CHAPTER V

CONCLUSIONS

1. All brands of 400 mg. norfloxacin tablets met the United State Pharmacopoeia XXII monograph for weight variations and contents of active ingredient.

2. All brands except brand C disintegrated in the range of limit time for film coated tablet. The disintegration times of brands C, D and F were significantly longer than that of brand A ($p < 0.05$). The rank order in terms of mean disintegration time was brands C > D > F > E > B > A.

3. Dissolution profiles were determined for each product in buffer pH 4.0. Major differences were observed for the rate and extent of dissolution among these brands. Only brand C failed to meet the specification of the United State Pharmacopoeia XXII with only 9% dissolved at 30 minutes. The rank order of the dissolution rate constants was brands B > A > D > F > E > C. Dissolution rate constant of brand A was statistically significant difference ($p < 0.05$) from those of brands C and E.

4. The bioavailability of brands A, B, C and D, with difference in dissolution characteristics were studies in 12 Thai healthy subjects. Single dose of 400 mg. norfloxacin tablet was administered to subject following a crossover experiment. Plasma norfloxacin concentrations were determined by a reversed phase high performance liquid chromatographic technique with single step precipitation and detected by fluorometer with excitation wavelength at 300-400 nm and emission wavelength at 450-800 nm. Individual plasma profile was analyzed for pharmacokinetic parameters according to compartmental method using the computer CSTRIP program.

The mean peak plasma concentrations were read directly from individual data and ranged from 0.60 to 2.05 µg/ml and statistical results revealed that only the mean peak plasma concentration of brand C was significant difference from that of brand A ($p < 0.05$).

The mean times to peak plasma level were also read directly from each data and ranged from 1.52 to 1.81 hours. No statistically significant difference of this parameter among the four different brands were observed at $p > 0.05$.

The area under the plasma concentration-time-curves of brands A, B, C and D ranged from 4.35 to 10.42 µg.hr/ml. Only brand C had an area significantly lower than that of brand A indicated that the amount of drug

absorbed from brand C was lower.

The relative bioavailability of three locally manufactured brands with respect to innovator's product, brand A were 120.88, 50.46, and 115.77, for brands B, C and D, respectively.

Since bioequivalence has been defined as equivalence in both rate and extent of drug absorption, it was thus concluded that only brands A, B and D were bioquivalent. Brand C was bioinequivalent, with any other brands. The observed differences in oral bioavailabilities were attributed to differences in manufacturing processes and/or formulations, which could affect the amount of drug dissolved in the gastrointestinal fluids available for absorption.

5. The pharmacokinetics of norfloxacin following oral administration of 400 mg tablet was best described by a mean of two-compartment open model with first order absorption and elimination rate and no lag time.

The absorption rate constants obtained from the CSTRIP program were 1.49, 1.96, 1.63 and 1. 46 hr^{-1} for brands A, B, C and D, respectively. There were no statistically significant difference among and between these parameters ($p > 0.05$).

The biological half-life of norfloxacin ranged from 3.98 to 5.36 hours. These results are in good agreement with those previously published data.

6. The correlations between the in vitro and the in vivo data for four different brands of norfloxacin seemed to be meaningless. When brand C was excluded due to the the poor disintegration time and dissolution rate constant, the correlation coefficient test for brands A, B and D revealed that there were no statistically significant correlation between the in vitro parameters with any of the in vivo parameters at all, unless the disintegration times versus the C_{max} appeared to be correlative ($0.05 < p < 0.1$). This indicated that the disintegration time might affect only the rate of absorption. However the in vitro parameters obtained in this investigation might not be used precisely to predict the bioavailability of norfloxacin tablet.