Chapter 1

Aim of the Present Work

PART I

INTRODUCTION AND LITERATURE REVIEW ON CANCER, DOSAGE FORMS AND DRUGS

1.1 INTRODUCTION

Cancer is a disease characterized by the formation of abnormal tissue (neoplasm), basically a change in the way cells proliferate and differentiate. Different anticancer drugs effect different parts of the cell cycle and may have varying side effects. Systemic treatments affect healthy tissue as well as diseased tissue. For this reason, the dose at which the drug is administered is restricted to avoid destruction of healthy tissue; this restricts the potential strength that the drug may have on the diseased tissue. Many approaches have been developed to overcomes side effects. This protection can be accomplished by two means: the drug structure can be chemically modified, and/or the drug can be associated to a drug carrier.

Anticancer drugs encapsulated within liposome carriers have been shown to reduce the toxic effects and enhance the therapeutic effects in animal tumor models. Liposomal delivery of anticancer drugs is essential for the preservation of normal cells and for a strong toxic effect against the infected tissue. It allows for the administration of the drug in high doses, having a much stronger effect on the region of interest than systemic administration. Conventional liposomes are limited in effectiveness because of their rapid uptake by macrophage cells of the immune system, predominantly in the liver and spleen.

One of the concepts of making the drug delivery system "invisible" to the macrophages is called 'Stealth' technology. This in turn allows them to selectively extravasate in diseased sites, like tumors and inflammation sites where the vasculature is leaky. The Stealth liposomes have a unique PEG (polyethylene glycol) coating that reduces mononuclear phagocyte system (MPS) uptake. They have a diameter of approximately 100nm, which is large enough to carry a substantial drug load but small enough to allow efficient extravasation through leaky tumor vasculature. Disappointments in performance of stealth liposomes include lack of general strategy for tissue targeting, drug concentrations, which are sometimes, lower than desired, difficulty of large scale production and unpredictable shelf life. Moreover, such lipids are very expensive, inherently unstable, very difficult to scale up to commercial production, and difficult to engineer.

The second concept revolves the use of ultrasound to externally control drug delivery. It coupled with the ideal situation of monitoring exact location of drug deposit led to the investigative use of ultrasound contrast agents as drug delivery systems. Microbubbles consist of a gas (air or perfluorocarbon), which is stabilized by shell (denatured albumin, phospholipids, or surfactants or cyanoacrylates) having diameter of from 1 to 10 μm. The formation of the monolayer microbubbles is solely by molecular self-assembly; no organochemical reactions or derivatization is needed to assemble the microbubble structure, which avoids all the potential problems and complications associated with PEGylation of liposomes.

At present, studies are going on for investigating the potential if other novel drug delivery systems can overcome the problems associated with liposomal drug delivery systems. The focus is also on the probable mechanisms of this kind of systems. Such studies will greatly enhance the applicability of these findings to routine therapy.

The aim of the present study was to develop delivery systems containing anti-cancer drugs with increased therapeutic efficacy, slow the systemic delivery and less side effects. The present investigation also describes the preparation and comparative evaluation of stealth liposomes and microbubbles as carriers for anti-cancer agents and diagnostic agents.

The anti-cancer agents selected for the studies are as follows:

Flutamide (FLT), anti-androgen is one of the most widely used anti-cancer agents. It is indicated for the treatment of prostate cancer. 6-Mercaptopurine (6-MP), an antimetabolite is the most commonly used drug for child leukemia. These anti cancer drugs are associated with hepatotoxicity and the therapeutic index of these agents is very narrow which demands the need for targeted delivery systems for delivering the drugs to the tumor site.

1.2 Proposed plan of work

The proposed plan of work is as follows:

1. Analytical method development of both selected drugs (FLT and 6-MP)

2. Preparation of conventional liposomes and microbubbles of FLT and 6-MP and optimization of the process and formulation parameters

3. Synthesis and characterization of methoxy polyethylene glycol derivatives using cyanuric chloride as coupling agent

4. Preparation of sterically stabilized liposomes by incorporating prepared polymer ($mPEG_{2000}$-PE) in to the conventional liposomes and optimization of the process

5. Characterization of the conventional and stealth liposomes as well as microbubbles of FLT and 6-MP

6. In vitro drug release studies, using an appropriate method, for evaluation of the sustained release of FLT and 6-MP from liposomes and microbubbles

7. In vitro cell cytotoxicity studies of liposomes and microbubbles of FLT and 6-MP using cancer cell lines by MTT assay.

8. Stability studies of liposomes and microbubbles of FLT and 6-MP

9. Pharmacokinetic and in vivo biodistribution studies of the prepared liposomes and microbubbles for evaluation of sustained and targeted delivery using suitable animal models

10. Hepatotoxicity studies (Histopathology and Biochemical analysis) for liposomes and microbubbles of FLT and 6-MP

11. Application of liposomes and microbubbles in diagnosis (Sonography and Doppler Studies)