CHAPTER – IV

OBJECTIVES OF THE STUDY

4.1 BACKGROUND

Human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) commonly referred to as HIV & AIDS have emerged as being amongst the most serious and challenging public health problems in the world. There are two species of HIV, namely, HIV 1 and HIV 2 with their respective subspecies. HIV 1 is the global common infection whereas the latter is restricted to mainly West Africa (Lucas, 2001). HIV infection in the human body results mainly from the integration of the viral genome into the host cell for the purpose of cell replication.

The advent of antiretrovirals (ARVs) such as the Nucleoside Reverse Transcriptase Inhibitors (NRTI), Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI), Protease Inhibitors (PI), and more recently fusion and integrase inhibitors have revolutionized the treatment of HIV and AIDS. However, eradication of the virus does not seem attainable with the present strategies of interventions which are due to two major obstacles: If resistant mutations appear the virus will escape further treatment, and latent virus reservoirs exist which cannot be reached with the current treatment regimens.

HIV is localized in certain inaccessible compartments of the body such as the CNS, the cerebrospinal fluid, and within the macrophages, where it cannot be reached by the majority of drugs in adequate concentrations or in which the drugs cannot be maintained for the necessary duration (Vyas, Subhedar, and Jain, 2006). One of the sanctuaries for HIV-1 target cells is the mononuclear phagocyte system (MPS), such as monocytes/macrophages (MO/MAC), dendritic cells (DC) and Langerhans cells which can be considered as primary cells for viral entry, and subsequently are responsible for distribution of the virus into...
various tissues. Insufficient concentrations of drug at this site and short residence time are amongst the major factors contributing to both the failure of eliminating HIV from these reservoirs and also the development of multidrug resistance against antiretroviral agents (Amiji, Vyas, and Shah, 2006, Balis et al., 1989). Moreover, the consequent large doses required to achieve a therapeutic effect contribute to the severe side effects associated with ARV therapy.

In order to fulfill the need of a long-term treatment with anti HIV agents, where most of them suffer from the drawbacks of frequent administration and plasma concentration fluctuation, it is desirable to have sustained-release drug delivery systems to improve the overall therapeutic benefit and to achieve an ideal therapy. By sustained delivery, it is possible to achieve effective plasma concentration without significant fluctuation, to avoid sub-therapeutic and toxic plasma concentrations, to facilitate release of the medication in a controlled manner to obtain a continuous delivery, to achieve an effective therapy with low dosage of the drug, to reduce the frequency of medication and thus to improve patient adherence.

Current attempts to overcome these limitations include the development of novel drug delivery systems that can improve the efficacy of existing ARV drugs. Colloidal drug carriers (niosomes) are easily phagocytosed by macrophages. Therefore, they can facilitate the uptake of antiviral drugs by these cells and may enable a considerably improved AIDS therapy.

Niosomes formed from self-assembly of hydrated synthetic nonionic surfactant monomers capable of entrapping variety of drugs. The size of these vesicles is in the nanometer range. This size range offers the decisive advantage of this class of pharmaceutical dosage forms as it allows drug targeting which often is not possible with free drug.

Zidovudine (AZT) the first anti-HIV compound approved for clinical use is still widely used alone or in combination with other antiviral agents for treatment
of AIDS and AIDS-related complex. The main limitations on the therapeutic effectiveness of AZT are its dose-dependent hematological toxicity, high first-pass metabolism, poor bioavailability and very short biological half-life (Kieburtz et al., 1992). After oral administration it is rapidly absorbed from the gastrointestinal tract with a peak plasma concentration of 1.2 µg/ml, at 0.8 h. It is also rapidly metabolized to the inactive glucuronide with a mean elimination half-life \( (t_{1/2}) \) of 1 h. This necessitates frequent administration of large doses (200 mg every 4 h) since it is crucial to maintain the systemic drug concentration within the therapeutic level throughout the treatment course. (Klecker et al., 1987). The challenges associated with ARV drug therapy have driven the impetus to explore nonionic surfactant vesicles (niosomes) delivery systems with the anti HIV drug to target macrophages. Little information is available in the literature about the optimization process variables that are important in the formulation of zidovudine niosomes.

