CHAPTER 6: CONCLUSIONS AND FUTURE DIRECTIONS

The therapeutic activity of any drug depends upon the bioavailability and it is identified as the main setback for majority of the drugs. Drugs classified in BCS class II, which are low soluble and high permeable face the challenge of bioavailability. Efavirenz, a non-nucleoside reverse transcriptase inhibitor used to treat HIV infections is a drug classified under BCS class II, which possess poor solubility with altered and low bioavailability. The challenge can be overcome by using different dissolution enhancing techniques such as solid dispersion, size reduction into micron and nanometer range etc.

Polymeric nanoparticulate systems have received more consideration and well accepted as a tool for targeting, carrying the moiety with environmental protection and for solubility and bioavailability enhancement. These systems can be administered through various routes for achieving enhanced efficiency. Vaginal route of administration is considered as an alternative to oral route and also to provide the site specific action. This route is well known for several decades for its improved therapeutic activity of many drugs. The advantages include larger surface area, avoidance of first pass metabolism and high peak plasma concentration achieved through vaginal absorption. Foam formulation for vaginal application is recognized to be more suitable dosage form compared to other vaginal formulations, due to its high contact area and prolonged residence time, which ultimately helps to enhance the bioavailability. Administration of anti-HIV drugs through vaginal cavity is preferred because genital tract is the major site for HIV cell replication and especially it is recommended for treating HIV infections during pregnancy.
With this background, the objective of the present research was developed, the suitable polymeric nanoparticulate system of Efavirenz for vaginal application and to demonstrate its efficiency through in-vitro and in-vivo studies. Various techniques available for improving efficacy of anti-HIV drugs including bioavailability enhancing methods are discussed extensively in the thesis. The objective of the study was to split the whole work into four specific aims; the first aim for the development and characterization of nanoparticles using Eudragit-E100 as polymer to enhance the solubility, the second aim to study the safety and efficacy of optimized nanoparticles, third aim to perform the in-vivo biodistribution studies and the fourth to convert the nanoparticles into aerosol foam for vaginal application.

Efavirenz loaded polymeric nanoparticles developed by solvent evaporation method, with 1:1 ratio of drug and polymer was found to be the optimized among other trial formulations. The characterization studies revealed formation of nanoparticles with average size and surface charge of 110 nm and -28.3 mV, respectively. Solid state transition of drug from crystalline to amorphous form, mild interaction of drug and polymer was confirmed by the XRD, FTIR and TG-DTA results.

The formulated nanoparticles were assessed for cellular uptake (confocal imaging), safety and efficacy against C8166 cell lines infected with HIV\textsubscript{IIIb} strain. The nanoparticles showed better efficacy with low toxicity and high permeability than the free drug.

The biodistribution studies performed in mice model, helped in understanding the nanoparticles deposition in various organs including brain. The concentration of drug in the organs harvested and blood samples collected was determined by LC-MS technique.
Formulation with 1:1 ratio was found to be highly stable in biological environment and also proved the capability of crossing the blood brain barrier and accumulating more next to the genital organs. The data obtained through biodistribution study and literature supported the importance of administration of anti-HIV drugs through vaginal route.

The nanoparticles were successfully developed into aerosol foam formulation and were characterized as type-5 of foam classification due to the formation of larger bubbles and its immediate breakage. The flux, lag time and permeation coefficient obtained by ex-vivo skin permeation study of the optimized formulation proved the effective drug intake through the biological membrane with cumulative amount of drug (500 µg/cm²) permeated at 24 h.

To conclude, Efavirenz loaded nanoparticles prepared using Eudragit-E100 at 1:1 ratio was found to be satisfactory in terms of smaller size of particles, higher entrapment, low toxicity, high genital and brain uptake, better anti-HIV activity, improved flux and permeation coefficient, which could ultimately improve the bioavailability of the drug.

The highlights of this research work can be stated in terms of

- Development of Efavirenz polymeric nanoparticles using Eudragit-E 100 is newly reported
- Conversion of nanoparticles into aerosol foam for vaginal delivery is documented for the first time
- Higher brain distribution of the nanoparticles in mice model is demonstrated
- Enhanced anti-HIV activity of the nanoparticles than the free drug is observed
The thesis may be considered as a model for relevant research areas for future works or as extension of the same. The other suitable drugs can also be converted into foam formulation with nanoparticles for vaginal administration as individual drug or combination therapy. The formulations can be subjected for ADME studies with suitable animal models and anti HIV activity studies against other HIV strains.