CHAPTER I
INTRODUCTION AND OBJECTIVES OF THE INVESTIGATION

The human immunodeficiency virus (HIV) infects cells of the immune system, destroying these cells as well as the immune system’s ability to fight off the invaders. The aim of antiretroviral therapy (ART) is to keep the amount of HIV in the body at a low level. This stops any weakening of the immune system and allows it to recover from any damage that HIV might have caused already.

Antiretroviral drugs (ARVs), which can significantly delay the progression from HIV to AIDS – have been available in developed countries since 1996. Unfortunately access to this treatment is limited in India. The antiretroviral drugs in usage are of the following three types.

1. **Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)** stall reproduction of HIV. They force the virus to use faulty versions of building blocks. US FDA has approved the following drugs under this category:

   Zidovudine , Lamivudine, Emtricitabine, Abacavir, Zalcitabine, Didanosine.

2. **Non-nucleoside RT inhibitors (NNRTIs)** bind to the RT protein. This disables it, keeping HIV from making copies of itself. The US FDA has approved the following under this category:
Efavirenz, Nevirapine, Delavirdine, Etravirine, Edurant.

3. **HIV-Protease inhibitors**

Ritonavir, Indinavir, Lopinavir, Saquinavir

Lamivudine is an analogue of cytosine. It is given orally, is well absorbed and excreted unchanged in the urine. The CSF level is 20% of the plasma concentration. Used alone, it could select for HIV mutants that are resistant to both the drug itself as well as other reverse transcriptase inhibitors. Lamivudine is also used in the therapy of hepatitis B infection.

Zidovudine is an analogue of thymidine. It can prolong life in HIV-infected individuals and diminish HIV-associated dementia. Given to the parturient mother and then to the new born infant, it can reduce mother-to-baby transmission by more than 20%. It is generally administered orally twice daily but can also be given by intravenous infusion. The bioavailability is 60-80%, and the peak plasma concentration occurs at 30 minutes. Its half life is 1 hour and intracellular half life of the active triphosphate is 3 hours. The concentration in cerebrospinal fluid (CSF) is 65% of the plasma level. Most of the drug is metabolized to the inactive glucuronide in the liver, only 20% of the active form being excreted in the urine.

Lamivudine and zidovudine are official in IP and USP. Lamivudine and zidovudine combination has significant therapeutic importance. The combination treatment is known as highly active antiretroviral therapy (HAART). Using a HAART protocol, HIV replication is inhibited, the presence of HIV-RNA in the
plasma is reduced to undetectable levels and patient survival is greatly prolonged. Zidolam tablets (a commercial brand) contain lamivudine (150 mg) and zidovudine (300 mg). Zidolam tablets are used in antiretroviral combination therapy for the treatment of HIV infection. Zidolam tablet reduces the amount of HIV in the body and keeps it at a low level. It also increases CD4 cell counts. CD4 cells are a type of white blood cells that plays an important role in maintaining a healthy immune system to fight against infection.

Studies were carried out on lamivudine and zidovudine drug combination with the following objectives:

1. To develop a simple, sensitive, precise and accurate RP-HPLC method for the simultaneous estimation of lamivudine and zidovudine combination in bulk and in dosage forms.

2. To validate the developed RP-HPLC method as per ICH guidelines.

3. Formulation development of combined drug tablets containing lamivudine and zidovudine and evaluation of the tablets for various physical characteristics and dissolution rate.

4. To evaluate the application of the developed HPLC method for the simultaneous estimation of lamivudine and zidovudine in the dissolution study.

5. To evaluate the application of the developed HPLC method for the simultaneous estimation of lamivudine and zidovudine in plasma samples in the pharmacokinetic studies.