Aim and Objectives
AIM AND OBJECTIVE OF THE PRESENT INVESTIGATION

Human immunodeficiency virus (HIV) infection, which leads to acquired immunodeficiency syndrome (AIDS), remains a serious worldwide health problem. The Government of India estimates that about 2.40 million Indians are living with HIV (1.93 - 3.04 million) with an adult prevalence of 0.31%. Children (<15 yrs) account for 3.5% of all infections, while 83% are in the age group 15-49 years. India’s highly heterogeneous epidemic is largely concentrated in only a few states in the industrialized south and west, and in the north-east.¹ The discovery of HIV protease inhibitors introduced new and effective first line therapies for HIV/AIDS. Helping to combat HIV-related diseases and prolong survival, protease inhibitors are commonly administered with reverse transcriptase inhibitors. However, poor patient compliance, noxious side effects, and viral resistance have led to a recommendation to treat with different kinds of protease inhibitors.

The most important HIV protease inhibitors in clinical use are saquinavir, nelfinavir, indinavir, lopinavir, ritonavir, atazanavir and amprenavir. These protease inhibitors are metabolized by cytochrome P450 3A (CYP3A) enzymes, are efflux transporter substrates (i.e. P-glycoprotein, P-gp), or both.²,³ These metabolism and transport mechanisms often result in widely variable drug absorption. In addition to the metabolism and transport issues, many protease inhibitors have poor aqueous solubility, which produces very low and variable bioavailability. As a result, HIV/AIDS patients require frequent and
large medication dosing and commonly are unable to adhere to their treatment regimes.

An archetypal protease inhibitor, saquinavir has poor water solubility and is reported to be an excellent P-gp and CYP3A substrate.\textsuperscript{4,5} As a result, the oral bioavailability has been reported to be very low (0.7-4.0\%) and dependent upon the dosage form used. Saquinavir has been available as hard gelatin capsules, containing saquinavir mesylate (200 mg strength as saquinavir free base).\textsuperscript{6} Typically, it is dosed 2 times daily as five 200 mg capsules in combination with ritonavir (100 mg twice daily). It is recommended that it should be taken with meals.

Ritonavir, a widely prescribed antiretroviral protease inhibitor drug belongs to Class II under BCS and exhibits low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Ritonavir, a CYP3A and P-gp inhibitor, helps to increase saquinavir oral bioavailability.\textsuperscript{7} However, because HIV/AIDS patients must take other drugs known to be metabolized by CYP3A or they are P-gp substrates, ritonavir has been shown to cause additional toxicity and safety issues.\textsuperscript{8} Therefore, novel pharmaceutical formulations that may safely enhance the bioavailability of protease inhibitors are needed.

Several approaches could be investigated to improve their oral bioavailability, among them; complexation with cyclodextrins is
drawing considerable commercial attention these times, because of their low toxicity, low cost, biocompatibility, biodegradability and abundant availability. CDs and their derivatives have received considerable attention in the pharmaceutical field for the past few years and an increased number of reviews have been dedicated to their industrial and pharmaceutical applications.9-14

Drug-CD complexation and improvement in solubility and dissolution rate is influenced by both nature of the cyclodextrin (native or chemically modified, crystalline or amorphous) and the method of complexation, viz co-grinding, kneading, solid dispersion, solvent evaporation, co-precipitation, spray drying, or freeze drying. The effectiveness of a method depends on nature of the drug and CD.15-18 In many cases, spray drying and freeze drying were found to be more effective for drug complexation.19-23

Therefore, the interest of the present investigation is to prepare series of binary systems of saquinavir and ritonavir with crystalline native β cyclodextrin and its amorphous and highly soluble derivatives, HPβCD, RMβCD and SBE7βCD for improving their solubility. The main aim of the study is to find out the effectiveness of the method of preparation and better cyclodextrin derivative in enhancing solubility and dissolution rate of saquinavir and ritonavir so that their bioavailability can be enhanced giving scope for reduction in drug dosing for minimizing side effects.
The major objectives of the present investigation are as follows

1. To conduct phase solubility studies of selected drugs with different cyclodextrins for the calculation of stability constants of drug-CD complexes and molar ratio of complex formation.

2. To prepare saquinavir and ritonavir cyclodextrin complexes using methods like physical mixing, kneading, solvent evaporation, physical mixtures, spray drying and freeze drying.

3. To evaluate prepared CD complexes for their drug content and reproducibility of the method.

4. To conduct in vitro dissolution studies for the prepared complexes and their optimization for complete drug release in minimum time i.e. not more than 60 min based on the dissolution studies, and on different dissolution and other parameters.

5. Identification of best optimized drug-CD complex by using statistical approaches like analysis of variance (ANOVA), Tukey multiple comparison test and their evaluation for stability.

6. Characterization optimized complexes for formation of inclusion complexes, drug-CD interaction studies using Infrared spectroscopy (IR), Differential Scanning Calorimetry (DSC), X-Ray Diffraction studies (XRD) and nuclear magnetic resonance spectroscopy (NMR).

7. To evaluate the in vivo performance of the optimized complexes in comparison with the pure drug using suitable animals like Wistar rats.
REFERENCES


