CHAPTER 1

INTRODUCTION AND OBJECTIVES
The clinical use of a therapeutic agent can only be justified if its beneficial effects outweigh its toxic effects. Generally, however, dose-related beneficial effects and toxic responses often result from similar pharmacological actions of a drug in tissues in which the drug action is desirable (therapeutic effects) and undesirable (toxic effects), respectively. Most medications are, thus associated to some degree with toxic side effects. This principle is best illustrated by the use of chemotherapeutic agents in the treatment of cancer, where inhibition of tumor growth is invariably accompanied by serious toxicity to rapidly proliferating normal cells.

Consequently, one can promote the therapeutic effects of an anticancer agent and minimize its toxic responses by augmenting the amount and persistence of agent in the vicinity of the cancer cells while reducing the drug exposure of non-target cells. The basic rationale for the introduction of controlled drug delivery, that is, the use of systems and techniques for altering and controlling the behaviour of pharmacologically active agents in cancer chemotherapy, lies in this basic hypothesis. The rate of delivery, intensity, and duration of the action of anticancer agents, therefore, has been the subject of increasing multidisciplinary research and many attempts have been made to search for ideal drug delivery devices (dosage forms) and/or chemical modifications of the drugs to improve their efficacy.

Cancer chemotherapy, ideally is expected to eliminate all cancer cells, with no or minimal injury to the healthy tissues. But none of all the therapeutic measures in use today has been able to achieve this goal. Most tumors can be controlled if detected and treated early. However, in many cases, the tumors are diagnosed after they are well advanced and even metastasis have set in. Surgery and radiotherapy which are the widely used methods of cancer treatment, can take care of localized disease only. Once metastasis is diagnosed, chemotherapy is the preferred method of therapy.

With rising cost of health care services and an increase in the geriatric population, there is a definite need for medication devices/delivery systems to guarantee long-term drug delivery for certain drugs that are administered over days, weeks or months. Controlled release drug delivery systems have received increasing attention both by industry and academia over the past two decades. The significant research interest in the development of subcutaneous injectables and implantable polymeric devices for long-term maintenance of therapeutic drug-levels coincides with the increased medical and public acceptance of such systems. Furthermore implantable drug delivery systems offer many advantages over the conventional drug therapies.

Thus the preamble is

Every second of every day, a man, woman or child dies of cancer. Infact, one of every six persons alive today will contract and die from cancer.

The malignant crab like cellular malfunction which began to multiply at bewildering speed in their body tissues, will for those countless millions, tragically bring the realization that their cancer could not be cured, controlled or even contained by the usual methods of surgery, radiotherapy and chemotherapy. Four out every five persons who receive one or all these treatments die within five years. This is not only an indication of the disease, but also shows the magnitude of challenge which this disease possess to the human race.
But, man with his uncanny sense to fight back has over the years blunted the attack of this disease and it is a question of time before we can vanquish this giant.

Biodegradable carriers both natural and synthetic have been extensively used to design drug delivery systems. Delivery systems employing chitosan, albumin, poly(lactic acid), poly (glycolic acid), poly(lactide)-co-glycolide, poly(ε caprolactone) for sustained release have been administered both by oral and parenteral routes. Carriers like betacyclodextrin and albumin have also been used to increase the aqueous solubility of poorly water soluble drugs. The major advantage of employing these biodegradable polymers are there non toxicity because they degrade into natural products which are metabolized or excreted by normal physiological pathways.

Considering the foregoing background regarding the potential applications of biodegradable polymers, an attempt has been made to envisage their advantage in the long term delivery and also to reduce the toxicity. Methotrexate and plumbagin have been chosen as the drugs for the present study. Attempt has also been made to increase the aqueous solubility of these poorly water soluble drugs through complex formation.

Various drug delivery devices which have been prepared for Methotrexate include microspheres using poly(lactic acid) and poly(lactide)-co-glycolide, microspheres employing chitosan and chitin, poly(lactic acid) and poly(ε caprolactone) implantable films, injectable gel implants using poly(lactide)-co-glycolide, complexes with betacyclodextrin, solid dispersions with albumin. Formulations for plumbagin include microspheres using poly(lactide)-co-glycolide, injectable gel implants using poly(lactide)-co-glycolide, complexes with betacyclodextrin. Detailed surface morphology characterization, particle size analysis, in vitro release, pharmacodynamic and pharmacokinetic evaluation using two tumor models viz Sarcoma-180 and Ehrlich ascites have been performed. Toxicity studies of plumbagin has also been carried out. The results of the studies have been encouraging in controlling the drug release and also reducing the toxicity and have been presented herewith.
"Probably every new and eagerly expected garment ever put on since clothes came in, fell a trifle short of the wearer's expectation.

- CHARLES DICKEN IN GREAT EXPECTATIONS