CHAPTER X

SUMMARY AND CONCLUSIONS

Ritonavir, a potent widely prescribed antiretroviral drug, belongs to Class II under 'BCS' and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Ritonavir is practically insoluble in water and aqueous fluids. As such oral absorption of ritonavir is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. In the case of poorly soluble drugs formulation variables greatly influence their dissolution rate and bioavailability from solid dosage forms.

The major objectives of the investigation are (i) to evaluate the effect of formulation variables such as binders, superdisintegrants, solubilizers and a new diluent Prosolve on the tablet qualities and dissolution rate of ritonavir from compressed tablets with a view to optimize the formulation of ritonavir tablets, (ii) to study the complexation of ritonavir with βCD and HPβCD and to evaluate the feasibility of employing cyclodextrin complexation for enhancing the solubility, dissolution rate and bioavailability of ritonavir. (iii) To prepare and evaluate solid dispersions of ritonavir employing various water soluble and water dispersible carriers for enhancing the dissolution rate and bioavailability of ritonavir. (iv) To evaluate a new class of tablet excipients, called superdisintegrants as carriers for solid dispersion systems, (v) To evaluate the feasibility of formulating selected solid dispersions and cyclodextrin complexes of ritonavir into compressed tablets and (vi) to evaluate the pharmacokinetics and bioavailability of ritonavir from selected formulated products.

The effect of seven binders (acacia, sucrose, PVP, methyl cellulose,
HPMC, starch paste and gelatin), five superdisintegrants (Primogel, croscarmellose sodium, crospovidone, Prosolve and modified starch), three solubilizers, (Tween 80, PEG 600 and SLS) and various concentrations of Prosolve (a new diluent) on the tablet qualities and dissolution rate of ritonavir from the tablets was studied. A total of 28 formulations of ritonavir tablets were prepared by wet granulation method and the tablets were evaluated for content of active ingredient, hardness, friability, disintegration time and dissolution rate.

From the results obtained the following conclusions are drawn.

1. The binder used has significant influence on the disintegration time and dissolution rate of ritonavir from the tablets.

2. Much variations were observed in the disintegration and dissolution characteristics of the tablets prepared with various binders.

3. The order of performance of binders based on increasing dissolution rate and dissolution efficiency was acacia > starch paste > sucrose > PVP > gelatin > HPMC > MC.

4. Tablets formulated with acacia, starch paste and sucrose exhibited higher dissolution rates and dissolution efficiency values fulfilling all other official (I.P) and GMP requirements of compressed tablets.

5. The superdisintegrant used also has significant influence on the dissolution rate of ritonavir from the tablets. The order of performance of the superdisintegrants based on increasing dissolution rate was Prosolve > modified starch > croscarmellose sodium > Primogel > crospovidone.

6. The aqueous solubility of ritonavir was markedly enhanced by the
solubilizers. The order of increasing enhancement in the solubility of ritonavir with various solubilizers was Tween 80 (14.77 fold) > PEG - 600 (9.28 fold) > SLS (5.47 fold).

7. Ritonavir tablets of good quality, fulfilling the official (I.P) and GMP requirements could be formulated employing the three solubilizers, Tween 80, PEG - 600 and SLS.

8. The dissolution rate and dissolution efficiency of ritonavir tablets could be significantly enhanced by incorporating the solubilizers (Tween 80, PEG - 600 and SLS) in the tablets. The order of increasing dissolution rate observed with various solubilizers was Tween 80 > PEG - 600 > SLS.

9. Ritonavir tablets of good quality, fulfilling the official I.P. and other requirements, could be prepared employing Prosolve as diluent by wet granulation method using PVP and acacia as binders.

10. The dissolution of ritonavir was rapid and higher from tablets formulated with Prosolve when compared to control formulations without Prosolve.

Solid dispersion technologies employing water soluble and water dispersible carriers were tried for enhancing the dissolution rate and oral bioavailability of ritonavir. Solid dispersions of ritonavir in three water soluble polymers (HPMC, PVP and HPC-L) and four water dispersible superdisintegrants (Prosolve, Primogel, crospovidone and croscarmellose sodium) were prepared using different ratios of drug and carrier in each case. A total of 21 solid dispersions of ritonavir were prepared and the dispersions prepared were evaluated by dissolution rate, XRD, DSC and FTIR studies. The feasibility of formulating selected solid dispersions into tablets and the dissolution
characteristics of the resulting tablets were also investigated. From the results obtained the following conclusions were drawn.

11. The dissolution of ritonavir from all the solid dispersions prepared was rapid and several times higher than the dissolution of ritonavir as such.

12. Among three water soluble carriers dispersions, PVP gave highest enhancement (9.93 fold) in the dissolution rate of ritonavir. The order of increasing dissolution rate observed with various water soluble carriers was PVP>HPC-L>HPMC.

13. Water dispersible superdisintegrants gave much higher enhancement in the dissolution rate of ritonavir.

14. Among the superdisintegrants tested, croscarmellose sodium and crospovidone gave markedly higher enhancement in the dissolution rate of ritonavir, 47.24 and 28.75 fold respectively. The order of increasing dissolution rate observed with various superdisintegrants was croscarmellose sodium > crospovidone> Primogel > Prosolve.

