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TARGETED DRUG DELIVERY SYSTEM – AN OVERVIEW

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ABSTRACT

Nowadays, most of the dosage form has a poor pharmacokinetic and biopharmaceutical properties. Hence there is need to develop a suitable drug system that distributed the active drug molecule only to the site of action, without affecting other tissues or organs. Targeted drug delivery is a method of delivering drugs to the patients at the targeted site or the site of action. This improves efficacy of treatment by reducing side effects of the drug administered. The inherent advantage of this technique leads to administration of required. drug with reduced dose and reduced its side effects. Various drug carriers which can be used in this advance delivery system are Lipoproteins, Liposomes, Microspheres. The present review deals with the Targeted drug delivery system its advantages, disadvantages, need of Targeted drug delivery system and research update on Targeted drug delivery system.(1)

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. (2)

Keywords: Drug Targeting, Drug Delivery System, Gold Nanoparticles, Pharmacological Action , Targeted Drug Delivery Drug Carriers Pharmacokinetics.

1. INTRODUCTION

The biological effects of a drug inpatient depend on the pharmacological properties of the drug.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. Targeted drug delivery, is the method of treatment that involves thetransportation of the therapeutic agent to specific tissue without reaching the remaining part of the body.Therefore, it delivers the medication only to areas of interest within the body. This offers an improved efficacy of treatment and reduces side effects. 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.Conventional dosage forms such as injections, oral formulations comprising of solutions and suspensions, tablets, capsules and topical creams and ointments, possess certain disadvantages.

Parenteral delivery of drugs is highly invasive with short time effects.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. These may be degraded in the gastrointestinal tract. Topical ointments and creams have a drawback of being limited to the local effects, rather than the systemic effects.The technology of the drug delivery system has become advanced and controls the drug bioavailability,drug absorption and pharmacokinetic parameters. 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. Different sites of interest within the body necessitate the use of different drug delivery systems, depending upon the route to be followed.Targeted drug delivery is a kind of smart drug delivery system which is miraculous in delivering the drug to a patient.(3)

This conventional drug delivery system is done by the absorption of the drug across a biological membrane, whereas the targeted release system is that drug is released in a dosage form.The drug delivery system is highly integrated and requires various disciplines, such as chemists, biologist and engineers, to join forces to optimize this system. When implementing a targeted release system, the following design criteria for the system need to take into account: the drug properties, side effects of the drugs, the route taken for the delivery of the drug, the targeted site, and the disease.the following design criteria for the system need to take into account: the drug properties, side effects of the drugs, the route taken for the delivery of the drug, the targeted site, and the disease.Targeted drug delivery system is preferred over conventional drug delivery systems due to three main reasons. The first being pharmaceutical reason. Conventional drugs have low solubility and more drug instability in comparison to targeted drug delivery systems. Conventional drugs also have poor absorption, shorter half-life and require large volume of distribution.These constitute its pharmacokinetic properties. The third reason constitutes the pharmacodynamic properties of drugs. The conventional drugs have low specificity and low therapeutic index as

compared to targeted drug delivery system. Due to these reasons targeted drug delivery system is preferred over conventional drug delivery systems.DDS is refers to the use of new technology and biological polymer materials technology to delivery gene or drugs to the designated the body parts according to the clinical need time and dose. Technology to delivery gene or drugs to the designated the body parts according to the clinical need time and dose. It can be designed to minimize drug degradation, increase bioavailability, allow targeting to specific cells and reduce the total amount of drug needed, it can be controlled release of drugs to decreasing toxicity and harmful side-effects .the idea of DDS drug research and development is to use the new technology and new materials to improve curative effect, reduce the effect of patients with adverse reaction and easy to use by changing the drug pharmacokinetic . DDS is the application and development in pharmacy by the modern science and technology, it has become the theme of the modern pharmacy innovation and development. Targeted drug research began in the 1970s, its main form is for injection, with the development, the current trend of DDS drug research and development is the use of liposome, lipid, protein, fat, microspheres and a biodegradable polymers as drug carrier.Targeted drugs originally is mainly used in cancer treatment, to maximize the efficacy of a drug is of prime importance during the choice of the delivery system. Among the currently available delivery systems, which include liposomes, emulsions, polymeric micelles and micro-particles, carbon nanotubes (CNTs) , and so on. The following we will illustrate the characteristic of all kinds of DDS respectively.

Targeted drug delivery is a kind of smart drug delivery system which is miraculous in delivering the drug to a patient. This conventional drug delivery system is done by the absorption of the drug across a biological membrane, whereas the targeted release system is that drug is released in a dosage form .Targeted drug delivery system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body. This helps maintain the required plasma and tissue drug levels in the body: therefore avoiding any damage to the healthy tissue via the drug. The drug delivery system is highly integrated and requires various disciplines, such as chemists biologist and engineers, to join forces to optimize this system.When implementing a targeted release system. the following design criteria for the system need to take into account: the drug properties. side effects of the drugs, the route taken for the delivery of the drug, the targeted site, and the disease.

