CHAPTER VI

CONCLUSION

1. All eight commercial brands of doxycycline capsules used in this study met the requirement of the British Pharmacopoeia 1988 for weight variation and the United State Pharmacopoeia XXI for percent labelled amount and content uniformity.

2. The disintegration times for each product were performed in water until no residue, except fragments of capsule shell, remains on the basket. The rank order in term of mean disintegration time was as following: brand B < E < F < H < A < D < G < C.

3. Dissolution profiles were determined for each product in 900 ml of water, using the USP Dissolution Apparatus Type II maintained at 75 rpm and a temperature of 37 $\pm$ 0.5 $^{\circ}$ C. All eight commercial brands of doxycycline capsules met the requirement of USP XXI for dissolution test. Dissolution rate constant from each product was slightly different. The rank order in term of mean dissolution rate constant was that brand H > A > B > E > G > F > D > C.

4. There were poor relationship between disintegration times and dissolution rate constants, indicating the independent of dissolution from disintegration of doxycycline capsules.

5. The comparative bioavailability of four brands [A, B, C and D] of doxycycline capsules, with difference in dissolution profiles, was studied in normal volunteers. Oral single dose of 100 mg doxycycline capsule was administered to 20 subjects in a crossover design. Plasma

doxycycline levels were determined by reverse-phase high-performance liquid chromatographic method. Individual plasma profile was analyzed according to noncompartmental and compartmental methods. By compartmental method one compartment opened model with or without a lag time was assumed using CSTRIP and PCNONLIN program. Statistically significant differences at $P < 0.05$ were observed regarding to specific parameters among drug products.

The area under the plasma concentration-time curve [AUC_o^∞] of brand A, B, C, and D obtained from noncompartmental program were 16.55, 30.99, 27.11 and 28.33 $\mu g.hr.ml^{-1}$, respectively, while those obtained from PCNONLIN program were 15.39, 24.65, 19.29 and 23.94 $\mu g.hr.ml^{-1}$. The rank order from both method was brand A < C ~ D ~ B [at $p < 0.05$]. Contrastly, AUC_o^∞ of brand A, B, C, D obtained from CSTRIP program were 19.54 , 28.02, 24.50 and 26.59 $\mu g.hr.ml^{-1}$ respectively and showed no significant difference [$P > 0.05$].

6. The absorption rate constant obtained from CSTRIP program ranged from 1.16 to 2.02 hr^{-1} while those obtained from PCNONLIN program ranged from 1.39 to 1.76 hr^{-1}. No statistical difference among brands was observed for this parameter.

The mean time to peak plasma level reading directly from each individual plasma data ranged from 1.55 to 2.25 hours while those obtained from CSTRIP program and PCNONLIN program ranged from 2.15 to 3.72 hours and 1.74 to 2.38 hours respectively. The difference in the results obtained from the computer program either CSTRIP or PCNONLIN and those from the reading directly values clearly showed that the way the program fit the experimental data does affect the real results. However, these results, are in good agreement with those previously published data.

The mean individual peak plasma concentration which was reading directly from each individual data and that obtained from PCNONLIN program ranged from 1.53 to 2.15 µg/ml and 1.02 to 1.54 µg/ml, respectively. In addition, the rank order from both methods was brand A < D ~ C ~ B [p < 0.05]. But those obtained from CSTRIP program ranged from 0.97 to 1.28 µg/ml and the rank order was brand A ~ C < D ~ B.

7. From this study, the rate of drug absorbed into the circulation was not significantly different among brands but the extent of drug absorbed was significantly different [brand A<C~D~B]. So we can conclude that the bioavailabity of the innovator's product [brand A] was less than the local manufactured products [brand B, C, D] in terms of the extent of drug absorption. This may be due to the content of each capsule of original product as shown in table 3 are rather less than those of other brands.

8. The correlation between the in vitro studies such as disintegration times, dissolution rate constants and the in vivo parameters [AUC_0^t, AUC_0^∞ and Cp_{max}] revealed that the bioavailability of doxycycline from oral capsules was independent of its in vitro properties.

9. The biological half-life of doxycycline obtained from various computer programs ranged from 7.79 to 16.67 hours.

10. The volume of distribution of doxycycline obtained from CSTRIP and PCNONLIN program ranged from 1.36 to 1.60 L/kg and 1.09 to 1.37 L/kg respectively.