Muhammad Qamar -Uz- Zaman
Assistant Professor
Department Of Pharmacy
The Islamia University Bahawalpur.

N 13/19

CHAPTER

4

Session: 2013–18
Page: 1–5

Targeted Drug Delivery Systems

P1

Drug targeting 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 but not to the non-target organs or tissues or cells.

The drug may be delivered

- To the capillary bed of the active site.
- To a specific type of cell (or) even an intracellular region.
- Ex: Tumor cell but not to normal cells.
- To a specific organ (or) tissues by complexing with a carrier that recognizes the target.
- Historical prospective

The concept of designing specified drug delivery system to ac hive selective drug targeting has been originated from the perception of **Paul elrich.** He described that the targeted drug delivery system as MAGIC BULLET. He in 1902 wrote the molecules with a affinity for certain tissues could be used as carriers of cytotoxic agents (these depends on their physicochemical (or) biophysical interaction with the body). In the early 1960's a British scientists **Alec Bangham** observed that the phospholipid films would form closed spherical structure when they came in contact with aqueous phase that encapsulated part of the liquid medium in the interior leads to the discovery of liposome. In the year 1972, **Gregoriadis** described targeting with the help of novel drug delivery systems as OLD DRG IN NEW CLOTHS. According to **Widder et al,** the drug targeting of intravascularly administered chemotherapeutic agents includes three different strategies which could be classified as first order, second order & third order drug targeting.

First order entrapment of carrier drug complex into the first capillary network is encountered after its intravascular administration. Eg: Chemoembolization is best example of such type of targeting which involves intra-arterial injection of drug carrier complex near diseased site, mostly incase of tumors thereby blocking the capillary bed which suppress to that diseased area leading to cell death due to starvation as well as by action of chemotherapeutic agent being released slowly from drug carrier complex in the diseased area. *Second order* refers to targeting of chemotherapeutic agents to specific diseased cells. *Third order* targeting involves carrier guided release of drug in intracellular sites. i.e., ability of drug carrier complex to enter the target cell by endocytosis (or) by phagocytosis, shown by target cells itself.

REASONS FOR DRUG TARGETING

The present conventional drug delivery system often has side-effects & complications due to their wide distribution throught the body fluids. In the treatment (or) prevention of diseases, the other modes of drug delivery system show **non-specificity, Non-selectivity** & many drugs are not able to arrive at the target site in the body. Some drugs may get inactivated due to first pass metabolism (or) other mechanism. The localization of drug action in injured tissues may solve this problem. To achieve a desired pharmacological response at a selected site without undesirable interactions at other site, thereby the drug have a specific action with minimum side effects & better therapeutic index.

Eg: Cancer chemotherapy & Enzyme replacement therapy.

IDEAL CHARACTERISTICS

Targeted drug delivery system should be

1. Biochemically inert (non-toxic), non-immunogenic
2. Both physically & chemically stable in vivo & in vitro.
3. Restrict drug distribution to target cells (or) tissues (or) organs & should have uniform capillary distribution.
4. Controllable & predicate rate of drug release.
5. Drug release does not effect drug action.
6. Therapeutic amount of drug release.
7. Minimal drug leakage during transit.
8. Carriers used must be biodegradable (or) readily eliminated from the body without any problem & no carrier induced modulation of diseased state.
9. The preparation of the delivery system should be easy (or) reasonably simple reproductive & cost effective.

CONCEPT AND COMPONENTS OF TDDS

Targeting of drugs to special cells & 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 site 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 drugs to specific receptors.
3. Ligands & physically modulated components.

Target

Target could be described as a cell (or) group of cells in minority, identified to be in the need of treatment. Two distinctive cellular elements present on the surface of the target cell(s) are considered in designing of carriers for targeting via:

1. Cell surface antigens, exploited in generating cell surface & non-cross selective antibodies.
2. Cell surface receptor's, which recognize & internalize the macromolecular ligands associated carriers.

