CHAPTER 8

SUMMARY AND CONCLUSIONS
8.1 LAMIVUDINE MATRIX TABLETS

The use of cellulose ether polymers in oral controlled release dosage forms, such as matrix tablets was investigated. Hydroxypropyl methylcellulose (HPMC) and Polyethylene oxide (PEO) polymers were used to formulate and control the release of active ingredients from the hydrophilic matrix tablet formulations. The processing parameters were developed and optimized in order to achieve desired rate of drug release from the prepared drug delivery system. Lamivudine standard calibration curve was constructed. The linearity of the standard curves was excellent with correlation coefficient in the range of 0.997-0.998.

Solubility study indicated the high solubility of the drug in the pH range of 1 to 7.

Dissolution of conventional marketed lamivudine formulation yielded more than 85 % of drug in 15 minutes in all the formulations. DSC results demonstrated a sharp endothermic peak for LAMI at 179-180°C, which corresponded to its melting point. FTIR results demonstrated the characteristic peaks confirm the pure lamivudine. Physical properties of the prepared granules for matrix tablets results good flow properties.

The matrix tablets of lamivudine were compressed with 9 mm flat faced round punch. Influence of polymer concentration and combination of polymers was investigated with HPMC and combination of HPMC and PEO. The matrix tablets prepared with combination of HPMC K 100 M and PEO, showed slower release when
compared the matrix tablets prepared with HPMC K 100 M alone. Variation in the polymer concentration yielded different drug release patterns. Effect of combination of polymer also influenced the drug release. Variation in drug release at initial hr was observed in the formulations. The release was extended up to 14 hr and more. Good correlation was observed in zero order plots with a correlation coefficient of 0.984-0.997. The release kinetics were best fitted to the Higuchi model kinetics, indicated the drug release mechanism was diffusion controlled.

The in vitro half life was found to be 6.96 - 8.16 hr in matrix tablets prepared with combination of HPMC and PEO and 5.39-7.96 for matrix tablets prepared with HPMC alone is clearly indicating the drug release for prolonged period.

Magnesium stearate concentration was optimized and 1 % magnesium stearate yielded good results w.r.t physical properties. DSC and FTIR studies demonstrated that there is no drug-polymer interaction at initial stage and during the stability studies at 40°C/75% RH.

Effect of tablet surface area (SA) and Surface area/volume (SA/Vol) on drug release was studied. The results suggested that the drug release mainly depended on the change in the SA/Vol values but not with the change in the SA. The release rate of Lamivudine increased with increasing SA/vol. The release rate was expected to be directly proportional to the SA/Vol.
The results of dissolution suggested that the prepared matrix tablets were stable up to three months. This was confirmed by the DSC and FTIR studies. Moisture uptake study suggested that the prepared matrix tablets and granules were less sensitive to 50% relative humidity.

**8.2 LAMIVUDINE MICROCAPSULES**

Lamivudine microcapsules were prepared with CAP, CAB, EC and HPMCP by using solvent evaporation method. The emulsion solvent evaporation method based on emulsification of the polymer solution containing the drug in an immiscible liquid medium, followed by evaporation of solvent to produce the microcapsules, was found suitable for microencapsulation by CAP, CAB, EC and HPMCP.

All the polymer microcapsules prepared were discrete, spherical and free flowing. The sizes could be separated and a more uniform size range of microcapsules could readily be obtained by sieving.

Good entrapment efficiency achieved with these polymers.

SEM photographs indicated that CAP, CAB, EC and HPMCP microcapsules were discrete, nearly spherical and covered with continuous coating of the polymer.

The microcapsules gave slow release of lamivudine spread over extended period of time. Combination of CAP and CAB yielded slower release than CAP and CAB alone.
The release kinetics was best fitted to the Higuchi model in the formulation prepared with CAP and EC. This confirms that the drug release was diffusion controlled. The release kinetics was best fitted to the Zero order model in the microcapsules prepared with CAB, HPMCP and combination of CAP and CAB.

DSC studies and FTIR of various microcapsules indicated no interaction between drugs and polymers employed in micro encapsulation.

Results of accelerated stability yielded good correlation in the assay at initial time and 3 months at 40°C /75% RH indicating good stability which was further confirmed by DSC and FTIR study.