Hence in this work an attempt was made

1. To formulate and optimize zidovudine niosomal formulation.
2. To develop zidovudine niosome vesicles with size 100 -1000 nm for targeting macrophages.
3. To study the effect of charge inducing agent as it has impact on the tissue distribution and pharmacokinetics of zidovudine niosomes.
4. To compare the efficiency of zidovudine niosomes and proniosomes in the selective uptake of zidovudine by macrophages.
5. To facilitate sustained release of zidovudine by niosomal delivery system.
6. To study the stability of zidovudine niosome vesicles formulated with different non ionic surfactants at room temperature and accelerated temperature.
7. To passively target the drug to macrophages with minimal dose to achieve the goals of NDDS.
4.2 RATIONALE BEHIND SELECTION OF RESEARCH TOPIC

1. Reason for choice of AIDS as the disease for drug delivery development

Acquired immune deficiency syndrome (AIDS) one of the most serious infectious disease challenges to public health globally, and has a crippling effect in certain parts of the World. Currently 33.2 million people living with AIDS globally. Of this total number an overwhelming 22.5 million are HIV positive. Every day, about 5,700 people in the world die from AIDS and 6,800 people become newly infected with HIV. Till date there is no drug available to cure AIDS. Hence it has become inevitable to develop effective drug delivery systems to target the site with minimum dose thereby reducing undesired side effects.

2. Reason for choice of Niosome delivery system

Literature reports reveal encapsulation of drug in vesicular structure may prolong the existence of the drug in the systemic circulation and thus enhance selective uptake of drug by tissues and reduce toxicity. The size and unique structure of niosomes are recognized and taken up in larger amounts by the Mononuclear Phagocyte System (MPS) after intravenous injection and are deposited in certain organs liver, spleen, lungs that are rich in macrophages (Poznansky and Juliano, 1984). Drugs encapsulated in niosomes reported to have pharmacodynamic and pharmacokinetic properties which are radically different from that of free drugs (Azmin et al., 1985). The chemical stability and low cost of materials make niosomes more attractive than liposomes in industry. The drawbacks of conventional dosage forms give researchers tremendous opportunities to design and develop novel drug delivery systems to overcome transport barriers and inherent elimination and metabolism problems associated with the anti HIV drugs which are significantly important phenomena for the delivery of anti HIV drug. Hence an attempt was made using niosomes as delivery system for the drug zidovudine.

3. Development of formulation for existing drug
It is estimated that the full development of new prescription medicine from discovery to marketing approval in the United States typically takes 10-15 years and costs more than $800 million on an average, according to the Tufts Center (Roghieh saffie siebert et al., 2005) for the study of drug development. Five out of every 5,000 potential drugs are qualifying for clinical trials, and of these only one will eventually be approved for use in patients. Hence an attempt was made to formulate niosomes for the existing drug zidovudine.

4. **Reason for choice of zidovudine as the candidate for niosome delivery**

    Zidovudine (AZT) is commonly used to treat patients with AIDS, but it is limited by toxicity and high dosing needs. The anti HIV drug have relatively short biological half life, significant first pass effect, low bioavailability, low protein binding and undesirable side effects. The adverse reactions and side effects of zidovudine are often related to the accumulation of the drug at inappropriate sites. Hence an attempt was made to deliver zidovudine to macrophages in the form of niosomes.

    The overall objective of the work is to formulate and evaluate the zidovudine niosomes for targeting macrophages. The plan of work is as follows

4.3 **PLAN OF WORK**

- Formulation of zidovudine niosomes by thin film hydration technique
- Optimization of process-related variables by trial and error method. The variables were optimized with respect to entrapment efficiency.
  - Concentration of Charge inducing agent
  - Centrifugation speed
  - Rotation Speed of flask.
  - Hydration time
- Physicochemical characterization of niosomes
Chapter IV

Objective of the Study

- Vesicle size, size distribution and shape
- Zeta potential, Polydispersity index
- Entrapment efficacy
- Osmotic shock
- Viscosity

- In vitro release
- Tissue distribution study of zidovudine niosomes in mice
- Pharmacokinetic studies of zidovudine niosomes in rabbits.
- Preliminary stability studies at long term and accelerated conditions.
- Proniosomes formulation and evaluation.