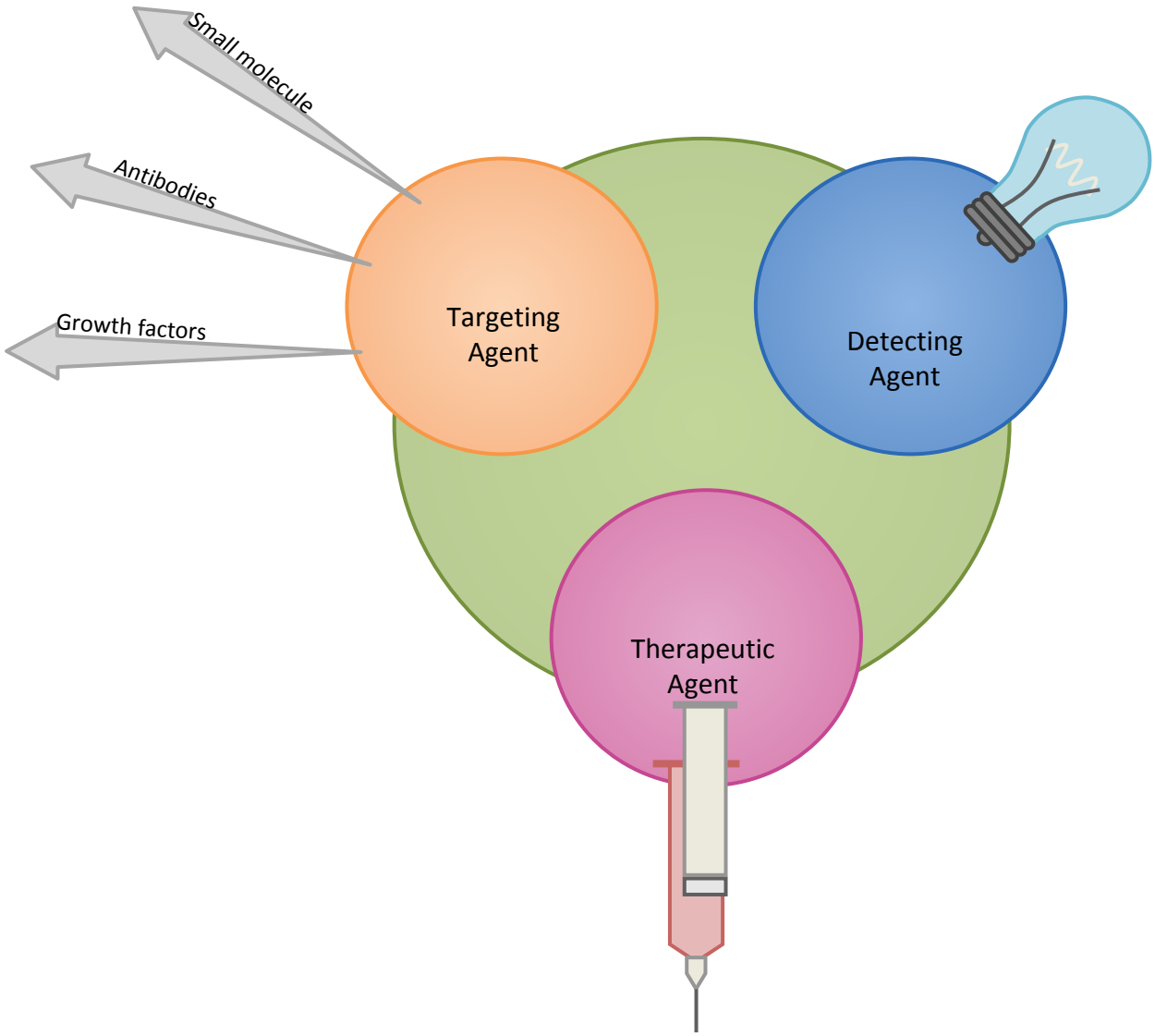
TARGETED DRUG DELIVERY SYSTEM


Small molecule
Antibodies
Growth factors
Targeting Agent
Detecting Agent
Therapeutic Agent

INTRODUCTION:

- DRUG DELIVERY is a special form of drug delivery system where the pharmacologically active agent or medicament is selectively targeted or delivered only to its site of action or absorption and not to the non-target organs or tissues or cells. The drug may be delivered
- To the capillary bed of the active sites,
- To the specific type of cell (or) even an intracellular region. Ex- tumour cells but not to normal cells,
- To a specific organ (or) tissues by complexing with the carrier that recognizes the target

REASON FOR DRUG TARGETING:

- In the treatment or prevention or diseases.
- Pharmaceutical drug instability in conventional dosage form solubility ,biopharmaceutical low absorption, high-membrane bounding, biological instability, pharmacokinetic / pharmacodynamic short halflife, large volume of distribution, low specificity, clinical, low therapeutic index.

