Review Article

Targeted Drug Delivery System: Advantages, Carriers and Strategies

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ABSTRACT

Drug targeting is a new drug delivery system that aims to deliver the drug to the target site of action or site of absorption without releasing the drug at any other non-target site. The delivery system is designed to retain the intact drug without any modification until reaching and releasing at the target site. The targeted drug delivery systems have several advantages over conventional ones as improvement of pharmaceutical activity, low side effects and reduction of the administered dose. The main purpose of the targeted drug delivery system is to obtain the pharmacological action of the therapeutic agent at diseased organs only without affecting the healthy one especially in the case of cancer treatment with chemotherapeutic agents. Drug targeting can be attained using different carriers that maintain and transport the intact drug to preselected organ or tissue. Different types of carriers can be used for drug targeting such as nanotubes and nanowires, nanoshells, quantum dots, nanopores, gold nanoparticles, dendrimers, noisome, ufasomes, virosomes, cubosomes, nanobots and transferosomes. There are different mechanisms of drug targeting such as passive targeting, inverse targeting, active targeting, ligand-mediated targeting, physical targeting, dual targeting and double targeting. The drug targeting is a useful delivery system for delivering the therapeutic agent to a specific site without causing toxicity in other organs.

Key words: Drug targeting, Drug delivery system, Pharmacological action, Chemotherapeutic agents, Gold nanoparticles.

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INTRODUCTION

The biological effects of a drug in a patient depend on the pharmacological properties of the drug.[1] These effects arise due to the interactions between the drug and the receptors at the site of action of the drug. The efficacy of this drug-target interaction has been undermined unless the drug is transported to its site of action at such a concentration and rate that causes the minimum side-effects and maximum therapeutic effects.[2] Targeted drug delivery, is the method of treatment that involves the transportation of the therapeutic agent to specific tissue without reaching the remaining part of the body.[3] Therefore, it delivers the medication only to areas of interest within the body. This offers an improved efficacy of treatment and reduces side effects.[4] It differs from the conventional drug delivery system in that, it gets a release in a dosage form while the former functions by the absorption of the drug through the body's semipermeable membrane.[5,6]

Conventional dosage forms such as injections, oral formulations comprising of solutions and suspensions, tablets, capsules and topical creams and ointments, possess certain disadvantages.[7] Parenteral delivery of drugs is highly invasive with short time effects.[8] Oral administration of the drug, although being immensely popular and appropriate but can't be used for certain drugs, such as peptide drugs, due to their poor absorption by the oral route.[9] These may be degraded in

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the gastrointestinal tract. Topical ointments and creams have a drawback of being limited to the local effects, rather than the systemic effects.[10]

The technology of the drug delivery system has become advanced and controls the drug bioavailability, drug absorption and pharmacokinetic parameters.[11] The process of drug targeting requires four principles, first, the ability to load the drug to the target site, second, avoid the degradation by body fluid, third, reaching the target site and fourth, release the drug at the specific site at the predetermined time.[12,13] Different sites of interest within the body necessitate the use of different drug delivery systems, depending upon the route to be followed.

In drug targeting, the drug may be delivered to[4,14]

- The capillaries of the target site.
- The specific type of cells as in the case of cancer cells.
- Specific tissues or organs which recognize the drug carrier.

Causes of using the targeted drug delivery systems

There are several causes for the application of a targeted drug delivery system which include:[15]

1. Low drug stability.
2. Poor drug absorption.
3. The short half-life of the drug.
4. The large volume of distribution of the drug.
5. Low drug specificity.
6. Narrow therapeutic index of the drug.

The ideal features of a targeted drug delivery system

The targeted drug delivery system must have certain properties which include:[4]

1. It should be stable, safe (non-toxic), compatible with body fluid and biodegradable.
2. Deliver the drug only to the target site.
3. Control the drug release at a predetermined rate.
4. The rate of drug release not affecting the pharmacological effect.
5. Minimum leakage of the drug during transportation to the target site.
6. Using an inert, biodegradable, or easily eliminated carrier.
7. The preparation process of the drug delivery system should be simple, easy and costless.

The advantages of drug targeting[13]

1. The protocol of drug administration becomes simpler.
2. The toxicity of the drug is decreased by targeting a specific site.
3. The desired drug response can be reached by a small dose.
4. Avoid the first-pass effect.
5. Improvement in the drug absorption from the target site.
6. Drug targeting resulted in no peak and valley plasma concentration.

The disadvantages of drug targeting[16]

1. Rapid drug elimination from the body results in high dose frequency.
2. The carrier of the targeted drug delivery system may result in the immune response.
3. The drug delivery system is not localized at the tumor tissue for sufficient time.
4. The diffusion and redistribution of released drugs.
5. The manufacturing, storage and administration of the targeted drug delivery system require high expertise in this field.
6. Toxicity may be raised from drug deposition at the target site.
7. The stability of the product will be difficult to be attained.

