ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

REVIEW ARTICLE

Targeted drug delivery system in cancer

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ABSTRACT

Drug targeting implied the method for localizing a therapeutic agent on the minority of cells that are actually in need of treatment. This system allows the administration of a drug to a selected target area at the proper therapeutic dosage by the use of colloidal drug carriers which includes liposome, Niosome, Microspheres, Released erythrocytes, Immunoglobulin, Serum-proteins, and Synthetic polymers. Enhancement of activity duration for short half-life drug; Elimination of side effects, Maintenance of optimum therapeutic drug concentration in the blood with minimum fluctuation can be achieved by this techniques.

Keywords: Prodrug, Liposomes, Nanoparticles, Niosomes, Released Erythrocytes.

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ISSN: 0975-8585

INTRODUCTION

Drug targeting implied the method for localizing a therapeutic agent on the minority of cells that are actually in need of treatment. The effectiveness of many drugs is often limited by their inability to fully reach the targeted site of action. This system allows the administration of a drug to a selected target area at the proper therapeutic dosage by the use of colloidal drug carriers which includes liposome, Noisome, Microspheres, Released erythrocytes, Immunoglobulin, Serum-proteins, and Synthetic polymers.

Controlled drug delivery is the use of system and techniques for altering and controlling the absorption, concentration, and organ distribution, and cellular uptake of therapeutic agents or drug. Drug targeting is the manipulation and if possible, the total control of the distribution of a drug by associating it to a drug-carrier. In other words a drug-carrier complex would only delivery the drug to specific target cell types. The distribution of the drug in the tissue will not depend on the properties of the drug but on the carrier, which will be chosen on the basis of the selected target. By improving the way drug are delivery to the target cell types a controlled release drug delivery system has the following benefits over conventional drug delivery. [1]

- Maintenance of optimum therapeutic drug concentration in the blood with minimum Fluctuation;
- Predictable and reproducible release rates for extended duration;
- Enhancement of activity duration for short half-life drug;
- Elimination of side effects, frequent dosing, and waste of drug; and
- Optimized therapy and better patient compliance.

Various therapeutic techniquenics are available as follows: Prodrug, Cell-receptor conjugates, colloidal drug delivery, Active targeting, Nanoparticles, Niosomes, Released erythrocytes, Polymer drug delivery.

Methods of Drug targeting;

Various Targeted Therapeutic Techniques are as follows:

- Prodrug
- Prodrug design using enzyme targeting [2].

Prodrugs can be designed to target specific enzymes or carriers by considering enzyme-substrate specificity or carrier-substrate specificity in order to overcome various undesirable drug properties.

In prodrug design, enzymes can be recognized as presystemic metabolic sites or prodrug in vivo reconversion sites. The enzyme targeted prodrug approach can be used as site-specific

drug delivery. These prodrugs have the additional advantage of producing nontoxic nutrient by products when they regenerate the active drug in vivo.

- Strategy for Site-Specific Drug Delivery[3]

These factors should be optimized for the site-specific delivery of drugs by using the prodrug approach.

1. The prodrug must be readily transported to the site of action, and uptake to the site must be rapid and essentially perfusion rate limited.
2. Once at the site, the prodrug must be selectively cleaved to the active drug relative to its conversion at other sites.
3. Once selectively generated at the site of action, the active drug must be somewhat retained by the tissue.

In the prodrug approach, site-specific drug delivery can be obtained from tissue-specific activation of a prodrug, which is the result of metabolism by an enzyme that is either unique for the tissues or present at a higher concentration (compared with other tissues); thus, it activates the prodrug more efficiently. This type of site-specific drug delivery has been of particular concern in cancer chemotherapy. New therapies have been proposed which attempt the localization of prodrug activating enzymes into the specific cancer cells prior to administration. These new approaches are referred to as [4].

- ADEPT(antibody-directed enzyme prodrug therapy) and
- GDEPT (gene-directed enzyme prodrug therapy).