Products based on such a delivery system are being prepared by considering the specific properties of target cells, nature of markers or transport carriers or vehicles which convey drug to specific receptors and ligands and physically modulated components.Ideally targeted drug delivery systems should be biochemicallyinert (non-toxic). Should be non-immunogenic, should be physically and chemically stable in vivo and in vitro conditions, and should have restricted drug distribution to target cells or tissues or organs and shouldhave uniform capillary distribution. It should have controllable and predictable rate of drug release and also drug release should not affect the drug action. It should have therapeutic amount of drug release and should have minimal drug leakage during transit .(4) Carriers used should be bio-degradable or readily eliminated from the body without any problem. The preparation of the delivery system should be easy or reasonably simple, reproductive and cost effective.A Targeted drug delivery system is preferred over conventional drug delivery systems due to three main reasons. The first being pharmaceutical reason. Conventional drugs have low solubility and more drug instability in comparison to targeted drug delivery systems. Conventional drugs also have poor absorption shorter half-life and require large volume of distribution. These constitute its pharmacokinetic properties. The third reason constitutes the pharmacodynamic properties of drugs. The conventional drugs have low specificity and low therapeutic index as compared to targeted drug delivery. System. Due to these reasons targeted drug deliverysystem is preferred over conventional drug delivery systems.(5)

Causes of using the targeted drug delivery systems:

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

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:

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:

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 Disadvantage of Drug Targeting:

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

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:

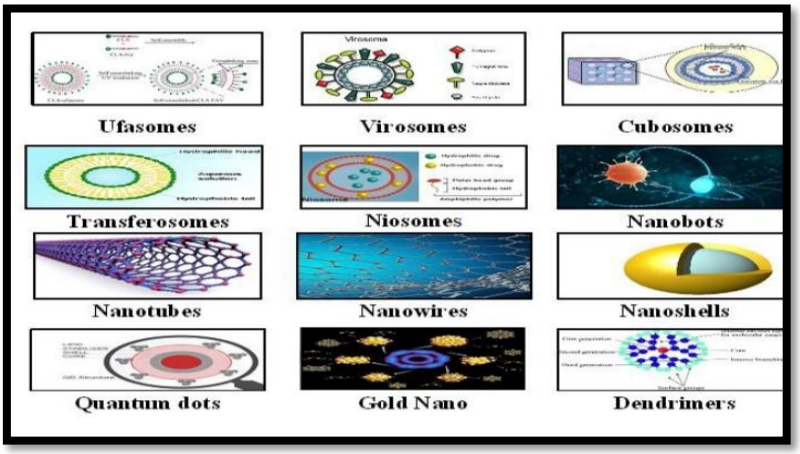


Fig no.1 Different types of carriers applied for drug targeting

1. 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.They are Usually used for delivering the drug to the cancer cell.Liu et al. applied carbon nanotube for targeting the Tumor in mice. Also, Mc Devitt et al. achieved tumorTargeting with antibody-functionalized, radiolabeled Carbon nanotubes.(6)

2. 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.This system can Treat Parkinson's and similar diseases. Also, it can be Used for the detection and localization of tumors.Hong et al. used fluorescent zinc oxide nanowires for Molecularly targeted imaging of cancer cells.(7)

3. Nanoshells

Nanoshells are new strategies of nanoparticles, consisting Of a hollow dielectric core of silica covered by a shell Of gold. 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.This technique is very effective In targeting the antineoplastic drug.Loo et al. studied The ability of nanoshells in imaging and treatment of Cancer.(8)

4. 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. This Carrier is effectively used for targeting cancer drugs.Pardo et al. used quantum dots and nanotubes for cancer Targeting and drug delivery.

5. 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.This technique has Potential in genetic engineering and biotechnology.Schneider et al. reported DNA translocations through Nanopores created in graphene membranes.(9)

6. Gold nanoparticles

The gold nanoparticles are used by scientists to develop An ultrasensitive detection system for DNAand the Protein markers associated with the presence of different Types of cancer,like breast and prostate cancer.PengEt al. used gold nanoparticles in the diagnosis of lung Cancer.

