Cancer - An enigma:

Cancer is one of the leading causes of death in the world today. There are a wide variety of malignancies, each one possibly due to many causes. The etiology of every class of tumors and among the same class of tumors occurring at different site is a complex problem. Cancers exert deleterious effects on the host because of their invasiveness and ability to metastasis. Neoplasms, the uncontrolled growth of cells, tissues or organs in the host, are not always fatal and are considered to be amenable to treatment.

Therapeutic modalities and their limitations:

The most commonly employed modalities for the treatment of cancer are surgery, radiotherapy and chemotherapy. Immunotherapy and gene therapy are the other two treatment modalities that are gaining importance in the recent years.

Surgery:

Surgery a locoregional therapy, is the oldest treatment for cancer. Even today, it continues to be the most important aspect in the treatment of patients presenting with solid tumors. The use of surgery has been limited to those cases in which the tumor has not yet spread beyond the limits of surgical excision. Unfortunately more than 70% of patients with solid tumors are reported to have developed secondary tumors when they are first diagnosed (De vita, 1985). This is due to the spread of micrometastasis beyond the primary site. Hence the advances in modern clinical research in oncology has combined surgery with other adjuvant therapies.

Radiotherapy:

In 1895 Roentgen discovered X-rays and their biological effects, cell killing effects in particular, became apparent. Soon then, radiotherapy established a major role in the radical and
palliative treatment for locally advanced malignant disease.

Despite the advancement in the field of radiotherapy, its success in clinics is hampered by the inherent factors such as tumor hypoxia, tumor size, normal tissue sensitivity and distant metastasis. Hence, radiotherapy is combined with surgery and/or chemotherapy.

Hyperthermia:

The beneficial effect of hyperthermia in the treatment of cancer was reported as far back as 400 B.C. The rationale for the use of hyperthermia are (Hall, 1984):

1. Heat kills cells in a predictable and repeatable way, like radiation and chemotherapeutic drugs.

2. The age response of heat complements that of X-rays, especially when the cycling tumor cells are killed selectively by hyperthermia compared with the slowly turning over normal tissues responsible for late effects.

3. Cell that are nutrient deficient and at low pH are more sensitive to killing by heat (Freeman et al, 1977).


5. The cell killing potential of some chemotherapeutic agents is enhanced substantially by temperature elevation of a few degrees (Engelhardt, 1987). Thus the addition of local hyperthermia to chemotherapy schedule has a advantage of "targeting" and localizing the principal effect of the drug, allowing greater tumor cell kill for a given systemic toxicity.
Chemotherapy:

Chemotherapy of cancer has survived several years of criticism and is now an established means of cancer treatment. It was almost three decades before firm evidence was obtained that chemotherapy could actually cure cancer. Today, with cures documented in some proportions over a dozen different malignancies, it can be said that chemotherapy has joined surgery and radiotherapy as a significant treatment modality. The utilisation of cancer chemotherapy breaks down into three major categories (Carter, 1981).

1. Curative to some degree in clinically evident disseminated malignancy e.g. childhood leukemia, Hodgkin's disease.

2. Curative to some degree in clinically evident localised and regional malignancy in combination with surgery and/or irradiation e.g. breast cancer, osteogenic sarcoma.

3. Palliative in clinically evident disseminated malignancy (prolongation of survival) e.g. ovarian cancer, multiple myeloma, breast cancer.

The ability to cure cancer with local means - surgery or radiotherapy - is hindered by the presence of viable metastasis outside the treatment field. Malignant tumors, as they grow, may invade their surrounding stroma and will pass through the basement membrane. During this process it would constantly shed cells. Some of these cells are able to establish metastatic clones even before the primary mass reaches a clinically detectable level. In such instances, systemic therapy of cancer using chemical agents has been proved to be useful (Carter, 1984). Drugs can in some instances cure by themselves or help to cure when combined with surgery and radiotherapy. For wide range of disseminated cancers, drugs can achieve clinical remissions and regressions which impact favourably on quality of life as well as survival.
Strategies to optimise cancer chemotherapy:

As fundamental advances continue in the chemotherapy of neoplastic disorders, the greatest progress in recent past is in the conceptual therapeutic developments. These include:

(a) The design of more effective regimens for concurrent administration of drugs, including combinations of neoplastic agents with 'biologic response modifiers'.

(b) The increased use of adjuvant and neoadjuvant chemotherapy.

(c) Greater insight into mechanisms of resistance to antineoplastic agents.

(d) The acquisition of knowledge of mechanism of action of many antitumor agents, which facilitates the design of new methods to prevent or minimise drug toxicity.

(e) Increased knowledge about such vital processes as tumor initiation and the dissemination, implantation and growth of metastasis.

Vexing problems with current chemotherapeutic approaches:

Major obstacles to the cure of neoplastic diseases using chemotherapeutic agents are:
1. Development of multidrug resistance.
2. Tumor heterogeneity, and
3. Dose dependent host tissue toxicity.

Tumor heterogeneity and development of multidrug resistance are the two unresolved problems in cancer research and no clear cut understanding in this regard has been achieved till date. Besides the above two, the inherent problem of non-specificity of chemotherapeutic agents is a major area of research interest. This non-specificity is due to very subtle metabolic differences that exists between a cancerous and a normal cell. So, unlike in a bacterial infection, a cancer chemotherapeutic agent cannot exclusively act on the metabolic pathways of cancer cells while leaving the rapidly dividing normal cells unaffected.
Methods developed to enhance specificity of chemotherapeutic agents:

Antineoplastic agents are, therefore, neither specific nor targeted to cancer cells. Improved delivery of anticancer drugs to tumor tissues, thus, appears to be a challenging and achievable effort. Significant efforts have been directed towards the improvement of anticancer drug delivery in recent years. Chemical modifications such as altering the partition coefficient, preparation of prodrugs, binding of immunological ligands has met with little success. Physical approaches for the delivery of anticancer drugs consist of microparticulate drug carriers (liposomes, microspheres, nanoparticles), magnetic microcapsules, implantable pumps and reservoirs. Some success has been reported in the areas of enhancing efficacy and reducing drug toxicity (Gabizon et al, 1982; Olson et al, 1982; Rahman et al, 1985).
OBJECTIVES OF THE PRESENT STUDY

In the present investigation, the approach explored is to alter the biological distribution characteristics and pharmacokinetic parameters of a widely used anticancer drug, Bleomycin, by incorporating it into drug carriers (vesicles) which are expected to target the drug to the desired site as well as control its release. The major objective to evolve such a strategy was to achieve optimal chemotherapeutic effect by using subtherapeutic doses of the drug. In other words, we have tried to address the question:

\[
\text{Whether packaging anticancer drug bleomycin in suitable - drug carriers would damage proliferating neoplastic cells while sparing the normal tissues such as bone marrow, intestinal mucosa etc. ?}
\]

Attempts have been made to activate and exploit macrophages in delivering niosomal bleomycin, more quantitatively, to tumor site using niosome encapsulated immunomodulators muramyl dipeptide and tuftsin. The formulated drug dosage form is compared with that of the standard marketed preparation, taking pharmacodynamic, pharmacokinetic and toxic side effects into consideration.