From the time in history, when mankind must have discovered the magic effect of wound healing of medicines present in plants and later in semi synthetic and synthetic molecules, it has been his constant endeavor to find newer ways to deliver the drugs in a way to achieve optimal effect of drug and at the same time minimizing side effects.

Drug delivery systems have contributed immensely in making available beneficial, i.e. therapeutic effect, of medicines. The field of drug delivery systems has undergone constant changes resulting in appearance of new systems which are safer and efficient in elicitation of therapeutic effect of drug. Various drug delivery systems have been broadly classified into two classes

- Conventional Drug delivery Systems
- Controlled drug delivery systems.

1.1 Controlled drug delivery systems:

In a controlled release product, one aims to achieve desirable effect of the drug through a control over release of drug from the dosage form.

In general, controlled delivery attempts to:

- Sustain drug action by maintaining a relatively constant, effective drug level in the plasma with concomitant minimization of undesirable side effects associated with a saw-tooth kinetic pattern.
- Localize drug action by spatial placement of a controlled release system (usually rate controlled) adjacent to or in the diseased tissue or organ
- Target drug action by using carriers or chemical derivatization to deliver drugs to a particular “target” cell type.
Advantages of controlled drug delivery systems:

- Reduction in dosing frequency,
- Reduced fluctuation in circulating drug levels,
- Increased patient compliance,
- Avoidance of night time dosing,
- More uniform effect,
- Reduction in GI irritation and other dose related side effects.

Disadvantages of controlled drug delivery systems:

- Unpredictable and often poor in-vitro and in-vivo correlation,
- Dose dumping,
- Reduced potential for dosage adjustment
- Increased potential for first pass clearance
- Poor systemic availability in general
- High cost.
1.2 Cancer and its treatment

Cancer is a group of diseases characterized by uncontrolled cell proliferation. The tissue developed due to uncontrolled cell division is called tumor or neoplasm. Tumors may be cancerous and sometimes fatal or they may be harmless. A cancerous neoplasm is called a malignant tumor & they have ability to undergo metastasis i.e. they spread to other parts of body where further proliferation starts.

Several factors may trigger a normal cell to lose control and become cancerous. One cause is chemical agent or radiation (carcinogens) that may induce mutations. Viruses are second cause of cancer. Although the link between viruses and cancer is strongly established for a variety of animal cancers, the relation in human cancers is less clear.

Following are the various forms of cancer:

- Carcinoma: Malignant tumors arising from epithelial cells.
- Melanoma: Malignant tumors arising from melanocytes which are skin epithelial cells producing melanin.
- Sarcoma: Malignant tumors arising from muscle cells or connective tissue.
- Osteogenic sarcoma: Malignant tumors arising from bone tissue.
- Leukemia: Malignant tumors arising from leukocytes.
- Lymphoma: Malignant tumors arising from lymphatic tissue.

Many cancers are removed surgically. However, when cancer is widely distributed throughout the body or exists in organs such as the brain whose...
functioning would be greatly harmed by surgery, chemotherapy and radiation therapy may be used instead. Chemotherapy involves administering drugs that poison cancerous cells. Radiation therapy destroys the chromosomes of cancerous cells, thus preventing them from dividing.

Intensive research is being carried out to explore new ways of treatment. These are gene therapy, manipulation of immune system, stimulation of normal hematopoetic elements, and induction of differentiation in tumor tissues & inhibition of angiogenesis.

Chemotherapy, though the preferred method of treatment, has many agonizing effects associated with it. Some of them are shown in table 1. In such case, it becomes utmost important to control the total concentration of anticancer drugs to which body is exposed.

1.2.1 Controlled drug delivery systems in the treatment of cancer:

The major problems in cancer chemotherapy are the toxic drug effects on normal cells and the rapid clearance of the drug from tumor tissues. Although anticancer drugs come from many different classes of chemicals and act by different mechanisms, they are toxic specifically to actively proliferating cells, regardless of whether they are malignant or normal, and rapidly eliminated from circulating blood by enzymatic degradation or urinary excretion. In many cases,
Table 1. Special adverse effects of some antineoplastic agents.

<table>
<thead>
<tr>
<th>Antineoplastic agents</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Busulphan</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Renal Toxicity, Ototoxicity</td>
</tr>
<tr>
<td></td>
<td>Peripheral Neuropathy</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Hemorrhagic cystitis</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Skin pigmentation</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Hepatic Damage</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Peripheral Neuropathy</td>
</tr>
<tr>
<td></td>
<td>Autonomic neuropathy</td>
</tr>
</tbody>
</table>
the toxic drug effects on normal cells are more profound and longer lasting than any therapeutic effects on tumor cells. Efforts have been, therefore, directed towards increasing therapeutic efficacy by:

I. Maintenance of drug plasma concentration in range of therapeutic window for sufficient period of time (i.e. sustained release) without significant fluctuation.

II. Placing the drug at the site of action & preventing the distribution of drug to other parts of body.

Both the purpose can be met by controlled drug delivery systems. Particulate systems like microspheres have been prepared using various biocompatible and biodegradable polymers to deliver the drug in controlled manner. At the same time, from the release pattern of the drug from such systems, it has been concluded that sustained release of drug will be obtained.

Extensive research work has been carried out to prepare particulate drug delivery systems as shown in Table 2 that can provide controlled delivery of drugs in treatment of cancer.
<table>
<thead>
<tr>
<th>Delivery system</th>
<th>Anticancer drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin microspheres</td>
<td>6-Mercaptopurine</td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td></td>
<td>Adriamycin</td>
</tr>
<tr>
<td>Poly(glutamic acid)</td>
<td>Phenylalanine mustard</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Agarose Beads</td>
<td>Mitomycin C</td>
</tr>
<tr>
<td></td>
<td>Cytosine arabinoside</td>
</tr>
<tr>
<td>Ethylcellulose microcapsules</td>
<td>Mitomycin C</td>
</tr>
<tr>
<td></td>
<td>Adriamycin, 5-Fluorouracil, Bleomycin</td>
</tr>
<tr>
<td></td>
<td>Carboquone</td>
</tr>
<tr>
<td></td>
<td>Peplomycin</td>
</tr>
<tr>
<td>Ferromagnetic ethylcellulose microcapsules</td>
<td>Mitomycin C</td>
</tr>
<tr>
<td>Magnetic albumin microspheres</td>
<td>Adriamycin</td>
</tr>
<tr>
<td>Poly(alkyl 2-cyanoacrylate)</td>
<td>Dactinomycin, Vinblastine, Methotrexate</td>
</tr>
<tr>
<td>Poly(L-lysine)</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Dextran</td>
<td>Mitomycin C</td>
</tr>
<tr>
<td>Gelatin Microspheres</td>
<td>Mitomycin C</td>
</tr>
</tbody>
</table>
These delivery systems also need to possess certain desired characteristics in order to make them acceptable for administration to achieve controlled drug delivery. Attributes for particulate drug delivery system to deliver the drug successfully in controlled manner are as follows:\(^\text{14}\):

- Restricted drug distribution to target
- Prolonged Control
- Ready access to tissue parenchyma
- Uniform carrier target tissue distribution
- Controllable and predictable rate of drug release
- High capacity for drugs and drug types
- Drug release unaffected drug action
- Therapeutic amounts of drug released
- Minimal drug leakage during carrier transit to target
- Drug protected
- Biocompatible surface properties
- Host protected from agent's allergic properties
- Biodegradable carrier
- No carrier-induced modulation of disease state
- Easy to prepare
1.3. References


