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SUWANNA TECHOWANICH : CHEMICAL STABILITY OF KETOCONAZOLE IN AQUEOUS SOLUTION. THESIS ADVISORS : VARAPORN JUNYAPRASERT, Ph.D., AMPOL MITREVEJ, Ph.D., OPA VAJRAGUPTA, Ph.D. 178 P. ISBN 974-662-472-5

The effects of pH, total buffer concentration, ionic strength and temperature on the degradation of ketoconazole in aqueous solution were studied in phosphate buffer solution at 65°C except for the Arrhenius study which was conducted at various temperatures. Chemical stability of ketoconazole in aqueous solution was determined using high performance liquid chromatography (HPLC) method. The results showed that, at constant pH and temperature, the degradation rate followed first-order kinetic. The pH-rate profile indicated that the ketoconazole degradation at pH between 2.97 and 5.21 in 0.1 M phosphate buffer solution with ionic strength of 0.35 M at 65°C involved three postulated reactions; specific acid-catalysis of fully protonated ketoconazole (AH_2^{2+}), specific acid-catalysis of monoprotonated ketoconazole (AH^+) and water-catalysis of AH^+. The rate constants of the three reactions were 40.76 M^{-1} day^{-1} (k_{H^+} for AH_2^{2+}), 51.53 M^{-1} day^{-1} (k'_{H^+} for AH^+) and 3.44×10^{-2} day^{-1} (k'_S for AH^+). Phosphate buffer enhanced general acid-catalysis on the ketoconazole degradation at pH between 3.0 and 5.0, for which the HPO_4^{2-} had 54 times more catalytic effect than the $H_2PO_4^-$. At pH 5.0, the degradation rate was accelerated with increasing ionic strength, therefore the reaction of like-charge species between monoprotonated ketoconazole and hydrogen ion would be involved in the ketoconazole degradation. From the Arrhenius study, it was found that the activation energies of ketoconazole degradation at pH 3.0, 4.0 and 5.0 were 22.09, 21.58 and 21.34 kcal/mole, respectively. The predicted degradation rates at 30°C were 1.15×10^{-3}, 9.21×10^{-4} and 9.16×10^{-4} day^{-1} at pH 3.0, 4.0 and 5.0, respectively, which revealed that the predicted shelf-lifes at 30°C were 91.3, 113.9 and 114.6 days at pH 3.0, 4.0 and 5.0, respectively.