OBJECTIVE:

- To achieve a desired pharmacological response at a selected sites without undesirable interaction at other sites, there by the drug have a specific action with minimum side effects & better therapeutic index. Ex- in cancer chemotherapy and enzyme replacement therapy.

IDEAL CHARACTERISTICS:

Targeted drug delivery system should be-

- biochemically inert (non-toxic), non-immunogenic.
- both physically and chemically stable in vivo and in vitro.
- restrict drug distribution to target cells or tissues or organs and should have uniform capillary distribution.
- controllable and predicate rate of drug release.
- drug release does not effect the drug action.
- therapeutic amount of drug release.
- minimal drug leakage during transit.
- carriers used must be bio-degradable or readily eliminated from the body without any problem and no carrier induced modulation of diseased state.
- the preparation of the delivery system should be easy or reasonably simple, reproductive and cost effective.

CONCEPT AND COMPONENTS OF TDDS

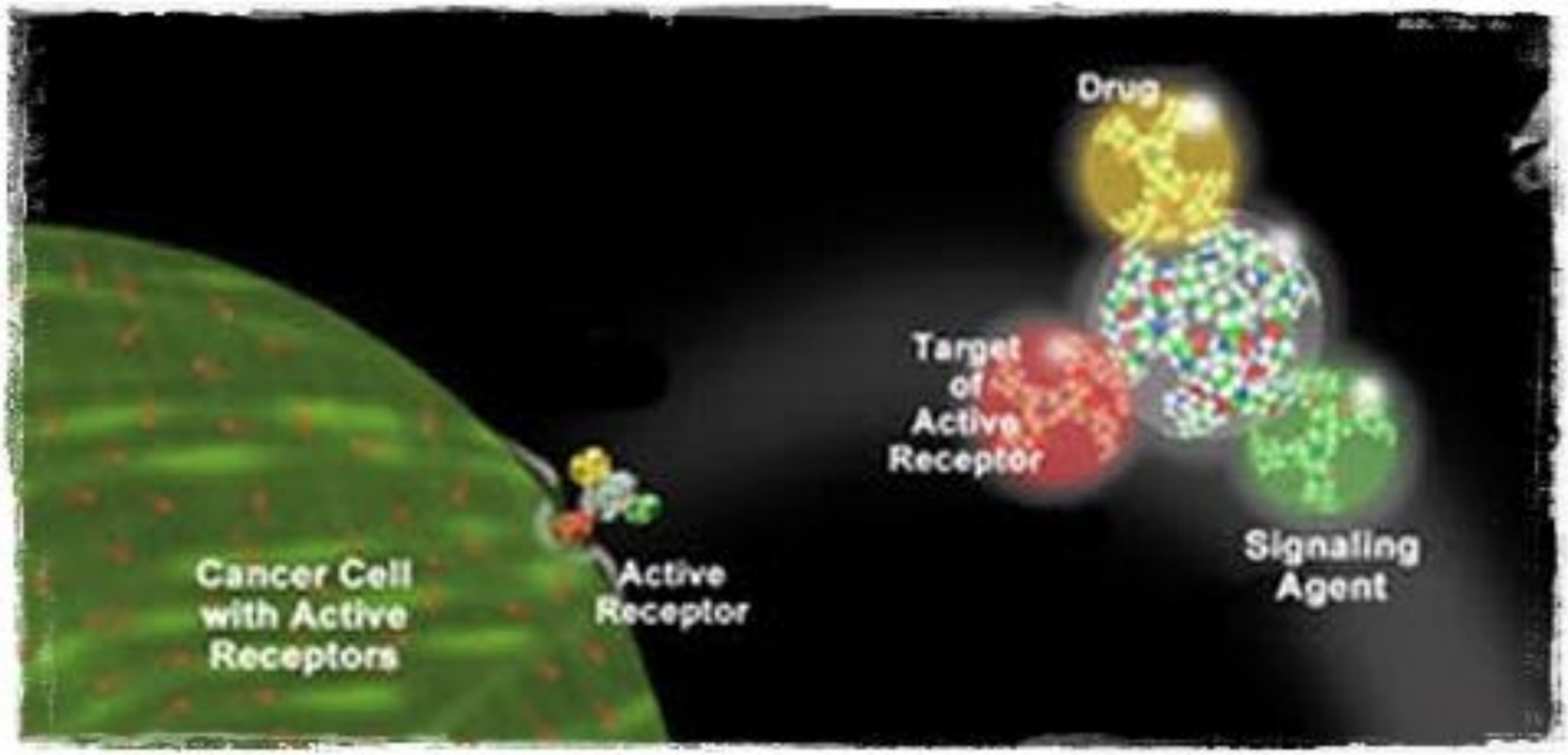
- Targeting of drugs to special cells and tissues of the body without their becoming a part of systemic circulation is a very novel idea. If a drug can be administered in a form such that it reaches the receptor sites in sufficient concentration without disturbing in extraneous tissue cells.

