Chapter IV

Conclusions

In Vitro Studies

1. The conventional wet granulation method could produce the granules of each formulation which had only a little difference in physical properties such as moisture content, particle size distribution, flowability and compressibility. The method also offered good homogeneity of drug, polymer and/or lactose in the matrices of which theophylline content ranging from 100.01-104.48 %.

2. The hardness of compressed tablets prepared from these granules was controlled at about 9.90 - 11.05 kp. Tablets of all formulations, with and without lactose, were not disintegrated in water within two hours.

3. The rate of drug release from tablets without lactose varied as the quantity of Methocel E4M.

4. The pH of dissolution medium had an effect on the release characteristics and all this depended upon the quantity of Methocel E4M in the formulation. For the tablets with 5 % and 7 % polymer, the release of theophylline in pH 6.8 buffer was slower than in 0.1 N HCl. For

the tablets with 10 % polymer, the release of drug in 0.1 N HCl was much more slower while the release in pH 6.8 slightly decreased, which made the release profiles in both medium more similar.

5. An increase of lactose from 20 to 40 % was found to proportionally increase the rate of drug dissolution. The tablets with 30 % lactose was considered to be the most suitable of all lactose-containing tablets because it could provide constant drug release over twelve hours, which was comparable to Theo-Dur®, with totally cumulative amount of about 80 %.

6. The dissolution rate constant of tablets prepared by different methods including Theo-Dur® and Nuelin® were ranked as follows : B>C>E>A>D. Nuelin® had the highest constant of all ($p < 0.05$) while Theo-Dur® and the other three experimental tablets were not significantly different ($p > 0.05$).

In Vivo Studies

7. The average values of C_{max}, t_{max} and AUC_0^∞ of all formulations ranged from 68.19 - 82.11 mcg/mL, 8.50 - 10.88 hr and 2.02 - 2.16 mg-hr/mL respectively. There were no statistically significant differences in these relevant bioavailability parameters among all formulations ($p > 0.05$). Therefore, it could be stated that the experimental tablets prepared by different techniques (C, D, E) were bioequivalent to

Theo-Dur® and Nuelin® and among each other, too.

8. The average values of K_a, K_{el} and $t_{1/2}$ of all formulations were ranged from 0.15 - 0.20 hr^{-1}, 0.07 - 0.10 hr^{-1}, and 7.18 - 11.01 hr respectively. Statistical comparison indicated that the absorption rate constants of all formulations were not significant different ($p > 0.05$), which was the same as biological half-life, while the elimination rate constant of product E was significantly more ($p < 0.05$) than that of Nuelin® and product D.

9. The AUC_0^∞ was found to have statistically significant correlation with the dissolution rate constant ($p < 0.05$). The other two bioavailability parameters, C_{max} and t_{max}, did not have this relationship. For this reason, it might be possible to use the dissolution rate consant in the early step of formulation development to predict the AUC_0^∞ of sustained-release theophylline tablets.

Suggestion

1. In spite of the existing bioequivalences between each of the experimental theophylline sustained-release tablets and Theo-Dur®, the selection of the suitable manufacturing method are to be considered. The conventional wet granulation may be the most simple method of all. However, it is difficult to uniformly disperse the retarding polymer in the matrices owing to its high viscosity. This directly causes the quite high

variation of drug release among tablets of either the same or different batch. On the other hand, the manufacturing using techniques of spray drying and fluidized-bed coating could produce the matrices of more homogeneous distribution of polymer when adjusting the appropriate precess condition. Nevertheless, both methods require the specific apparatus which may be the limitation of their use.

2. Because this study is conducted in rabbits and do not aim to extrapolate the animal results to human. Therefore, it is necessary to carry out the further investigation in human in order to assess the clinical efficacy of the three experimental products.