Carries applied for drug targeting[17]

a. Drug targeting can be attained by using carrier systems.
b. The carriers are systems which required for transportation of entrapped drug to target sites.
c. The carriers entrap the drug moiety and deliver it into the target site without releasing it in the non-target site.

Different types of carriers applied for drug targeting

There are lots of carriers applied in the targeted drug delivery system as shown by Figure 1, which include:

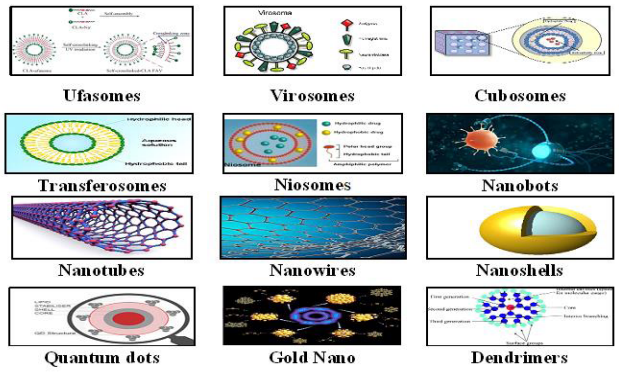

Figure 1: Different types of carriers for drug targeting.

Nanotubes

Nanotubes are a type of drug delivery system which is a hollow cylindrical tube made of carbon that can be easily filled and sealed with the required drug.[18,19] They are usually used for delivering the drug to the cancer cell.[20,21] Liu *et al*. applied carbon nanotube for targeting the tumor in mice.[22] Also, Mc Devitt *et al*. achieved tumor targeting with antibody-functionalized, radiolabeled carbon nanotubes.[23]

Nanowires

It is a wire with a very small diameter made of metal or other organic compounds. It possesses a large surface area, so the surface can be treated to allow the nanowire to bind with specific biological molecules when inserted inside the body. It can be used for detecting the causes and treatment of brain diseases, such as seizures, parkinsonism and similar diseases.[24,25] This system can treat Parkinson's and similar diseases.[26] Also, it can be used for the detection and localization of tumors.[27] Hong *et al*. used fluorescent zinc oxide nanowires for molecularly targeted imaging of cancer cells.[28]

Nanoshells

Nanoshells are new strategies of nanoparticles, consisting of a hollow dielectric core of silica covered by a shell of gold[29,30] It may be used for diagnostic or therapeutic purposes. Nanoshells can be attached with antibodies on their surfaces, allowing them to conjugate certain areas such as cancer cells.[31] This technique is very effective in targeting the antineoplastic drug.[32] Loo *et al*. studied the ability of nanoshells in imaging and treatment of cancer.[33]

Quantum dots

Quantum dots are nanocrystalline semiconductor particles that possess distinctive optical characters which import them the ability to be used in imaging of tumors.[34-36] This carrier is effectively used for targeting cancer drugs.[37] Pardo *et al*. used quantum dots and nanotubes for cancer targeting and drug delivery.[38]

Nanopores

They have very tiny holes that allow the passage of DNA molecules in one strand at a time. So, allow highly exact and effective DNA sequencing.[39,40] This technique has potential in genetic engineering[40,41] and biotechnology.[42] Schneider *et al*. reported DNA translocations through nanopores created in graphene membranes.[43]

Gold nanoparticles

The gold nanoparticles are used by scientists to develop an ultrasensitive detection system for DNA[44] and the protein markers associated with the presence of different types of cancer,[45] like breast and prostate cancer.[46] Peng *et al*. used gold nanoparticles in the diagnosis of lung cancer.[47]

Dendrimers

Dendrimers are synthetic nanoparticles with a specific diameter.[48] They consist of a control core surrounded by layers of polymers.[49] There are several sites at the surface of the dendrimers to which the drug may be attached.[50] They are used in gene transfection and medical imaging.[51–55] Abd-El-Aziz and Agatemor, reviewed the biomedical applications of dendrimers.[56]

Liposomes

Liposomes are microscopic bilayer structure vesicles prepared using natural phospholipid.[57] They can entrap both hydrophilic and lipophilic drugs in the aqueous space or the phospholipid bilayers.[58,59] The percentage of entrapped drug depend on the physical and chemical properties of the drug and the composition of the lipids.[60] Huwyler *et al*. studied the tumor-targeting using liposomal antineoplastic drugs.[61]

