CHAPTER V

CONCLUSIONS

1. All four brands of 10 mg simvastatin tablets met the general requirements for the content of active ingredient which ranged from 97.11 to 103.10%.

2. Dissolution profile for each brand was performed in 0.05 % SLS in 0.01 M monobasic sodium phosphate buffer (pH 5.5 ± 0.02). The rank order of the dissolution rate constant was D>A>B>C. The dissolution rate of brand C was significant by ($p<0.05$) lower than that of brand A while the other two brands were not significantly different.

3. The bioavailability of brands A, B, C and D were studied in twelve healthy mongrel dogs, the best paradigm for man. An oral single dose of twenty-10mg simvastatin film-coated tablets was administered to each dog. Plasma simvastatin hydroxy acid concentrations were determined by HPLC with organic solvent protein precipitation and detected by UV detector at 238 nm. This analytical method demonstrated good reproducibility and precision from the validations. The individual plasma data were analyzed following a model independent manner. The observed values of relevant pharmacokinetic parameters (C_{max}, t_{max} and AUC) were used for bioavailability comparison.

The mean peak plasma concentrations for the four different brands ranged from 148.74 to 170.46 ng/ml.

The average time to peak plasma concentrations of the four different brands ranged from 1.38 to 2.25 hr.

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The area under the plasma concentration-time curves from 0 to 8 hr of four brands ranged from 438.03 to 484.08 ng hr/ml.

There were no statistically significant differences of the log AUC ($p > 0.05$, ANOVA) and t_{max} ($p > 0.05$, Friedman test) values between the four brands, but there were significant differences of the log C_{max} value between the four brands (90% confidence intervals). It was concluded that all four brands were considered to be bioequivalent with respect to the extent of drug absorption because AUC is the most precise and important parameter in comparative bioavailability. C_{max} and t_{max} , on the other hand, are more variable than AUC and their differences should be considered as less critical than AUC.

The average elimination rate constants obtained were 1.31, 1.12, 1.92, and 1.05 hr^{-1} for brand A, B, C and D, respectively.

The mean elimination half-life of simvastatin hydroxy acid ranged from 0.47 to 1.66 hr.

4. The mean percent reduction in TC of brand A, B, C and D were 1.8 ± 1.3, 3.3 ± 2.2, 2.6 ± 5.0 and 1.7 ± 1.4, respectively. There was no statistically significant difference between the mean in TC level at 2 hr after administration and the initial value within each brand ($p > 0.05$, paired student's t-test).

5. The correlation study between the *in vitro* and *in vivo* data of the four different brands of 10 mg simvastatin film-coated tablets revealed that there

was no statistically significant correlation of all parameters between the two data sets. Therefore, it was not recommended to use the *in vitro* data obtained under the present testing condition to predict the *in vivo* bioavailability of simvastatin film-coated tablets.

6. The further clinical trial of these four brands of simvastatin tablets in hypercholesterolaemia patients could be performed to confirm the present pharmacokinetic results and compare medical efficacy in multiple dose administration.