General Concept Of Antibody Directed Enzyme Prodrug Therapy (ADEPT) [5,6]

Enzymes that activate prodrug can be directed to human tumor xenografts by conjugating them to tumor-selectivity monoclonal antibodies. As illustrated in Figure 1, an antitumor antibody is conjugated to an enzyme not normally present in extra -cellular fluid or cell membranes and then these conjugated are localized in the tumor via intravenous infusion. After allowing for the conjugate to clear from the blood, a prodrug is administered that is normally inert but is activated by the enzyme delivered to the tumor. This is the ADEPT procedure. Using different combinations of antibody, enzyme, and prodrug, many classes of human tumor xenografts have been shown to be very sensitive to this procedure, although in most cases they are quite to conventional chemotherapy Early clinical are promising and indicate that ADEPT may become an effective treatment for solid cancers for which tumor-selective antibodies are known. **(**Figure-1)

ISSN: 0975-8585

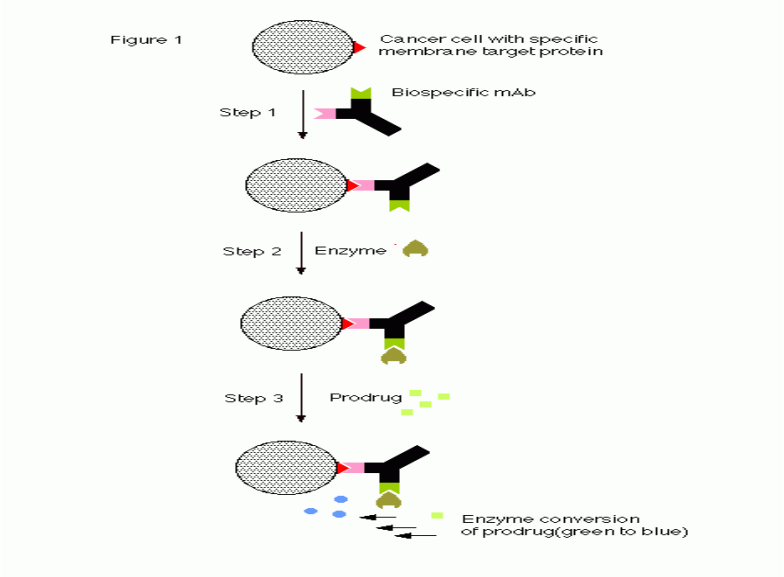

Figure-1:General Concept Of Antibody Directed Enzyme Prodrug Therapy (ADEPT)

General Concept of -directed enzyme prodrug therapy (GDEPT) [7,8]

Tumors have also been targeted with genes encoding prodrug activating enzymes. This approach can use a viral vector (E.g. retroviral or adenoviral) to carry a prodrug-activating enzyme gene into both tumor and normal cells (fig.2) by linking the foreign gene downstream of tumor-specific expression of the foreign gene can be achieved. This approach has been called virus-directed enzyme prodrug therapy (VDEPT) or more generally gene-directed enzyme prodrug therapy (GDEPT). In additions to viral vectors, several methods for delivery of the genes to the target tumor, under the control of tumor-selected promoters have been proposed using liposome and cationic lipids.
(Figure:2)

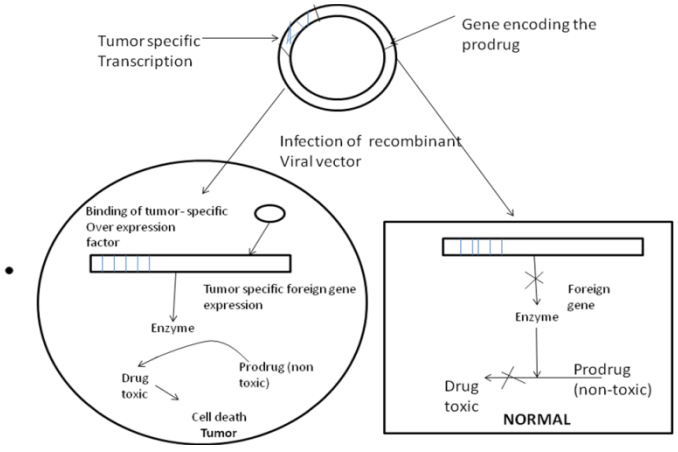

Figure-2: gene-directed enzyme prodrug therapy (GDEPT) concept

ISSN: 0975-8585

For the appropriate combinations of an enzyme and a prodrug, the choice of enzyme is very important because the appropriate prodrugs can be designed for almost any enzyme.

