CHAPTER V

CONCLUSION

1. Nine brands of 200 mg ketoconazole tablets were subjected to standard *in vitro* test as specified in the United State Pharmacopoeia XXII. In no instance did any of the product fail to meet the United State Pharmacopoeia XXII specifications for content assay, uniformity of dosage units and disintegration.

2. Disintegration performed in carbon dioxide-free water classified nine products into three groups, with brands I, C, B and A being rapidly disintegrated, brands E and F being intermediately disintegrated and those G, D and H having the longest disintegration time.

3. Well-documented as a sensitive method for indicating the effect of formulation factors on bioavailability of drugs, dissolution characteristics of all nine brands were determined in simulated gastric fluid and simulated intestinal fluid without enzyme. Dissolution in simulated gastric fluid without pepsin can be divided into three groups, with brands C, B, F, and I being relatively rapidly dissolved, brands E being relatively slowly dissolved, and the remainders having an intermediately dissolution rate.

4. In simulated intestinal fluid, dissolution

of tablets occurred with much slower rate than those in acidic medium. According to dissolution characteristics in simulated intestinal, nine formulations can be divided into three groups with brands B, I and F having relatively high dissolution rate and brands D, C, H and A having intermediately dissolution rate and brands G and E having relatively low dissolution rate.

5. Five brands of ketoconazole tablets, including an innovator's product being assigned as a reference and four brands with fast, medium, and slow dissolution rates in simulated gastric fluid, were selected and studies in twelve male healthy volunteers using a complete cross-over design in order to assess a single dose bioavailability. Results from the CSTRIP analysis indicated that one compartment open model with first order absorption and elimination rate without lag time can be best used to describe most of the concentration-time curves for ketoconazole obtained over 12 hr sampling times after a single 200 mg dose administration.

6. Based on the results of ANOVA and t- test (α = 0.05) for the C_{max}, t_{max} and AUC, all four test brands did not show any differences of statistical significance from the reference and they were considered to be bioequivalent and interchangeable. Relative bioavailabilities, with respect to the reference, were 104.00, 99.47, 108.69 and 101.76% for brands B, C, D and

E, respectively (determined from the ratio of AUC of test to reference.

7. After a single 200 mg dose of ketoconazole tablet administration, maximum concentration attained in 1.52 hr (0.56-2.20 hr) indicating rapid absorption with 3.58 mcg/ml of maximum concentration (0.81-6.92 mcg/ml). The biologic half life and elimination rate were 2.48 hr (1.71-4.15 hr) and 0.29 hr^{-1} (0.17-0.40 hr^{-1}). Most pharmacokinetic parameter reported in the present study are in agreement with those reported by the other researchers except AUC which is somewhat higher than that reported by Daneshmend (1983).

8. No statistical differences of any of pharmacokinetic parameters between coated tablets' and uncoated tablets' were observed.

9. No adequate correlation between the *in vivo* parameters and any of the dissolution and disintegration parameters existed, and the prediction of *in vivo* bioavailability was not sufficient precise to permit application of the *in vitro* testing procedure to evaluate the products.