Various types of targets

1. Cells, invitro for genome grafting (or) manipulation of DNA (Genetic material).
2. Accessible anatomical compartment I.e., peritoneal cavity, cerebral ventricles, pleural cavity, lungs, lymphatics etc.
3. Macrophages and other phagocyte cells including kupffer cells, tissue macrophages & the blood macrophages (or) monocytes of MPS.
4. Non-phagocytic cells of RES (Reticulo endothelial system) including the liver endothelial cells.
5. Lymphocytes and antigen presenting cells.

Carriers or markers

Carrier is one of the important entity essentially required for effective transportation of the loaded drug(s). They are vectors, which sequester, retain drug and transport or deliver it into the vicinity of the target cells. Carriers can do so either through an ability inherent or acquired (through structural modification) to interact selectively with biological target or otherwise they are engineered to release the drug in the proximity of target cell lines, that demand optimal pharmacological action (therapeutic index).

Types of carriers or markers

1. Physical markers such as liposomes, microspheres etc.
2. Biological markers such as monoclonal antibodies, erythrocytes etc.
3. Chemical markers such as prodrugs.

Characteristics of ideal carrier:

It must be able to cross-anatomical barrier.
The target cells must recognize it specifically & selectively.
The linkage of the drug & the directing unit should be stable in plasma, interstitial and other biological fluids.
After recognitions and internalization, the carrier system should release the drug moiety inside the target organs, tissues and cells.
Carrier should be non-toxic, non-immunogenic & biodegradable particulate.

Ligands

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

APPROACHES

Now-a-days, present drug targeting is achieved by one of two approaches

1. Chemical modification of the parent compound to a derivative which is activated only at the target site.
2. Utilization of carriers such as Liposomes, microspheres, nanoparticles, monoclonal antibodies, cellular carriers (erythrocytes & lymphocytes), Macromolecules, platelets to direct the drug at its site of action.

a. Prodrug approach

A prodrug is an inactive chemical derivative of a parent compound that is activated predictably in vivo to the active drug species.

b. Chemical delivery system

It involves transformation of the active drug by synthetic means into an inactive derivative which when placed in the body, will undergo several; predictable enzymatic transformations principally at its site of action. This approach has proven to be successfully in delivery of drugs to the eye, brain & testis.

Although all the above mentioned techniques are quiet efficient in delivering drugs to preselected site but drug carrier complexes incase of liposomes, erythrocytes, platelets suffer majority stability problem, hence shelf-life of such preparation is tremendously reduced (or) they need to be stored under rigorous conditions which is not economically suitable. Monoclonal antibodies can deliver drugs to the targeted cells with very high degree of specificity, but selection & isolation of an appropriate antigen for developing monoclonal antibodies is again a very brain-taxing problem. Microspheres do not show any serious stability problem & also they can be easily prepared, hence, economically viable, but microspheres as such are also not free from disadvantages. They show poor specificity rapidly cleared off by reticulo endothelial system (RES).

These approaches can be further explained by

❖ Active targeting: (Ligands mediated targeting)

In active targeting the natural disposition pattern of a carrier is modified to target specific organs, tissues or attachment of cells specific ligands and monoclonal antibodies. It adopts modified drug-drug carrier molecules capable of recognizing and interacting with a specific cell, tissues or organ in the body. Modification of the carrier system includes, a change in the molecular size, alteration of the surface properties by incorporation of antigen specific antibodies or attachment of cell receptor specific ligands.

❖ Passive targeting(Natural targeting)

This refers to the natural distribution pattern of the carrier in vivo. Their particle size, shape, surface characteristics and the surface charge and particle numbers largely determine the disposition of the carrier. Hence it is possible to target to lungs and reticules endothermic system passives.

Ex: smaller particles can be readily removed from the blood by macrophages of RES, when administered systemically. This natural mechanism of a drug thus provides an opportunity to target drug encapsulated in or conjugated to an appropriated carriers system to macrophages. Passive targeting also includes deliver of drug carrier system directly to discrete compartment in the body.