Cell-receptor conjugates[9].(Figure:3)

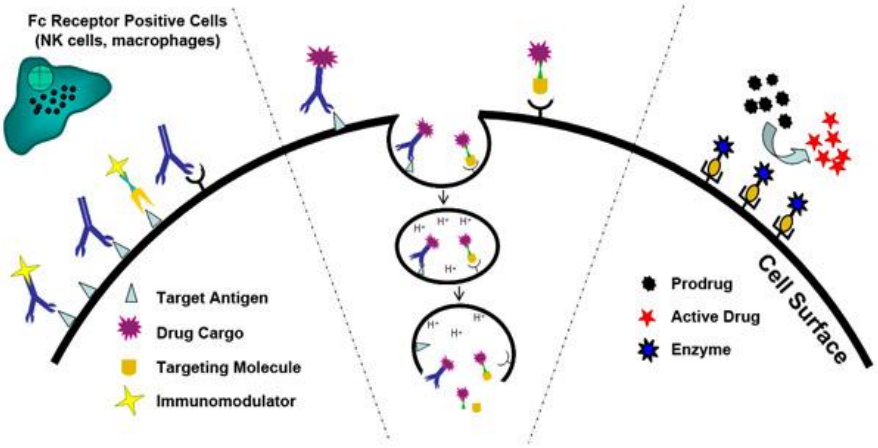

Figure:3 Cell-receptor conjugates

- **Drug Targeting and delivery using vitamin conjugates**:

The vitamin folate, which is required for cellular division, is used to deliver drug to rapidly dividing cancer cell. In order to capture the folate needed to divide, cancer cells over-express a folate receptor on the cell member. Folate binds to the folate receptor and the folate-drug conjugate is delivered into the cell via a process called endocytosis. Endocytosis allows cells to absorb selected materials, such as vitamins, from outside the cell. Once the drug is delivered inside the cell, the drug is released and the receptor recycles back to the surface to capture-more folate.

Vitamin receptors are over expressed on cancer cells, allowing the delivery of the drug specifically to the cancer cell. A member of researchers have compared the number of folate receptors on malignant tissue versus normal tissue. Research shows that malignant ovarian, endometrial and brain tissue all have significantly higher numbers of folate receptors than normal tissues. Folate receptors have also been detected in breast, lung, colon, kidney, and head/neck cancers.

The specificity of folate conjugate for cancer cells can be demonstrated by exposing both normal and cancer cells to a folate-targeted fluorescent probe. A few hours after being treated with folate-targeted fluorescent probe, the cells were examined using a microscope that detects fluorescence. As shown in the right hand panel, all of the cancer cells showed significant uptake of the probe, while the normal cells showed no uptake.
Technology Advantages:

ISSN: 0975-8585

1) Endocyte's vitamin-based drug delivery system has many advantages over other drug delivery technologies, such as monoclonal antibodies, for the following reasons:
2) Folate's much smaller size make it easier for the conjugate to penetrate deep into the tumor and reach all cancer cells.(folate's molecular weight is 441, while many monoclonal's molecular weights are 150,000)
3) The affinity of folate for its receptor on cancer cells is make is 100x higher than the affinity for monoclonal antibodies increasing the like likely hood that the folate-drug conjugate will bind to the receptor.
4) Since the folate receptor on cancer recycles, a large number (20-60 million) of folate-drug conjugate can be delivery into the cell in 4hours.
5) Folate conjugate are not destroyed by lysosomes inside the cell. In order
6) To destroy potentially harmful substances, cells have compartments called lysosomes that are designed to destroy molecules. Since folate is brought into the cell for consumption not destruction folate are not targeted by lysosomes. This is essential for the delivery of many types of drug includes genes and proteins.
7) Folate is a natural substance and does not elicit an immune response from the body. It can, therefore be administered, any times. On the other hand, unless humanized (an expensive process), monoclonal's prompt an immune response that destroys the monoclonal antibody before it can reach the cancer cell.
8) Finally, folate is readily available, easy to synthesize and manufacture, stable during synthesis and storage, and can be attached to a wide variety of drugs.

