Chapter – 3

AIM, SCOPE and OBJECTIVES
AIM, SCOPE AND OBJECTIVES OF THE INVESTIGATION

The Human Immunodeficiency Virus (HIV) is a retrovirus that infects cells of the immune system, destroying or impairing their function. As the infection progresses, the immune system becomes weaker, and the person becomes more susceptible to infections. The most advanced stage of HIV infection is Acquired Immunodeficiency Syndrome (AIDS). It takes 10-15 years for an HIV-infected person to develop AIDS; antiretroviral drugs can slow down the process even further. Almost 16 million people received antiretroviral therapy in 2015 \(^{(84)}\).

There's no cure for HIV/AIDS, but a variety of drugs can be used alone and in combination to control the virus. Each class of anti-HIV drugs blocks the virus in different ways. It's best to combine at least three drugs from two classes to avoid development of strains of HIV that are immune to single drugs.

The frequent administration of several drugs in relatively high doses is the main cause of patient incompliance and a hurdle toward the fulfillment of the pharmacotherapy. With the aim to reduce dosing frequency, to improve the compliance of the existing pharmacotherapy and to target viral reservoirs, the design of novel and controlled drug delivery systems is becoming complementary to new drug discovery \(^{(8,9)}\).

Controlled drug delivery systems are designed to achieve a continuous delivery of drugs at predictable and reproducible kinetics over an extended period of time in the circulation. The potential advantages of this concept include minimization of drug-related side effects due to controlled therapeutic blood levels instead of oscillating blood levels, improved patient compliance due to reduced frequency of dosing and the reduction of the total dose of drug administered. Since HIV/AIDS treatment involves combination drug therapy, the potential of these novel drug delivery systems for simultaneous loading of various drug combinations needs to be investigated \(^{(10)}\).

Nucleoside reverse transcriptase inhibitors (NRTIs) have been cornerstones of HIV therapy since the first NRTI was introduced in 1987. NRTI monotherapy was the standard of care for HIV through the early 1990s. This treatment often resulted in significant toxicity due to the administration of high doses of medication, such as zidovudine, in patients with advanced HIV infection. Disease progression was determined by declining CD4+ lymphocyte cell counts and/or the development of opportunistic infections. Virologic and clinical failure prevailed
despite therapy, and medical treatment was mainly confined to managing opportunistic infections as they arose and offering palliative care for patients with advanced AIDS (85).

These agents, in order to inhibit reverse transcription, have to be phosphorylated by cellular kinases to their triphosphate derivatives. All NRTIs follow the same mechanism of RT inhibition: once activated to their triphosphate form, they are incorporated by RT into the growing primer, competing with the natural dNTPs and terminating DNA synthesis due to their lack of the 3′-hydroxyl group. Therefore, once incorporated into dsDNA, they prevent the incorporation of the incoming nucleotide. Importantly, while HIV-1 RT uses these NRTIs as substrates, the cellular DNA polymerases do not recognize them with the same affinity (86).

NRTIs are usually given as paired agents with at least one other antiretroviral medication that has a different mechanism of action, such as a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or an integrase inhibitor. The current preferred dual NRTI combination for the treatment-naive patient is Tenofovir-Emtricitabine because of its superior virologic efficacy, side effect profile, and low pill burden and dosing frequency, compared with other NRTI combinations (eg, Zidovudine and Lamivudine) (87).

Hence, this research work is aimed to design and develop oral controlled release formulations for antiretroviral drugs. In this study, three antiretroviral drugs by names Emtricitabine, Lamivudine and Tenofovir were selected to design controlled release dosage forms to maintain the plasma concentrations to the desired levels during every dose of these modified release drug delivery systems without a reduction in the dose that is given conventionally. The controlled release formulations of Lamivudine & Emtricitabine alone and the combination of Lamivudine with Tenofovir DF & Emtricitabine with Tenofovir DF (Tenofovir as immediate release) were selected. Oral controlled release can be achieved by employing different techniques like prodrugs, ion exchange resins, buffered tablets, microcapsules, compression coated tablets, film coating, osmotic pump, matrix tablets and others. Generally, tablets are more familiar as they are easy to prepare and having a more industrial feasibility.

