CHAPTER V

CONCLUSIONS

1. All brands of 5 mg. glibenclamide tablets met the British Pharmacopoeia 1988 monograph for content of active ingredient, uniformity of content, weight variation and disintegration time.

2. All brands of 5 mg. glibenclamide tablets disintegrated within the limit time of uncoated tablet. The disintegration time of brands B and E were statistically significant longer than that of brand A ($p < 0.05$). The rank order in term of mean disintegration time was brands E > B > C > F > G > D > A.

3. Dissolution profile for each brand was performed in simulated intestinal fluid TS without enzyme (pH 7.5 $\pm$ 0.1). Major differences were observed for the rate and the extent of dissolution among these brands. The rank order of the dissolution rate constant was brands A > D > G > F > B > E > C. The dissolution rate constant of brand A was statically significant ($p < 0.05$) higher than those of brands B, C, E, F and G, except for that of brand D.

4. No statistical correlation ($p > 0.05$) was found between the disintegration time and the dissolution rate constant of each brand.

5. The bioavailability of brands A, C, D and F with difference in dissolution characteristics were studied in twelve Thai healthy volunteers. A single dose of 5 mg. glibenclamide tablet was administered to each subject in a crossover design. Plasma glibenclamide concentrations were determined by a reversed phase high performance liquid chromatography with solvent extraction and detected by UV detector at 230 nm. Individual plasma concentration-time profile was analyzed using the CSTRIP computer program for compartmental analysis. The data were well described by a biexponential equation.

The mean peak plasma concentrations of each treatment ranged from 62.26 to 138.1 ng./ml. Statistical results indicated that peak plasma concentrations of brands C and F were significant difference from that of brand A ($p < 0.05$).

The average times to peak plasma level ranged from 2.34 to 2.68 hours for the four different brands. There were no statistically significant differences of this parameter among these brands ($p > 0.05$).

The area under the plasma concentration-time curves of all brands ranged from 449.0 to 843.8 ng.hr./ml. The rank order of these values was brands A > D > F > C. Only brand C had an area significant lower than that of brand A ($p < 0.05$).

The relative bioavailability of the three locally manufactured brands with respect to the innovator's product (brand A) were 67.16, 104.09 and 82.95 percent for brands C, D and F, respectively.

Only brand D was complete bioequivalence to brand A. Brand F was almost bioequivlence to brand A unless its peak plasma level was significant difference ($p < 0.05$) from that of brand A. Brand C was bioinequivalent to brand A. Many factors may influence the bioavailability of glibenclamide tablets such as the difference of glibenclamide raw material source, drug formulation and/or manufacturing process.

6. The pharmacokinetics of glibenclamide following oral administration of 5 mg. tablet was well described by a means of one compartment open model with lag time.

The average absorption rate constant obtained from the CSTRIP program for brands A, C, D and F were 0.92, 0.87, 0.75 and 0.77 hr^{-1}, respectively. No statistical significant difference was found among these values ($p > 0.05$).

The average elimanation rate constant also obtained from the CSTRIP program were 0.29, 0.24, 0.26 and 0.25 hr^{-1} for brands A, C, D and F, respectively. There wwre no statistically significant difference among these values ($p > 0.05$).

The mean biological half-life of glibenclamide ranged from 2.46 to 3.18 hours and no statistically significant difference ($p > 0.05$) among these values.

The results of pharmacokinetic parameters established in this study were in agreement with those previously published data.

7. The correlation study between the in vitro and in vivo data of the four different brands of glibenclamide tablets revealed that the disintegration time showed statistically significant correlation with the C_{max} ($p < 0.05$) and only the dissolution rate constant showed statistically significant correlation with both of the C_{max} and the AUC ($p < 0.05$). The dissolution rate constant might be used to predict the bioavailability of glibenclamide tablet in term of the extent of drug absorption.