CHAPTER I

OBJECTIVES OF THE INVESTIGATION

The most important property of a drug delivery system is its ability to deliver the active pharmaceutical ingredient (API) to the site of action in the body in an amount sufficient to produce the desired therapeutic response. This property of the drug delivery system is referred to as bioavailability. Bioavailability is more precisely defined as the rate and extent of absorption (availability) of drug to the systemic circulation. About 95% of all new potential therapeutics (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pHs and consequent low dissolution rate. These drugs are classified as class II drugs under Bio-Pharmaceutical System (BCS) and pose challenging problems in their pharmaceutical product development process.

The drug in solid dosage form (tablet) must undergo dissolution before it is available for absorption from gastrointestinal tract. Dissolution forms the rate limiting step in the absorption of drugs from solid dosage forms especially when the drug is poorly soluble.

Several modern organic drugs belong to class II category under BCS, exhibit low and variable dissolution rates. These drugs need enhancement in dissolution rate and bioavailability to derive their maximum therapeutic efficacy. Several conventional methods such as micronization, chemical modification, use of surfactants and solubilizers, solid dispersion and a few new emerging technologies such as cyclodextrin complexation, mucoadhesive microspheres, nanoparticles, nanosuspensions, microemulsion and self-emulsifying systems are available to enhance the bioavailability of BCS Class II drugs.
Efavirenz and ritonavir, widely prescribed anti-retroviral drugs belong to class II under BCS, they exhibit, low and variable oral bioavailability due to their poor aqueous solubility. They are practically in soluble in water and aqueous fluids. As such their oral absorption is dissolution rate limited and they required enhancement in solubility and dissolution rate for increasing their oral bioavailability. Among the various approaches complexation with cyclodextrins has gained good acceptance in recent years in industry 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. (Fromming and Szejtli,1994, Duchene and Woussidjewe,1996) Cyclodextrins have been receiving increasing application in pharmaceutical formulation in recent years due to their approval by various regulatory agencies (Thompson and Crit,1997: Hedges, 1998).

Surfactants also increase the solubility of lipophilic water-insoluble drugs by micellar solubilization. Solutol HS15 (polyethyleneglycol660-12-hydroxystearate) is a non-ionic surfactant used for pharmaceutical purposes produced from 1 mol 12-hydroxystearic acid and 15 mol ethylene oxide. The product is very efficient in solubilising substances like fat-soluble vitamins, and active ingredients of hydrophobic nature. Solutol HS15 is approved by the HPB (Canada) for human application. Solutol HS15 has been used to enhance the solubility of insoluble drugs such as nifedipine (Rajebahadur et al., 2006) and paclitaxel (Alani et al., 2010) and as carrier in solid dispersions for increasing the dissolution rate and bioavailability of poorly soluble drugs such as curcumin (Seo et al., 2011) and biochanin A (Han et al., 2011).
Though cyclodextrin complexation and use of surfactants for enhancing the solubility and dissolution rate of poorly soluble drugs have been investigated individually, no reports are available on their combined use in enhancing the solubility and dissolution rate.

In the present investigation cyclodextrins (βCD and HPβCD) and surfactant, Solutol HS15 were tried to enhance the solubility, dissolution rate and bioavailability of efavirenz and ritonavir. The major objective is to evaluate the individual main effects and combined (interaction) effects of cyclodextrins (βCD and HPβCD) and surfactant Solutol HS15 on the solubility, dissolution rate and bioavailability of efavirenz and ritonavir in a series of $2^2$ factorial experiments and to evaluate the feasibility of formulating efavirenz and ritonavir tablets with enhanced dissolution rate and dissolution efficiency employing drug-CD-surfactant complex systems.

The specific objectives of the investigation are as follows:

1. To evaluate the individual main effects and combined (interaction) effects of cyclodextrins (βCD and HPβCD) and surfactant Solutol HS15 on the solubility and dissolution rate of efavirenz and ritonavir in a series of $2^2$ factorial experiments.

2. To evaluate the feasibility of formulating the Drug-CD-Solutol HS15 complex systems in to compressed tablets with enhanced dissolution rate. The individual main and combined (interaction) effects of cyclodextrins (βCD and HPβCD) and Solutol HS15 on the dissolution rate of (i) efavirenz and (ii) ritonavir from tablet formulations was investigated in a series of factorial experiments.

3. To evaluate the dissolution kinetics and characteristics of Drug-CD and Drug-CD -Surfactant inclusion complexes and tablets formulated employing them.
4. To evaluate the compatibility of the selected drugs with cyclodextrins (βCD and HPβCD) and surfactant Solutol HS15 by FTIR and DSC studies.

5. Pharmacokinetic evaluation of efavirenz - βCD and efavirenz- βCD-Solutol HS15 complexes in comparison to efavirenz pure drug with a view to evaluate their *in vivo* performance.

6. To evaluate the stability of selected tablets formulated employing drug-CD-Solutol HS15 inclusion complexes.

   Extensive experimentation, both *in vitro* and *in vivo* was conducted to achieve the objectives and the results obtained are presented and discussed in the subsequent chapters.