Ex: Different regions of GI tract, eye, nose, knee joints, lungs, vagina, rectum and respiratory tract.

❖ Physical targeting

It refers to drug delivery systems that release a drug only when exposed to specific microenvironment such as a change in PH or temperature or the use of an external magnetic field.

Ex: in the presence of certain serum proteins (lipoproteins), unilamellar liposomes can be designed to release their pay loads efficiently at their liquid crystalline phase transition temperature. Liposomes with transition temperature of about 42C , can be made to release their drug preferentially in a capillary bed subjected to local hyperthermia. Thus increased tumor uptake of methotrexate has been achieved resulting in moderate effects in suppressing tumor growth. Magnetically responsive microspheres such as Albumin microspheres of approximately 1mm diameter containing magnetite when injected they localize in the area of applied magnetic field.

❖ Chemical targeting

A prodrug is a pharmacologically inert form of an active drug that must undergo transformation to the parent compound in vivo by either a chemical or enzymatic reaction to exert its therapeutic effects.

For a drug to be useful in site-specific delivery it must exhibit adequate access to its pharmacological receptors. Enzymes are chemical agents responsible for reactivating the prodrug. Prodrug should be able to show major effect on the target site. The active drug produced inside must be retained at the target site and should not leak out into the systemic circulation, which could lead to adverse effects. Thus, prodrugs are designated to alter the absorption, distribution and metabolism of the parent compound, there by increase its beneficial effects and decrease its toxicity.

Prodrugs are also used to reduce (or) overcome the formulation problem and to avoid an unpleasant taste and odour of the parent compound.

Eg: 1. Epinephrine to eyes in the treatment of Glaucoma.
2. Acyclovir an antiviral drug in herpes infection.

Advantages

1. Toxicity is reduced by delivering a drug top its target site, thereby reducing harmful systemic effects.
2. Drug can be administered in a smaller dose to produce the desired effect.
3. Avoidance of hepatic first pass metabolism.
4. Enhancement of the absorption of large molecules such as peptides and particulates.
5. Dose is less compared to conventional drug delivery system.
6. No peak and valley plasma concentration.
7. Selective targeting to infections cells that compare to normal cells.
8. Reduce toxicity of drugs to non-target site.

Disadvantages

1. Requires highly sophisticated technology for the formulation.
2. Requires skill for manufacturing, storage and administration.
3. Drug deposition at the target site may produce toxic symptoms.
4. Difficulty to maintain stability of the dosage form.
   Eg: released erythrocytes have to be stored at 4° C.
5. Drug loading is usually low. Ex: As in micelles. Therefore it is difficult to predict/fix the dosage regimen.
6. Higher cost of formulation.

Targeted Bioavailability-Pharmacokinetic and Pharmacodynamic Issues in Drug Delivery

Pharmacokinetics and pharmacodynamics have always had major role in drug delivery research. Investigating pharmacokinetic and pharmacodynamic issues during lead optimization is a critical part of the drug discovery and development process. The decision to move forward with a particular compound often depends on pharmacokinetic (PK) and pharmacodynamic (PD) evaluations at several stages in drug development, from early preclinical through Phase I, II, and III studies. It is recognized that it is in the early phase of drug discovery and development that optimization of key parameters that describe the absorption, distribution, metabolism, and excretion (ADME) of a drug candidate is required to reduce the failure rate at later stages of development. With the advent of combinatorial chemistry and high-throughput screening, the bottleneck in drug development is not in the identification of new active compounds, but rather in the optimization of lead compounds. Therefore, decision making at every stage of development becomes crucial. PK and PD can identify the key properties of a compound that will help in the decision to move forward with development. Because of this critical position in drug discovery and development, it is necessary to constantly review and assess the purpose of PK and PD analyses and to develop new ways to view and apply these concepts. Therefore, it is the intent of this chapter to describe an approach for considering