**8.3 ZIDOVUDINE MATRIX TABLETS**

Zidovudine matrix tablets were prepared with HPMC K 100 M. Wet granulation process was found to be highly feasible process for the zidovudine matrix tablets.

Zidovudine standard calibration curve was constructed. The linearity of the standard curves was excellent with correlation coefficient in the range of 0.992. Solubility study showed the high solubility of the drug in the pH range of 1 to 7.

Dissolution of conventional marketed lamivudine formulation yielded more than 88 % of drug in 15 minutes in all the buffers.
DSC and FTIR results confirm the purity of Zidovudine.

The physical characterization of the granules yielded good flow properties of the zidovudine with HPMC K 100M.

The matrix tablets of zidovudine were compressed with 15 X 7.5 mm partial scored capsule shaped punch embossed with ‘E’ on upper punch and ‘38’ on lower punch. Good physical properties were observed with aesthetic look. The friability and drug content of the matrix tablets was found within the pharmacopoeial limits.

The in vitro dissolution of the matrix tablets prepared with HPMC K 100 M released 50-94 % of the drug in 12 hr depending on the proportion of the polymer used in the formulation.

The physical observation of the matrix tablets showed good gel forming characteristics and good swelling property.

Feasibility study of zidovudine matrix tablets with different rate controlling polymers such as Carbopol 971, Eudragit L100 and PEO was investigated. Different granulation processes such as direct compression, wet granulation with water and wet granulation with IPA were studied. The physical properties of the granules with each polymer were studied.

The results of zidovudine matrix tablets prepared with PEO suggested that wet granulation with water is highly feasible with excellent flow properties. The directly compressible blend and wet granulation using IPA yielded fine powder with fair flow property. In vitro dissolution of the matrix tablets with PEO yielded above 90 % of
the drug release in 12 hr. The release kinetics followed first order with diffusion release mechanism.

The results of zidovudine matrix tablets prepared with Carbopol 971 suggested that wet granulation with water was not feasible because of lump formation. The directly compressible blend yielded fine powder with poor flow property. Wet granulation with IPA resulted in good flow properties. In vitro dissolution of the matrix tablets with Carbopol 971 yielded above 27% of the drug release in 12 hr. Decrease in the Carbopol concentration showed 60% of the drug release in 12 hr. The release kinetics followed mixed order with diffusion release mechanism.

The results of zidovudine matrix tablets prepared with Eudragit L 100 suggested that all the three granulation process such as wet granulation with water, directly compressible blend, and wet granulation with IPA yielded good flow properties and good physical properties. However, wet granulation with IPA yielded more consistent results. In vitro dissolution of the matrix tablets, prepared with direct compression method release around 97% of drug in 7 hr. The matrix tablets prepared with water and IPA granulation yielded 100% of the drug release in 12 hr. The release kinetics followed zero order with diffusion controlled release mechanism.

DSC and FTIR studies of initial and accelerated stability samples demonstrated that there is no drug polymer interaction.
8.4 ZIDOVUDINE MICROCAPSULES

Zidovudine microcapsules were prepared with Eudragit RL 100 and Eudragit RS 100 by using solvent evaporation method.

The solvent evaporation method was found suitable for microencapsulation of Zidovudine with RL 100 and Eudragit RS 100.

All the polymer microcapsules prepared were spherical discrete and free flowing. The sizes could be separated and a more uniform size range of microcapsules could readily be obtained by sieving.

Good entrapment efficiency achieved in all the formulations.

Microscopic photographs indicated that the microcapsules were discrete, free flowing. Spherical microcapsules were formed with Eudragit RL 100 while irregular shaped microcapsule were obtained with Eudragit RS 100.

The microcapsules gave slow release of lamivudine spread over extended period of time.

The release kinetics was best fitted to the Zero order model with diffusion mechanism.

DSC studies and FTIR of various microcapsules indicated no interaction between drugs and polymers employed in microencapsulation.
8.5 STAVUDINE MATRIX TABLETS

Stavudine matrix tablets were prepared using HPMC 100 K LV. Various formulation parameters and process parameters were studied. Patent non infringing formulation strategies were developed for the matrix tablets.

Stavudine standard calibration curve was constructed. The linearity of the standard curves was excellent with correlation coefficient in the range of 0.9982-0.9998.