7. Dendrimers

Dendrimers are synthetic nanoparticles with a specific Diameter.They consist of a control core surrounded By layers of polymers.There are several sites at the Surface of the dendrimers to which the drug may be Attached. They are used in gene transfection and medical Imaging.Abd-El-Aziz and Agatemor, reviewed the Biomedical applications of dendrimers.(10)

8. Liposomes

Liposomes are microscopic bilayer structure vesicles Prepared using natural phospholipid.They can entrap Both hydrophilic and lipophilic drugs in the aqueous Space or the phospholipid bilayers.The percentage Of entrapped drug depend on the physical and chemical Properties of the drug and the composition of the lipids.Huwyler et al. studied the tumor-targeting using liposomal Antineoplastic drugs.(11)

9. 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.It was found that niosomes Are effective for targeting antineoplastic drugs, anti-Inflammatory, anti-bacterial, anti-fungal and antiviral Drugs. Liu et al. designed and evaluated a novel niosomal Delivery system of daunorubicin (DNR) for targeting Against acute myeloid leukemia (AML).Ahmed et al. Prepared piroxicam niosomes to target the analgesic and Anti-inflammatory effect at the pain area.

10. 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.(12)

11. Pharmacosomes

Pharmacosomes are a neutral molecule which carries Both positive and negative charges and possesses bothhydrophilic 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." 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.* Semalty et al. developed and evaluated pharmacosomes of aceclofenac.(13)

12. Virosomes

Virosomes are drug delivery systems described as unilamellar vesicles prepared from phospholipids.7¹.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." Lucarini et al. design an innovative platform for the treatment of cerebral tumors using erythro-magneto-HA-virosomes.

13. 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. Azhari et al. used Tween 80 to stabilize phytantriol-based cubosomes for delivering macromolecular therapeutics to the brain.(14)

14. Nanocrystal

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

15. Nanobots

Nanorobotics is a new technology of drug delivery systems. They are a nanoscale machine with a diameter of 10 m. Andhari et al. prepared self-propelling targeted magneto-nanobots for deep tumor penetration." H2(15)

16. 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.This willavoid complete rupture of the vesicle and remaining the drug intact after penetrating the skin. Qushawy et al. prepared miconazole nitrate transferosomal gel for effective treatment of skin candida infection.(16)

2. STRATEGIES FOR DRUG TARGETING

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

1. Passive targeting

Drug delivery systems which are targeted to systemic circulation are characterized as Passive delivery systems. In this technique drug targeting occurs because of the body's natural response to physicochemical characteristics of the drug or drug carrier system. The ability of some colloid to be taken up by the Reticulo Endothelial Systems (RES) especially in liver and spleen made them ideal substrate for passive hepatic targeting of drugs.

Passive targeting usually refers to the drug delivery systems which target the drug to the systemic circulation. 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, see Figure 3. Zhang et al. used salinomycin passive targeting micelles for suppression of breast cancer and stem cell cancer.(17)

2. Active targeting

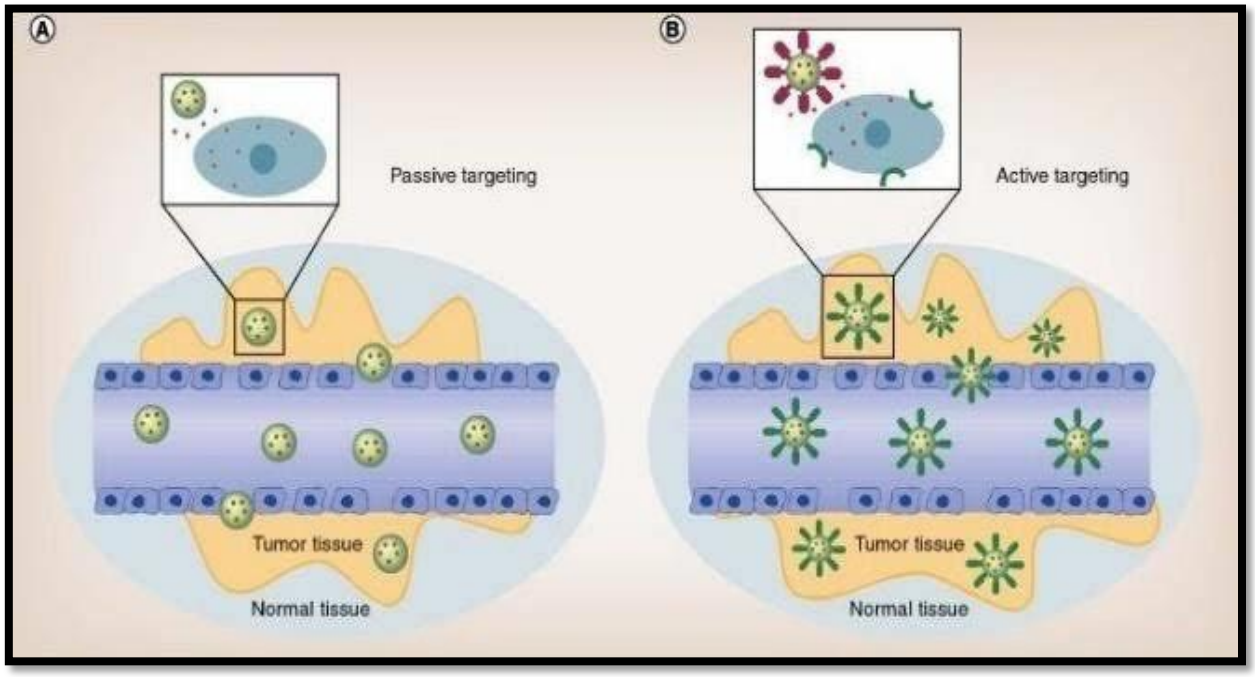
Active targeting means a specific ligand- receptor type interaction for intracellular localization which occurs only after bloodcirculation and extravasations. This active targeting approach can be further classified into three different levels of targeting which are 1) First order targeting refers to restricted distribution of the drug carrier systems to the capillary bed of a predetermined target site, organ or tissue e.g. compartmental targeting in lymphatics, peritoneal cavity, plural cavity, cerebral ventricles and eyes, joints. 2) Second order targeting refers to selective delivery of drugs to specific cell types such as tumour cells and not to the normal cells e.g. selective drug delivery to kupffer cells in the liver. 3) Third order targeting refers to drug delivery specifically to the intracellular site of targeted cells e.g. receptor based (18).

