CHAPTER I

INTRODUCTION AND OBJECTIVES OF THE INVESTIGATION

Bioavailability is the most important property of a dosage form. It is the ability of the dosage form to deliver the active ingredient to its site of action in an amount sufficient to elicit the desired pharmacological response. Bioavailability is defined more precisely as the rate and extent of absorption of a drug from its dosage form into the systemic circulation. It is affected by a number of factors related to the drug, dosage form and patient. Dosage form related factors which can produce profound differences in the drug bioavailability include formulation and manufacturing variables such as particle size, the chemical form, solubility of the drug, the type and quantity of excipients used, the compaction pressure etc. It is well known that the drug bioavailability and efficacy are severely limited by its poor aqueous solubility and dissolution rate. The drug in a solid dosage form (tablet) must undergo dissolution before it is available for absorption in the gastrointestinal tract. Dissolution forms the rate limiting step in the absorption of drug from solid dosage forms especially when the drug is poorly soluble.

Many of the modern drugs belong to the Class II category under biopharmaceutical classification system\(^1\) (BCS), which are characterized by low solubility and high permeability. These drugs are insoluble in water and aqueous fluids in the pH range of 1.0 - 7.5 and exhibit low and variable dissolution and bioavailability. There is a great need to develop technologies for these 'BCS' Class II drugs for enhancing their dissolution rate and bioavailability. The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the
most challenging aspects of drug product development.

Ritonavir, a widely prescribed anti-retroviral drug$^{2-5}$, 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. Its aqueous solubility was reported$^6$ to be 2.56 mg/100 ml. As such oral absorption of ritonavir is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability.

The poor aqueous solubility of the drug gives rise to difficulties in the formulation of solid dosage forms such as tablets and capsules. In the case of poorly soluble drugs formulation variables greatly influence their dissolution rate and bioavailability from solid dosage forms. Though ritonavir tablets are available commercially, no work was reported on the pharmaceutical formulation aspects of ritonavir. Ritonavir tablets are official in I.P. 2010 which prescribed a dissolution rate test specification of NLT 70 % in 60 min to check the quality of commercial brands.

The present investigation was undertaken with an overall objective of developing ritonavir tablet formulations. Studies were carried out on ritonavir tablets to evaluate the effect of formulation variables such as binders, superdisintegrants, solubilizers and diluents on the tablet qualities and dissolution rate of ritonavir from compressed tablets with a view to optimize the formulation of ritonavir tablets. Studies were also carried out on enhancement of the dissolution rate and bioavailability of ritonavir. The feasibility of employing cyclodextrin complexation
and solid dispersion technologies for enhancing the dissolution rate and bioavailability of ritonavir and their application in the formulation development of ritonavir tablets was investigated.

Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years for enhancing the solubility and dissolution rate of poorly soluble drugs. Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity, which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties, such as solubility, dissolution rate, stability and bioavailability can be favourably affected. Cyclodextrins have been receiving increasing application in pharmaceutical formulations in recent years due to their approval by various regulatory agencies. In the present investigation, complexation of ritonavir with two cyclodextrins, β-cyclodextrin (βCD) and hydroxypropyl β-cyclodextrin (HPβCD) and the feasibility of employing cyclodextrin complexation for enhancing the solubility, dissolution rate and oral bioavailability of ritonavir were investigated.

Among other techniques for enhancing the dissolution rate and bioavailability of poorly soluble drugs, solid dispersion technologies were also found to be very successful with a number of poorly soluble drugs. Solid dispersion technologies include preparation of solid dispersions and solvent deposited systems. In solid dispersions the poorly soluble drug is dispersed in an inert water soluble carrier such as urea, polyethylene glycol and polyvinyl pyrrolidone at solid state. In the case of solvent deposited systems the drug is deposited in miniscular form on the
surface of an inert water insoluble excipient such as silica gel, microcrystalline cellulose and starch at solid state.

In the present work three water soluble carriers namely hydroxy propyl methyl cellulose (HPMC), polyvinyl pyrrolidone (PVP) and hydroxy propyl cellulose-L (HPC-L) and four water insoluble and dispersible carriers namely sodium starch glycolate (Primogel), crospovidone (cross-linked polyvinyl pyrrolidone), croscarmellose sodium (a modified cellulose) and Prosolve (a mixture of 98% microcrystalline cellulose and 2% silicon dioxide) were used as carriers for solid dispersions and for enhancing the dissolution rate and bioavailability of ritonavir.

Thus, the specific objectives of the investigation are as follows.

1. To evaluate the effect of formulation variables such as binders, superdisintegrants, solubilizers and diluents on the tablet qualities and dissolution rate of ritonavir from compressed tablets with a view to optimize the formulation of ritonavir tablets.

2. To prepare and evaluate solid dispersions of ritonavir employing various water soluble and water dispersible carriers for enhancing the dissolution rate of ritonavir.

3. 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.
4. To evaluate a new class of tablet excipients, called superdisintegrants as carriers for solid dispersion systems.

In recent years, several newer tablet disintegrants have been developed. Superdisintegrants are excipients used to promote rapid breakdown of oral solid dosage forms to aid dissolution *in vivo*. Commonly used superdisintegrants include sodium starch glycolate, croscarmellose sodium, crospovidone, pregelatinized starch and microcrystalline cellulose. Superdisintegrants differ from traditional starch in that they are effective in much lower concentrations due to their rapid and greater swelling character. This lower concentration provides formulation scientists greater flexibility, particularly in designing compressed tablets. The Superdisintegrants rapidly swell and disperse in water. These Superdisintegrants were evaluated as carriers for solid dispersions and for enhancing the dissolution rate and oral bioavailability of poorly soluble drugs.

5. To evaluate the drug and excipient interactions by IR and DSC spectral studies.

6. To evaluate the physical state of drug in the solid dispersions by XRD study.

7. To evaluate the kinetics and mechanism of drug dissolution from various formulations developed.

8. To evaluate the feasibility of formulating the solid dispersions and cyclodextrin complexes into compressed tablets and to evaluate various characteristics of the resulting tablets including dissolution rate and dissolution efficiency.
9. To evaluate the stability of selected tablet formulations as per ICH guidelines.

10. To evaluate the pharmacokinetics and bioavailability of ritonavir from selected formulated products.

Extensive laboratory experimentation was carried out to achieve the above objectives and the results obtained are presented in the subsequent chapters.
REFERENCES


