CHAPTER 6

SUMMARY & CONCLUSION
6.1 Summary

✓ Zidovudine is widely used antiviral drug. This drug gets absorbed rapidly and reaches peak plasma concentration immediately. Like other nucleoside elimination, half-life of Zidovudine is 3-4 hrs. Thus, necessitating frequent administration leading to many adverse drawbacks. To overcome these adverse effects; Zidovudine extended release matrix tablets were formulated.

✓ For the solid state characterization of Zidovudine API, different tests were performed like FTIR, optical microscopy, powder X-ray diffractometry (XRD), differentials scanning calorimetric (DSC) and dynamic vapor absorption (DVS). Stress stability data was also generated on Zidovudine API. API and excipient compatibility was conducted at different ratios using moist and dry conditions. Samples were kept at 50°C and 40°C/75 % RH and evaluated for impurities.

✓ Matrix tablets were prepared with composition qualitatively similar to that of the innovator IR tablet except controlled release excipient i.e. HPMC.

✓ Zidovudine matrix tables were prepared using both dry and wet granulation techniques. Dry granulation method showed processing issues so, this method was not continued further. In wet granulation technique, non-aqueous granulation with IPA was tried but the residual solvent content in final coated tablet was out of ICH specifications. Finally, aqueous granulation was adopted for development.

✓ Different design batches were prepared using different viscosity polymer such as HPMC K4M, K15M and K100M in different polymer ratio i.e. 20-25%. All these formulations were characterized for weight variation, hardness, friability and in vitro dissolution studies. Based on release profile of formulation, ZID/11 was selected as optimum formulation which was further subjected for in vivo animal study. Pharmacokinetics of ER formulation was compared with marketed IR formulation in rabbit.

✓ Process optimization was performed on prototype formulation and different critical process parameters were studied like dry mixing time, kneading time, inlet drying temperature, milling parameters and lubrication time.
✓ Scale up batch (ZID/SCA/01) was manufactured with final composition at higher scale (1X-5X) and all process parameters were optimized. Further, this batch was subjected to stability study for 3 months at 40°C/75% RH.

6.2 Conclusion

✓ Characterization of Zidovudine API and excipients were found satisfactory. IR spectrum of Zidovudine API was found comparable with standard spectrum. Assay of API was found to be 99.70% w/w. The DSC thermogram of drug test sample recorded single sharp melting endotherm with onset temperature of 119.09°C, similar to that of reported in literature. From the optical microscopy, drug substance appeared crystalline in shape and some longer shaped particles were seen under cross-polarized light.

✓ Based on excipient compatibility data, all the excipients were found compatible with drug.

✓ From the formulation development study, aqueous granulation process seemed to be more robust and satisfactory physical attributes were obtained.

✓ Based on in vitro dissolution profile, batch ZID/11 showed satisfactory dissolution, so this batch was finalized for in vivo study.

✓ In the formulation ZID/11 evaluated for in vivo drug release profile, data of conventional tablet was fitted in first order equation ($r^2 = 0.936$), while drug release data of batch ZID/11 matrix tablets showed good fit into the Higuchi equation ($r^2 = 0.991$). Tablets of batches ZID/11 showed high linearity with Korsmeyer equation ($r^2 = 0.999$) indicating combined effect of diffusion and erosion mechanisms for controlled drug release.

✓ The formulated matrix tablets (batch ZID/11) showed significantly lower $C_{\text{max}}$ than conventional tablets ($P < 0.05$) and required significantly more time to reach $C_{\text{max}}$ ($T_{\text{max}} 4.3 \pm 0.2$ hours) as compared with conventional tablets ($T_{\text{max}} 1.45 \pm 0.2$ hours). However, these tablets maintained constant plasma concentration above 20 hours.

✓ The in vitro & in vivo (IVIVC) correlation was determined by plotting a graph showing the fraction of drug absorbed versus the fraction of drug released in vitro. A high value of correlation coefficient ($r^2 = 0.9082$) suggested good correlation between in vitro & in vivo (IVIVC) studies. This can be expected to reduce the frequency of administration and
decrease the dose-dependent side effects associated with repeated administration of conventional tablets.

✓ Scale up of finalized formulation was carried out successfully after process optimization. Based on optimization study, following parameters were finalized.

Dry mixing time 5 mins, Kneading time 4 mins 50 sec, inlet drying temperature $60^\circ$C $\pm 5^\circ$C ($55^\circ$C - $65^\circ$C), LOD of granules 1.5 - 2.0% and compression speed 30 - 60 rpm.

✓ Stability data of scale up batch showed that all the known and unknown impurities were found to be within limit as per ICH guideline.

✓ Finally, stable Zidovudine ER matrix tablets were manufactured and scale up study was performed successfully.
PART II

Preparation, Optimization and Scale up of Extended Release Matrix Tablets of Nevirapine 400 mg