CHAPTER IV
CONCLUSIONS

In vitro studies :

In this study, the stavudine pellets were prepared by extrusion and spheronization process. The pellets possessed the spherical shape, smooth surface, and narrow size distribution. The factors which affected the appearance and physical properties of stavudine pellets were spheronizer speed and spheronization time.

Increasing spheronizer speed and spheronization time lead to sphericity, smooth surface, and mean particle size of the pellets were obtained increased. Pellets using Avicel® PH101 as diluent, were spherical and had a narrow size distribution with high desirable particle size and high flow rate compared with pellets using lactose. The pellets also have a low angle of repose, a low percent friability, and no difference between bulk density and tapped density. The best formulation for preparing stavudine pellet consisted of 40%w/w of stavudine, 60%w/w of Avicel® PH101 and %65w/w of water base on a dry basis during wet mass process. The suitable condition for preparing stavudine pellets was spheronizer speed of 860 rpm with spheronization time at 10 min.

The stavudine controlled released pellets were prepared by coating the previous core pellets with Ethylcellulose aqueous dispersion (Surelease®) and HPMC E15 LV via Wurster column process. The composition and amount of film coating were modified. The ratio of Surelease® to the HPMC E15 LV had a major effect on the drug release rate. High proportions of HPMC E15 LV component in Surelease® membrane caused a rapid release of drug even at high coating loads due to leaching of the HPMC from the Surelease® film, which led to the formation of pores. The pores were thought to act as points for entry of dissolution medium through the film into the core and consequent dissolution and release of drug from pellets. The combination of Surelease® and HPMC E15 LV of 95 : 5 at 20% coating level provided the drug release profile as requirement and no crack was found on the film surface after dissolution test. The mechanism of drug release from coated pellets followed zero-order kinetic and this formulation was chosen to study in vivo.

The in vitro-HPLC analytical method was developed and validated over a concentration range of 0.01-0.12 mg/ml. The chromatographic conditions proved to be simple, accurate, precise and specific. The mobile phase consisted of methanol : H_2O (20 : 80), the analyses were conducted with Zobrax Eclipsex DB-C_{18} reversed-phase column at ambient temperature with flow rate of 1.0 ml/min, detection wavelength at 260 nm, injection volume of 20 µl and retention time of stavudine was 3.8 mins.

In stability study, drug content and dissolution profiles were determined and compared with the results at initial time. Both products were successful to keep stable for at least 6 months when products were stored at 30 ^{0}C, 65 %RH and at 40 ^{0}C, 75 %RH.

In vivo studies :

The high-performance liquid chromatographic method for determination of stavudine in plasma has been developed and validated. Stavudine and zidovudine (internal standard) were extracted by acetronitrile protein precipitation. The method was validated over a concentration range of 0.5-20 µg/ml. The mobile phase consisted of 0.025 M Ammonium acetate (pH 3.8) : MeOH (70 : 30), the analyses were conducted Apollo -C_{18} reversed-phase column at ambient temperature with flow rate of 1.0 ml/min, detection wavelength at 265 nm, injection volume of 20 µl and retention time of stavudine was 4.8 mins. This method showed specificity, accuracy and precision. The bioanalytical assay was also validated to prove the stability of plasma samples.

The comparative bioavailability of d4T pellet and Zerit® IR was conducted in 12 White New Zealand rabbits using randomized replicated crossover design with 2 weeks washout period between treatments.

After an orally single dose administration, serial blood samples were collected for 24 hours and stavudine plasma concentrations were determined by HPLC.

Relevant pharmacokinetic parameters of the two products were calculated from stavudine plasma concentration-time profiles and compared.

The comparison of pharmacokinetics parameters between stavudine pellets and Zerit® IR indicated that the extent of drug absorption depended on dose given. Two products are different in rate absorption. However, stavudine pellet dosage form can be an extended release product and this pharmaceutical dosage form had good trend to reduce the risk of dose dumping.