Niosomes

Niosomes are non-ionic surfactant vesicles which can entrap both hydrophilic and lipophilic drug. The stability of niosomes is higher than liposomes due to the natural properties of phospholipid.[62-64] It was found that niosomes are effective for targeting antineoplastic drugs, anti-inflammatory, anti-bacterial, anti-fungal and antiviral drugs.[65] Liu *et al*. designed and evaluated a novel niosomal delivery system of daunorubicin (DNR) for targeting against acute myeloid leukemia (AML).[66] Ahmed *et al*. prepared piroxicam niosomes to target the analgesic and anti-inflammatory effect at the pain area.[67]

Ufasomes

Ufasomes are a dispersion of unsaturated fatty acid vesicles prepared from fatty acid and ionic surfactant (soap) in presence of cholesterol. Ufasomes are a good carrier for drugs intended for topical application. The outermost layer of the skin, which is the stratum corneum, is considered the main barrier for drug penetration. This problem can be overcome by using ufasomes as DDS because the ufasomes consist of lipid membrane which has the ability to attach to the skin. Kaur *et al*. studied and enhanced the antifungal activity of oxiconazole loaded ufasome against *Candida albicans*.[68]

Pharmacosomes

Pharmacosomes are a neutral molecule which carries both positive and negative charges and possesses both

hydrophilic and lipophilic characters with an optimum ratio of polyphenol with phospholipids in form of a complex. The drug is conjugated to the lipoidal complex by electrostatic force or by forming a hydrogen bond.[69] The term pharmacosome is derived from the word Pharmakon, meaning drug and soma, meaning carrier. The conjugation of the drug to the lipoidal complex may be in the form of micelles or hexagonal aggregates.[4] Semalty *et al.* developed and evaluated pharmacosomes of aceclofenac.[70]

Virosomes

Virosomes are drug delivery systems described as unilamellar vesicles prepared from phospholipids.[71,72] The surface of virosomes contains sites to which the virus-derived glycoproteins are attached to facilitate the recognition and targeting of the virosomes to the target site inside the body.[73] Lucarini *et al.* design an innovative platform for the treatment of cerebral tumors using erythro-magneto-HA-virosomes.[74]

Cubosomes

Cubosomes are nanostructured drug delivery systems prepared from certain lipids. They are described as liquid crystalline nanoparticles having a cubic structure suitable for injection.[75] Azhari *et al.* used Tween 80 to stabilize phytantriol-based cubosomes for delivering macromolecular therapeutics to the brain.[76]

Nanocrystal

Nanocrystals are the material having a dimension less than 100 nm and present in the form of one crystalline structure.[77] The nanocrystals differ from nanoparticles in that nanoparticles have a dimension of less than 1000 nm.[78] Liu *et al.* studied the importance of drug loading nanocrystals in targeting and treatment of cancer.[79]

Nanobots

Nanorobotics is a new technology of drug delivery systems.[80,81] They are a nanoscale machine with a diameter of 10^{-9} m.[80] Andhari *et al.* prepared self-propelling targeted magneto-nanobots for deep tumor penetration.[82]

Transferosomes

Transferosomes are such a novel vesicular drug delivery system. Transformers are specially self-optimizing, self-regulating, ultra deformable "ultra-flexible". possessing an inner aqueous core surrounded by a complex lipid bilayer with unique properties, due to the presence of "edge activators" into a vesicular membrane, the surfactant has been used as edge activators. So it can penetrate the skin efficiently by squeezing themselves through pores from 5 to 10 times less than their diameter.[83,84] This will avoid complete rupture of the vesicle and remaining the drug intact after penetrating the skin.[85] Qushawy *et al.* prepared miconazole nitrate transferosomal gel for effective treatment of skin candida infection.[86]

Strategies for drug targeting

There are several strategies for drug targeting as shown by Figure 2 which include:

Passive targeting

Passive targeting usually refers to the drug delivery systems which target the drug to the systemic circulation.[87] The passive targeting is done as a response from the body to the physicochemical properties of the drug or the drug delivery system which entrap the drug till reaching the target site,[88] see Figure 3. Zhang *et al.* used salinomycin passive targeting micelles for suppression of breast cancer and stem cell cancer.[89]

Active targeting

In this strategy, the drug targeting is done as a result of the identification of the target group which is attached at the surface of the drug delivery system to the receptors in the target cells.[4] The target group include bioadhesive nonionic surfactant, antibodies, or albumin protein.[90] The active targeting has three types, First-order targeting (organ targeting), Second-order targeting (cell targeting) and Third-order targeting (intracellular targeting),[91] see Figure 3. Zwicke *et al.* utilized the folate receptor for active targeting of anticancer drugs.[92]

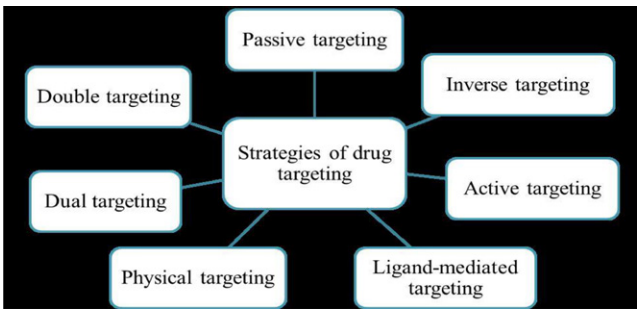

Figure 2: Different strategies for drug targeting.

