reagent grade Itcz was obtained from Glenmark pharmaceuticals Ltd. Mumbai. A working standard solution of 0.01M of Itcz was prepared by dissolving 0.706g. pure drug in 100 ml of water containing a few drops of H2S04 acid about (0.9 M) followed by further diluting 5ml of this solution to 100ml.

Estimation of Itraconazole

A new spectrophotometric method is proposed for the estimation of Itcz in pharmaceutical preparations. Method is based on the coupled redox- complexation reaction, which proceed in the Itcz V(v)- micellar systems. In this method Itcz react with V (v) in micellar media forms a wine red colored complex having absorption maxima at 385 nm.

Solubility Determination

The solubility of Itcz in water- acid and water-acid containing various concentrations of SLS and CTAB was determined. Excess Itcz was added to 15 ml of each fluid taken in 25 ml stoppered conical flask and the mixtures were shaken for four hr. at room temperature (28 ±10) on a rotatory flask shaker. After four hr. of shaking 1ml. aliquots were withdrawn at 30 min. time interval and filtered immediately using a 0.45 disc filter. The filtered samples were diluted suitably and assayed for Itcz by UV-spectrophotometric method. Shaking was continued until two consecutive estimations are the same. The solubility experiments were conducted in triplicate table 1.

Table 1 Solubility of Itcz in various fluids

Fluid Composition	Concentration of surfactant				
	0 M	**0.000lM**	**0.0004 M**	**0.0006 M**	0.0008
Purified Water	0.01	-	-	-	-
0.1 N HCL	0.04	-	-	-	-
0.l N HCL + CTAB	0.04	0.206	0.723	0.727	0.739
0.1 N HCL + SLS	0.04	0.695	0.824	0.894	0.932
0.8 M-H_2SO_4	0.794	-	-	-	-
0.8 M-H_2SO_4 + CTAB	-	4.75	5.91	6.91	7.45
0.8 M- H_2SO_4 + SLS	-	7.88	8.99	9.73	9.91
Water + CTAB	0.01	0.819	0.875	0.919	1.156
Water + SLS	0.01	0.975	1.769	2.19	2.37

The proposed method is simple, rapid and precise. It does not suffer from any interference due to common excipients of drug. The solubility of Itcz in water and acid was increased in the presence of surfactants (Table 2). The solubility increased linearly as the concentration of surfactant increased with both SLS and CTAB. SLS gave higher increase in solubility of Itcz compared to CTAB. 13 fold and 9.1 fold at 0.008 M concentration respectively, with SLS and CTAB. The higher solubility of Itcz observed with SLS is due to the more number of miceller formed as to CTAB.

Kinetic Study

Critical micellar (CMC) concentration

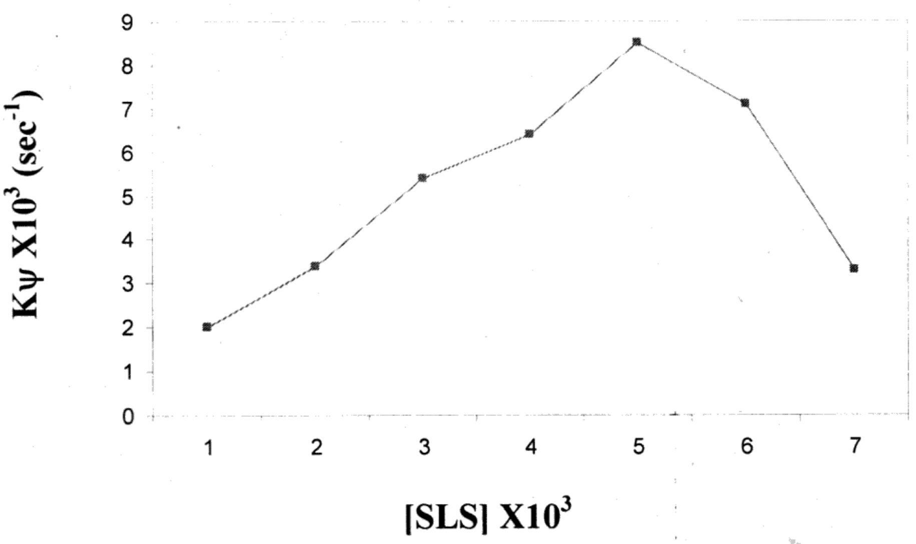
The CMC value for reaction solution of SLS obtained by Broxton method[5]. The reaction was studied at different concentration of anionic surfactant i.e. Sodium lauryl sulphate [SLS].The plot of observed rate constant (k'l') versus (surfactant) shows that reaction increase up to maximum and then decreases with concentration of SLS. The maximum value of rate constant (k'l') is taken as CMC (Table-2).

Table 2 Dependence of the rate constant on (SLS) at temperature 25°C

[SLS]x 10^3 (mol. dm^3)	1.0	2.0	3.0	5.0	8.0	10.0	11.0
kψ x 10^3 (sec^{-1})	2.0	3.4	5.4	6.4	8.5	7.1	3.3

[Vanadium (V)] x 10^2 mol dm^{-3} [Itcz] x 10^2 (mol. dm^{-3}) H+ = 0.8M (mol dm^{-3})

Fig. 1: Dependence of the rate constant [SLS] at temperature 25^0C



The formation of polymeric product by the addition of acrylonitrile to the aliquot, indicated that V(V) behaves as an one-equivalent oxidant.