Drug targeting can be done by using various carriers, as follows:

- Liposomes
- Implants
- Niosomes
- Emulsions
- Released Erythrocytes
- Nanoparticles
-

The ultimate goal of drug delivery is the administration of the therapeutic agents, drugs to the target cells with the minimization of harmful side effects. Drugs can be delivery in the two ways;

- passive targeting.
- active targeting.

In passive targeting the natural course followed by the liposome after injections is used as the method of drug delivery. While in active targeting there is directed movement of the liposome to a specific organ, tissue or cell.

ISSN: 0975-8585

- Passive Targeting

Conventional liposomes lend themselves to passive targeting exclusively; they are removed from the blood stream too quickly to be involved in active targeting. However, they are quite effective in treating diseases the macrophages are directly involved.

Sterically stabilized liposomes can also be used in passive targeting. When sterically stabilized liposomes injected into a person with either a solid tumour or an internal infection the liposome will migrate and aggregate in the diseases area naturally. As the liposome degrade they will release their content to the target area. Thus, once again the liposome is following its nature course while targeting a specific area.

- Active targeting

Active targeting can only be done sterically stabilized liposome and is divided into three categories. This division include delivery to an organ or tissue or a particular cell and finally the most difficult an intracellular compartment. Active targeting involves the attachment of ligands to the surface of liposomes. These ligands have complementary ligands on the target cell. Therefore, when the liposomes get close to a target call it will bind to it and release its content.

Routes of Drug Release into the Cell;

➢ Passive Transport

Once the liposomes reach its target destination it must be relived of its contents. The way this is done depends on both type of liposome and mode of delivery. For conventional liposome and passive targeting, the cell as mentioned earlier engulfs the entire liposome. The digestive enzymes of the cell will then begin to degrade the liposome and release the drug. The rate of this degradation tends to follow a Michaelis-Menten reaction:

$$R_{degradation} = V_{max}\, C/Km+C \qquad (1)$$

Where Vmax is the maximum rate of reaction Km is the substrate concentration corresponding to half the maximum reaction rate, and C is the concentration of the substrate.
For sterically stabilized and passive targeting, the drug will be release from the from the liposome as it is degraded over time. Therefore, since these liposomes have accumulated near the diseased cells, the drug will diffuse into the cells through the passive transport modal. The mass flux is given by:

$$N_A = P_{Am} (C_{As}^{1} - C_{As}^{2}) \qquad (2)$$

Where C_{As}^{1} and C_{As}^{2} are the concentration of the drug in the solvent outside and inside the cell respectively and Pam is the permeability of the drug given by

$$P_{Am} = D_{Am}\, \lambda/Lm \qquad (3)$$

Where D_{Am} is the diffusion coefficient of the drug through the members, Lm is the thickness of the members and λ is the coefficient between the members and the solvent.

- Active Transport

There are four main ways by which the active transport may occur.

They are

1) Lipid exchange
2) Endocytosis
3) Adsorption and
4) Fusion

In lipid exchange the liposome and cell members will exchange lipids due to similarity of their membranes. The mechanism of this exchange is not entirely understood. Along with this exchange of membrane lipids there can be an exchange of lipophilic drugs located in the bilayer. However, this does not represent a major transport mechanism for delivering drugs to the target cells.

Endocytosis is the most common mechanism of delivery. In this case the liposome is adsorbed on the cell's surface will the help of the identifying ligands and engulfed into phagosomes, which transport them to liposome. These liposomes then use digestive enzymes to degrade the liposomes, releasing its contents. This degradation follows the same enzyme kinetics as equation [1].

However, there are only a few cell types that can effectively phagocytes larger liposomes. Therefore liposomes often adsorb to the surface and remain there until they are degraded by lipid depletion, oxidation and hydrolysis. Once degraded the liposomes will release their contents and the drugs will diffuse into the cell. This diffusion will be governed by the same equations as for the passive transport of a sterically stabilized liposome namely equation [2] and [3]. The final mechanism of active transport is fusion. This is where the liposome actually fuses to the cell membrane and releases its contents directly into the cytoplasm. This mechanism requires a virosome containing reconstituted viral surface proteins which allows it to the target cell.

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