Solubility study indicated the high solubility of the drug in the pH range of 1 to 7.

Dissolution of conventional marketed lamivudine formulation yielded more than 90 % of drug release in 5 minutes from all the formulations.

DSC and FTIR studies of the pure drug confirmed the lamivudine.

Lamivudine immediate and extended release granules were prepared to develop various formulation strategies. Good flow properties were observed in the granules.

Compression coated tablets were prepared with immediate and extended release granules. Good physical properties were observed. Zero order release was observed with diffusion release mechanism in the extended release matrix tablets used in the compression coated tablets.
Initial rapid release of the drug during first hour and extended for prolonged period was observed in the prepared compression coated tablets.

Bi-layer immediate-extended release matrix tablets were prepared. The physical properties of the prepared bi-layer matrix tablets were within the pharmacopoeial limits.

In vitro dissolution studies from the bi-layer tablets yielded a rapid initial drug release and the remaining drug was released for a prolonged period of time.

Immediate and extended release mini tablets were compressed with 5 mm round punch. The physical and chemical properties were within the pharmacopoeial limits.

The prepared mini tablets were filled in the size 0 transparent HPMC capsules. The in vitro dissolution studies were conducted and the results demonstrated that a rapid drug release was observed. The release from the extended release mini matrix tablets was prolonged up to 12 hr. However the drug release was faster in the mini matrix tablets when compared with the extended release matrix tablets prepared in the compression coated tablets. This is because of the larger surface area of the mini matrix tablets.

Multiple mini tablets for immediate and extended release of stavudine were prepared with 3 mm multi tip punches. The physical and chemical properties of the prepared multiple mini tablets were within the pharmacopoeial limits. Immediate rapid drug release was observed for the immediate multiple mini tablets. Prolonged drug
release was observed from the extended release tablets. However the release was faster in the extended release matrix tablets of FS-11 when compared with the matrix tablets of FS-2 and FS-9. This was because of the larger surface area of the tablets. FTIR and DSC studies demonstrated that there is no drug and polymer interaction.

8.6 STAVUDINE MICROCAPSULES

Stavudine microcapsules were prepared with CAB, EC and HPMC by using solvent evaporation method.

The emulsion solvent evaporation method was found suitable for microencapsulation of Stavudine with CAB, EC and HPMC.

All the polymer microcapsules prepared were spherical discrete and free flowing. The sizes could be separated and a more uniform size range of microcapsules could readily be obtained by sieving.

SEM photographs indicated that the microcapsules were discrete, free flowing and spherical.

In vitro dissolution studies demonstrated that the drug release was mainly depended on the type of polymer and polymer proportion used in the formulation. The release kinetics was best fitted to the first order model with diffusion mechanism.

DSC studies and FTIR of various microcapsules indicated no interaction between drugs and polymers employed in microencapsulation.
8.7 In vivo bio availability studies of Lamivudine matrix tablets in rabbit

In vivo clinical study of Lamivudine extended release tablets was performed in healthy rabbits.

HPLC method for the determination of lamivudine was developed.

Pharmacokinetic analysis of lamivudine in rabbit indicated rapid drug absorption for lamivudine conventional formulation. The $C_{\text{max}}$ of conventional tablet has reached in 1.6 hr, whereas in case of lamivudine matrix tablets, the peak plasma concentration achieved in 4 hr. A five-fold increase in AUC was observed in the lamivudine matrix tablet when compared with the conventional tablets.

8.8 Conclusions

The results of the present research work have potential industrial application. The results suggested that the prepared formulations were stable and globally acceptable. In the wake of patentability of extended release dosage forms, the present work has huge scope for the pharmaceutical industry to apply the formulation technology of this research work for further development.
8.9 FUTURE PROSPECTIVE

The results of the present research work gives idea about the formulation of various antiretroviral drugs as extended release dosage forms. The research work was done with economical, commercial and regulatory point of view. This study will definitely useful for the researchers and scientists working in the same field. The final products developed in the research may be commercialized after the establishment of the safety and efficacy in the human volunteers.

8.10 ON GOING RESEARCH

Formulation of oral floating extended release dosage forms of Atazanavir.

Formulation enteric coated extended release matrix tablets of Didanosine.