Table 3 Dependence of oxidation on reactants

[Vanandium(V)]x10^2 (mol dm^{-3})	[Itcz] x 10^2 (mol dm^{-3})	[H_2SO_4] (mol dm^{-3})	K_0 x 10^3	Km x 10^3
0.2	5.0	0.8	7.82	8.32
0.5	5.0	0.8	7.96	9.0
0.8	5.0	0.8	8.0	9.86
1.0	5.0	0.8	8.19	10.1
1.0	4.0	0.8	6.9	7.78
1.0	5.0	0.8	8.0	9.86
1.0	6.0	0.8	1.0	11.62
1.0	8.0	0.8	11.2	12.6
1.0	5.0	0.2	4.2	5.78
1.0	5.0	0.4	5.8	6.99
1.0	5.0	0.8	8.0	9.86
1.0	5.0	1.0	11.6	12.32

Fig. 2: Dependence of substrate concentration on the rate of reaction

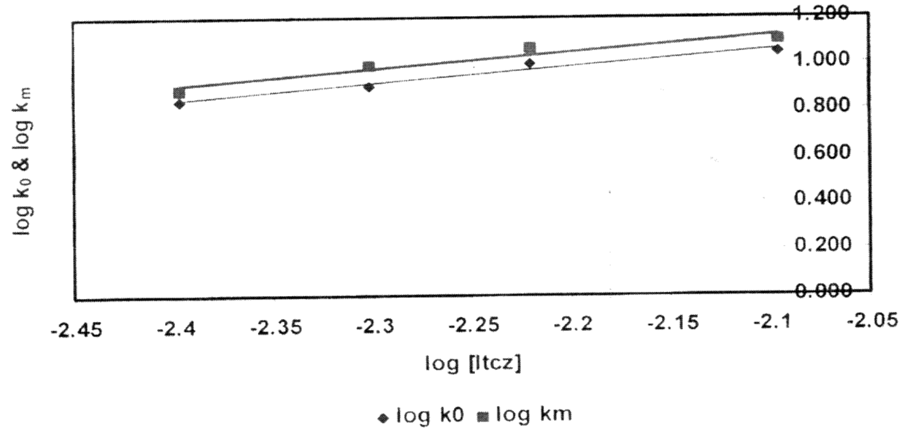


Fig. 3: Reciprocal plots in absence and presence of micelles

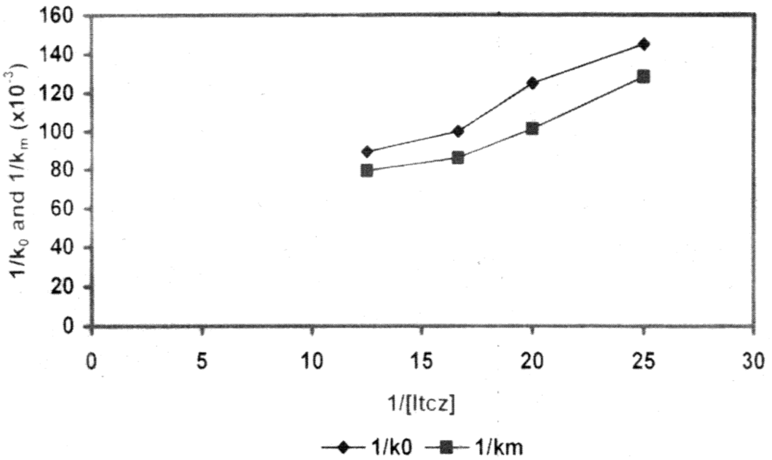
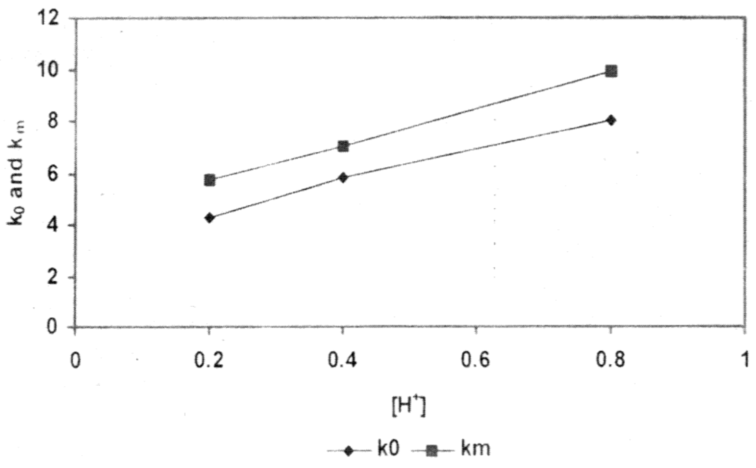


Fig. 4: Dependence of the acid concentration on rate of reaction



DISCUSSION AND CONCLUSION

The wine red coloured species is formed which turn darkens after some time. It was assumed that Vanadium (V) exists as $[V(OH)_3HSO_4]^+$ under acidic conditions. In attempting to eluciate the mechanism by which micelle enhance the solubility of Itcz it assumes that absorption of Itcz into micelles takes place at rates much faster than the rates of commonly observed (Figure : 2 & 4). The greater solubility is observed at near the cmc of SLS (Table:2). Increasing substrate concentration increases the rate of reaction to certain point in presence and absence of micelles as shown in figure 2. Rate of reaction increased with H^+ concentration presence and absence of micelles as shown in figure 4. It has been found that Itcz first oxidised to hydroxy - Itcz and then a second oxidation to keto-Itcz. Keto-Itcz oxidised to undergo M-dealkylation to ND-Itcz [R]. The rate of chemical reaction may be modified by the presence of micellar aggregates in the system understudy. The investigation of micellar catalysis has provoked a great interest since the study might provide a basic model for the interpretation of some aspects of enzymatic catalysis. Both catalytic micellar and enzymes bind substrate in a non-covalent manner and the kinetics and micellar catalysis resemble that of enzymatic catalysis in that the micellar may be saturated by the substrate.

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