Hence different types of tablets like matrix tablets by embedment technique, compression coated tablets and microcapsules assisted bilayered tablets of ARV’s for controlled release are selected for the present research work.
The main objectives of this investigation are as follows

- To carry out the preformulation studies like Organoleptic properties, Melting point, Loss on drying, Solubility, Partition coefficient, and Flow properties for the drugs i.e., Lamivudine, Emtricitabine and Tenofovir DF.
- To select the excipients for the development of controlled release formulations.
- To conduct drug-excipient compatibility studies by FTIR and DSC.
- To develop and validate the analytical methods for the estimation of drug substances.
  - UV spectroscopic method for the estimation of Lamivudine, Emtricitabine and Tenofovir DF.
  - HPLC method for the simultaneous estimation of Lamivudine with Tenofovir DF and Emtricitabine with Tenofovir DF.
  - HPLC method for the estimation of Lamivudine & Emtricitabine in biological samples (rabbit plasma).
- To formulate and characterize controlled release matrix tablets of Lamivudine.
  - To isolate, purify and characterize the selected natural gums
  - To develop formulations using natural gums as release-retarding polymers by using embedment technique and wet granulation method.
  - To optimize the polymer concentration and evaluate the influence of concentration and nature of the polymer for controlled release of Lamivudine.
  - To conduct comparative studies on different techniques employed to prepare tablets & to select the best technique.
  - To characterize the drug release mechanism from matrix tablets.
- To formulate and characterize Emtricitabine controlled-release tablets by using Compression Coating Technology.
  - To formulate and evaluate the core tablets containing Emtricitabine.
  - To prepare the granules of polymer(s) for compression coating.
  - To optimize the polymer concentration and evaluate the influence of concentration and nature of the polymer for controlled release of Emtricitabine.
  - To characterize the drug release mechanisms from compression coated tablets.
➢ To formulate and characterize the bilayered tablets of Lamivudine with Tenofovir DF & Emtricitabine with Tenofovir DF using Lamivudine & Emtricitabine for control release and Tenofovir DF for immediate release.

a) **Tenofovir DF for Immediate release**
   - To develop immediate release tablets by using wet granulation method with different binders and disintegrants and water as the granulating agent.
   - To optimize the disintegrant and binder concentration for immediate release of Tenofovir DF

b) **Lamivudine & Emtricitabine for Controlled release**
   - To prepare controlled release microcapsules of Lamivudine & Emtricitabine by employing the polymers, Ethyl Cellulose of different viscosities, Eudragit RLPO and Eudragit RSPO at various concentrations by using emulsion solvent evaporation technique.
   - To investigate the effect of viscosity of the polymer on the formation of microcapsules and influence of process and formulation parameters on the morphology of microcapsules by conducting SEM analysis
   - To perform evaluation tests for microcapsules such as flow properties, Product yield, entrapment efficiency, dissolution studies.
   - To characterize drug release mechanism from microcapsules.

c) **Bilayered tablets of Lamivudine with Tenofovir DF and Emtricitabine with Tenofovir DF**
   - To select the optimized formulation from the microcapsules of Lamivudine & Emtricitabine for controlled release and from the immediate release tablets of Tenofovir DF for immediate release.
   - To prepare the bilayered tablets of Lamivudine with Tenofovir DF and Emtricitabine with Tenofovir DF.
   - To evaluate the physical parameters for bilayered tablets.
   - To perform dissolution studies for the bilayered tablets of Lamivudine with Tenofovir DF and Emtricitabine with Tenofovir DF.
   - To characterize the drug release mechanism from bilayered tablets.

➢ To perform accelerated stability studies for the optimized formulations.
➢ To perform *in vivo* studies for estimation of pharmacokinetic parameters for the selected formulations.