15. Crystalline ritonavir is converted in to amorphous form in the solid dispersions as evidenced by XRD studies.

16. No interaction was observed between ritonavir and the carriers (PVP and croscarmellose sodium) used in the solid dispersions by FTIR and DSC studies.

17. Solid dispersions of ritonavir in PVP, crospovidone and croscarmellose sodium could be formulated into tablets by both wet granulation and direct compression methods.
18. Ritonavir tablets formulated employing solid dispersions gave much higher dissolution rates and \( \text{DE}_{30} \) values when compared to plain tablets.

Complexation of ritonavir with \( \beta \)-cyclodextrin (\( \beta \text{CD} \)) and hydroxyl propyl \( \beta \)-cyclodextrin (\( \text{HP} \beta \text{CD} \)) was studied by phase solubility studies. The feasibility of enhancing the solubility and dissolution rate of ritonavir from tablets by cyclodextrin complexation was also studied. Ritonavir - CD tablets were formulated and evaluated. From the results obtained the following conclusions are drawn.

19. Ritonavir formed inclusion complexes with \( \beta \text{CD} \) and \( \text{HP} \beta \text{CD} \) at a 1:1 M ratio in solution. The complexes formed are quite stable.

20. The solubility and dissolution rate of ritonavir were markedly enhanced by complexation with \( \beta \text{CD} \) and \( \text{HP} \beta \text{CD} \).

21. Ritonavir - \( \beta \text{CD} \) tablets exhibited significantly higher dissolution rate and efficiency than plain ritonavir tablets.

22. A 15.35 fold increase in the dissolution rate of ritonavir was observed with ritonavir - \( \beta \text{CD} \) (1:2) tablets when compared to plain tablets.

Pharmacokinetic and bioavailability evaluation of selected ritonavir products, which exhibited markedly higher dissolution rates, was carried out in rabbits as per a crossover RBD. Ritonavir, ritonavir - croscarmellose sodium (1:1) solid dispersion and ritonavir - \( \beta \text{CD} \) (1:2) Kneaded complex were tested for \textit{in vivo} performance. The products were tested at a dose of 10 mg / kg of ritonavir. Plasma concentration of ritonavir was determined by a known HPLC method. From the time Vs plasma concentration data various pharmacokinetic parameters
such as $C_{\text{max}}$, $T_{\text{max}}$, AUC, $K_{\text{el}}$, $t_{1/2}$ and $K_a$ were calculated in each case. From the results obtained the following conclusions are drawn.

23. Pharmacokinetic studies indicated rapid and higher oral absorption of ritonavir when administered as solid dispersion in croscarmellose sodium (SDF 20) and as ritonavir - $\beta$CD (1:2) complex.

24. The absorption rate constant ($K_a$) was increased from 0.4141 h$^{-1}$ for ritonavir to 4.606 h$^{-1}$ and 4.606 h$^{-1}$ respectively with ritonavir - croscarmellose solid dispersion (SDF 20) and ritonavir $\beta$CD (1:2) complex.

25. $(\text{AUC})_{0-\infty}$ was increased from 31.23 µg.h/ml for ritonavir to 81.06 µg.h/ml and 83.83 µg.h/ml for solid dispersion SDF 20 and $\beta$CD (1 : 2) complex respectively.

26. The results of stability studies indicated that the ritonavir tablet formulations developed in the present study are quite stable with regard to various physical characters such as hardness, friability, disintegration and dissolution rate.

27. The rapid dissolution characteristics of the ritonavir tablets formulated employing its solid dispersion in croscarmellose sodium and $\beta$CD complexes remained unaltered.
Significant Contributions and Recommendations

The results of the present investigation clearly indicated that the binder and super disintegrant used have significant influence on the dissolution rate of ritonavir from the tablets. Acacia, starch paste and sucrose were found to be good binders for ritonavir tablets giving higher dissolution rates apart from fulfilling all other official (I.P) requirements of compressed tablets. Prosolve, modified starch and croscarmellose sodium were found to be better super disintegrants for ritonavir tablets giving higher dissolution rates and dissolution efficiency values. Solubilizers such as Tween 80, PEG 600 and SLS could be incorporated in the tablets to enhance the dissolution rate of ritonavir from tablets. Prosolve can also be added as a diluent to ritonavir tablets to enhance their dissolution rate.

The dissolution rate and the bioavailability of ritonavir could be markedly enhanced by solid dispersion technology and cyclodextrin (βCD and HPβCD) complexation. Superdisintegrants (croscarmellose sodium and crospovidone) and βCD gave much higher enhancement in the dissolution rate of ritonavir. These solid dispersions and βCD complexes could be formulated into tablets with higher dissolution rates. Ritonavir croscarmellose solid dispersion and ritonavir-βCD complexes also exhibited higher rates and extent of absorption (bioavailability) upon oral administration when compared to ritonavir.

Thus, solid dispersion in superdisintegrants such as croscarmellose sodium and crospovidone and complexation with β-cyclodextrin are recommended for enhancing the dissolution rate and bioavailability of ritonavir, a BCS- Class II drug. These solid disperse systems and β-CD complexes could be formulated into tablets retaining their enhanced dissolution rate characteristics.