Such products are prepared by considering-

1.specific properties of target cells.

2.nature of markers or transport carriers or vehicles, which convey drug to specific receptors.

3.ligands and physically modulated components.


Drug
Target of Active Receptor
Signaling Agent
Cancer Cell with Active Receptors
Active Receptor

DEFINITIONS

TARGET:

- Target may be defined as a cell or group of cells in minority, identified to be in the need of treatment.

CARRIERS OR MARKERS:

- Carrier is one of the important entity essentially required for effective transportation of loaded drugs. They are vectors, which sequester, retain drug and transport or deliver it into the vicinity of the target cells.

LIGANDS:

- The ligands confer recognition and specificity upon carrier/vector and lend them to approach the respective target and deliver the drug. Ex-antibodies, polypeptides, endogenous hormones etc.

TARGETING OF MICROSPHERES

- Targeting is achieved by exploiting the natural distribution pattern of a drug carrier called passive targeting or by changing the natural distribution pattern of the carrier by some means there by directing the drug to the specific organ or tissue; this is called as active targeting.

PASSIVE TARGETING:

- Particles administered into the body intravenously will distribute itself in different organs depending on the size of the particles.
- Particles <7µm enter into the systemic circulation.
- Bigger particles may cause toxicity, particles of size 10-15µm can be used for lung targeting.
- Particles of 60-150nm size coated with the polymer such poloxamer are taken upto considerable extent by the bone marrow.

ACTIVE TARGETING:

- Active targeting includes coating of the microspheres with hydrophilic coating agents which suppress the opsonisation.
- When colloidal particles are administered into the blood stream, they may be coated with the proteins such as albumin, globulin etc., depending on the nature of the material surface charge & hydrophobicity of the particles. This is called as "opsonisation".

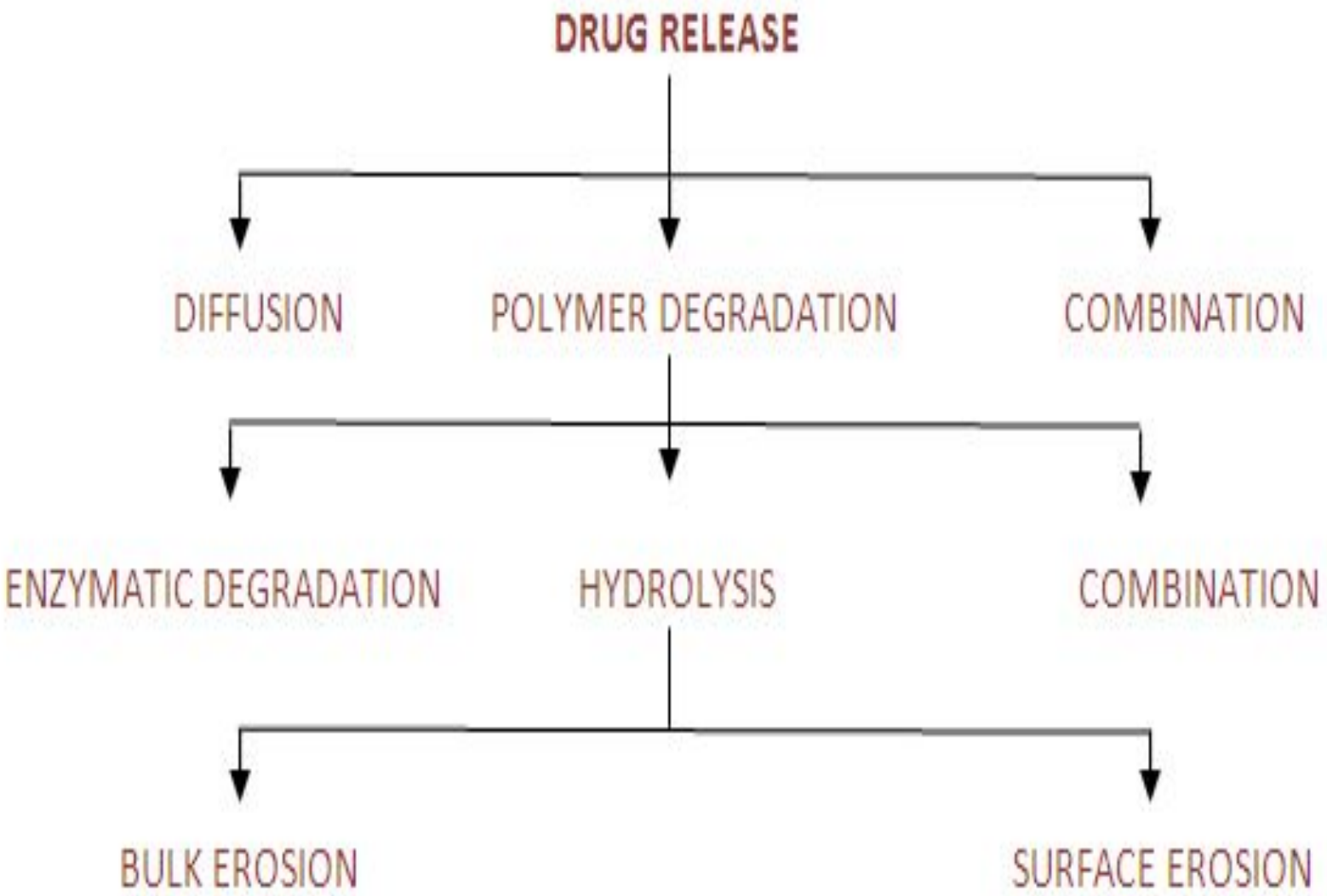
TARGETING USING MAGNETIC MICROSPHERES:

