CHAPTER V

CONCLUSION

1. All brands of theophylline sustained-release tablets met the general requirements of the U.S.P.XXII for weight variation (range from 299.39 to 685.22 mg). The content of active ingredient ranged from 101.22 to 109.71 %.

2. All brands of theophylline sustained-release tablets met the U.S.P.XXII requirement for identification and dissolution. The dissolution rate constant of brands A and D were not statistically different from that of brand B ($p < 0.05$) while the value of brand C was statistically higher than that of brand B ($p > 0.05$). The rank order in term of mean dissolution rate constant was C > A > B > D.

3. The bioavailability of brands A, B, C, and D were studied in thirteen Thai healthy volunteers. Multiple dose of theophylline sustained-release tablets was administered to each subject. Plasma theophylline concentrations were determined using high performance liquid chromatography with zinc sulfate and organic solvent extraction and detected by UV detector at 280 nm. The plasma concentration-time profile of each subject was analyzed using the conventional method. The observed values of relevant pharmacokinetic parameters (C_{max}, t_{max}, AUC, and % fluctuation) were used for bioavailability comparison.

The mean peak plasma concentration of each treatment ranged from 5.23 to 5.99 mcg/ml.

The average times to peak plasma concentrations range from 3.56 to 8.92 hr. for the four different brands.

The area under the plasma concentration-time curves of all brands ranged from 97.28 to 109.60 mcg x hr./ml.

The %fluctuation of all brands range from 58.72 to 155.72 %

There were no statistically significant difference of the relevant pharmacokinetic parameters between the values of brand B and those of brand A and brand C ($p>0.05$). However the t_{max} and % fluctuation values between those of brand B and brand D were significantly different ($p<0.05$).

It was concluded that brand A and brand C were considered to be equivalent to brand B with respect to the rate and the extent of drug absorption while brand D was not.

4. From these data, it is seen that dose used in this study was not therapeutically appropriate since peak and through plasma concentration were not in the therapeutic range. Dose of each brand should be adjusted by multiplying with a suitable therapeutic factor in order to raise the C_{max} and C_{min} of the patient to the therapeutic range.

It is founded that A, B, C and D have nearly same therapeutic factor (about 3-4 times of the study dose).

For each brand, therapeutic factor for multiply was significant vary for each subject. Brand A was from 1 to 8 (200-1600 mg twice a day), brand B from 2 to 8 (400-1600 mg twice a day), brand C from 1.5 to 7 (300-1400 mg twice a day): this brand can be breakable to adjust dose), and brand D from 1 to 5 (200-1000 once a day)

However, for individual subject, it is found that there are significant variable in therapeutic factor. Hence, adjusting to appropriate plasma theophylline concentration (10-20 mcg/ml) for each subject should be considered individually.

5. The correlation study between the in vitro and in vivo data of the four different brands of theophylline sustained-release tablets revealed that there was no statistically significant correlation of parameters between the two data. By this mean, it was not able to use the parameters from in vitro studies to predict the bioavailability of theophylline sustained-release tablets.