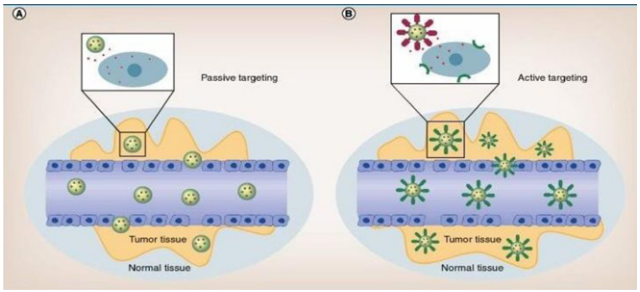

Figure 3: Mechanism of passive targeting and active targeting.[93]

Inverse targeting

The inverse targeting aims to avoid the passive uptake of the drug delivery system by the reticulum-endothelial system (RES).[94,95] This process can be achieved by suppressing the normal uptake function of RES via injection of a large amount of the blank drug delivery system or large molecules of dextran sulfate to make a saturation of RES and suppress the defense mechanism.[90] The inverse targeting is very useful for drug targeting to non-RES organs.[96] Balthasar and Fung, used an inverse targeting strategy for targeting methotrexate to peritoneal tumors.[95]

Ligand mediated targeting

This type of drug targeting depends on the receptor uptake of natural low-density lipoprotein (LDL) particles and synthetic micro-emulsions of LDL particles covered with Apo proteins.[97] Veiseh *et al.* applied a ligand-mediated targeting strategy for the treatment of cancer.[98]

Physical targeting

The physical targeting strategy aims to achieve external physical change in the drug delivery systems to allow targeting them to the specific site. The physical changes include temperature change, change in pH and applying an electric field.[99] This method is very potential for tumor targeting and gene targeting.[100,101] Weichselbaum *et al.* applied physical targeting in gene therapy.[102]

Dual targeting

The dual targeting mechanism involves a drug delivery system in which the carrier has a synergistic effect on the entrapped drug and hence increase the therapeutic effect.[4] For example, a carrier molecule with antiviral activity when loaded with antiviral drug the therapeutic effect is enhanced. Cui *et al.* applied dual-targeting for delivery of paclitaxel and curcumin for management of brain tumors.[103]

Double targeting

The double targeting strategy is a combination of both temporal and spatial, so it is called double targeting.[90] The spatial delivery involves the targeting of the drug to the target site, while the temporal delivery involves the controlling of drug release at the target site.[4] Pitto-Barry *et al.* applied a double targeting mechanism for targeting a dendrimer-loaded anticancer drug to the tumor site.[104]

CONCLUSION

Drug targeting is a new approach intended for delivering the drug molecules to a specific site or organ inside the body. This delivery system resulted in a reduction in the dose and thus the side effect of the drugs. There are several delivery systems used in drug targeting such as liposome, transferosome, gold nanoparticles, niosomes, cubosome, virosome, nanotube. The targeted drug delivery system is very important in the treatment of several types of cancer such as brain cancer, breast cancer, prostate cancer and colon cancer. Now, there is progress in the field of drug targeting to overcome the problems associated with conventional drug delivery systems.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DNA: Deoxyribonucleic acid; **DNR:** Daunorubicin; **AML:** Acute myeloid leukemia; **RES:** Reticulum-endothelial system; **LDL:** Low-density lipoprotein

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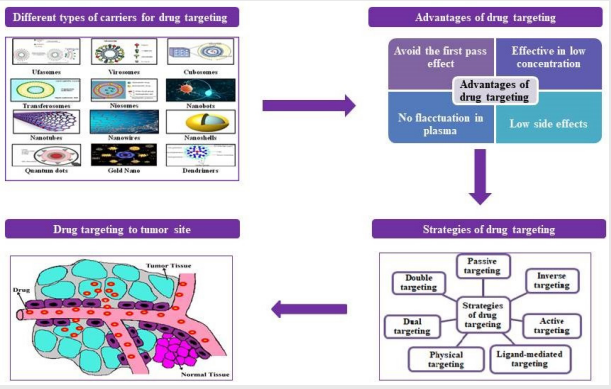
PICTORIAL ABSTRACT



SUMMARY

- A targeted drug delivery system is a special form of drug delivery system where the 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.
- Drug targeting improves the drug efficacy and reduces its side effects.
- A targeted drug delivery system is very important in the treatment of different types of cancer.

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