- Another approach in this area is by using magnetic microspheres. In this method the magnetic loaded microspheres. In this method the magnetic loaded microspheres is infused into an artery supplying a given target site.
- For example:- the anti-cancer effect of magnetic albumin microspheres containing Adriamycin in a rat model is found that the particles can be guided to the target site by magnetic means & a sustained release will be observed.

INTRACELLULAR TARGETING:

- Certain cytotoxic drugs are active intracellular, but are normally discarded due to their poor intracellular influx.
- The poor efficacy of many therapeutic substances for intracellular bacterial & parasitic therapy is known.
- The intracellular delivery of the drugs by suitable means can obviate these problems.
- For e.g. the biologically active streptomycin was released from albumin microspheres inside the phagocytic cells after ingestion and intracellular degradation of microspheres.

RELEASE MECHANISMS OF MICROSPHERES



Advantages:-

- Incorporation of magnetically responses materials into microspheres makes them susceptible to applied magnetic field, so that they are concentrated to the target site by the application of magnetic field externally to that site.
- Due to this rapid clearance of these microspheres by RES is prevented.
- Difference occurs maximally in capillary network so efficient delivery of drug to diseased tissue is achieved.
- Microspheres can transit into extravascular space creating an extravascular depot of drug for sustained released of drug with in the target areas.
- Increase of tumour targeting microspheres can be internalizing by tumour cells due to its which increased phagocytic activity as compared to normal cell. So the problem of drug resistance due to inability of drug to be transported across the cell membrane can be prevented.

Disadvantages:

- One of the major limitations of this system is, the drug cannot be targeted to deep seated organism in the body. This approach is confined to the targeting of drugs to superficial tissues like skin, superficial tumours or to the joints.
- Thrombosis at the site of catharization.
- The unknown toxicity of magnetic beads.
- The possible unwanted localisation of the product in the liver and at the regions of RES and the dangerous effects of self-flocculation of the magnetic particles causing vascular obstruction to vital organs in the body.

Concept of drug targeting by monoclonal antibody:

- Targeting with Ab depends on the presence of new Ag from the tumor cells Ab the ability to obtain specific Ab against them in normal cell the antigen are absent.
- The antigen associated with tumor cells are called as the" ***TUMOR MAKER".*** Antibodies produced as the results of the specific markers monoclonally can be conjugated with drug molecule which in turn can be targeted to the specific cells or tumor tissues.

Targeting antibodies with drugs involve the following steps:

- Identification of the antigen produced by the tumor cells.
- Production of antibody monoclonally against the identified antigen.
- Formation (or) producing drug antibody conjugate or complexes.
- These complexes concentrate at the tumor site and deliver the drug.

Drug antibody conjugate advantage:

- There are several advantages when drugs are delivered as antibody conjugates.
- The conjugates can specifically reach the target cells without causing any damage to the normal tissue.
- The drug antibody conjugate could be expected to be the ideal agents for drug targeting in chemotherapy.

Drug carrying capacity of antibody:

- The no. of drug molecules carried per antibody molecules is usually too low to be highly effective. Increasing the no. of drug molecules conjugated to antibody will eventually destroy its antigen binding capacity.