Ligand mediated entry of a drug complex into a cell by endocytosis.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. The target group include bioadhesive nonionic surfactant, antibodies, or albumin protein. The active targeting has three types, First-order targeting (organ targeting), Second-order targeting (cell targeting) and Third-order targeting (intracellular targeting)," see Figure 3. Zwicke et al. utilized the folate receptor for active targeting of anticancer drug (19).

3. Inverse targeting

This approach leads to saturation of RES and suppression of defense mechanism. This type of targeting is a effective approach to target drug(s) to non-RES organs.

The inverse targeting aims to avoid the passive uptake of the drug delivery system by the reticulum-endothelial system (RES). 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." The inverse targeting is very useful for drug targeting to non-RES organs." Balthasar and Fung, used an inverse targeting strategy for targeting methotrexate to peritoneal tumors.(20)



4. 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."7 Veisch et al. applied a ligand-mediated targeting strategy for the treatment of cancer.

5. 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." This method is very potential for tumor targeting and gene targeting. Weichselbaum et al. applied physical targeting in gene therapy.These targeting systems are equipped with cariers, polymers and homing devices of molecular specificity that could Provide a direct approach to target site.(21)

6. Dual targeting

The dual targeting mechanism involves a drug delivery system in which the carriers has a synergistic effect on the entrapped drug and hence increase the therapeutic effect. 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." In this targeting approach carrier molecule itself have therapeutic activity and thus increase the therapeutic effect of drug. For example, a carrier molecule having its ownantiviral activity can be loaded with antiviral drug and the net synergistic effect of drug conjugate was observed.(22)

7. Double targeting

The double targeting strategy is a combination of both temporal and spatial, so it is called double targeting." 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. Pitto-Barry et al. applied a double targeting mechanism for targeting a dendrimer-loaded anticancer drug to the tumor site. When temporal and spatial methodologies are combined to target a carrier system, then targeting may be called double targeting. Spatial placement relates to targeting drugs to specific organs tissues, cells or even subcellular compartment .whereas temporal delivery refers to controlling the rate of drug

3. CHARACTERISTICS OF AN IDEAL DRUG VEHICLE

An ideal drug vehicle should be able to cross blood brain Barriers. It must be recognized by the target cells specifically And selectively The drug vehicle used should be non-toxic, Nonimmunogenic and biodegradable. After recognition, the Carrier system should release the drug moiety inside the Target organs, tissues or cells.

- Liposomes
- Monoclonal antibodies and fragments
- Modified (plasma) proteins
- Quantum dots
- Microspheres and Nanoparticles
- Lipoproteins

1. Liposomes

Delivery of larger fraction of drug to the desired (diseased) site, by reducing the drug's exposure To normal tissues can be achieved by site specific targeting. Encapsulating the drug in liposomes can be used for both active and passive targeting of drugs in order to achieve a safer and Efficacious therapy.On systemic administration, long circulating immunoliposomes Are able to recognize and bind to target cells with greater specificity.In patients with Recurrent osteosarcoma, there was an enhanced tumoricidal activity of monocytes, when muramyl Peptide derivatives were formulated systemically.As liposomes and administered(24)

2. Monoclonal antibodies and fragments

The use of monoclonal antibodies (mAbs) as therapeutic agent is gaining importance is the treatment of various conditions such as cancer, cardiovascular diseases and viral infections. In concert with their clinical acceptance,mAbs have become commercially viable drug.In addition, mAbs that target tumors have been conjugated to radioisotopes, chemotherapeutic agent, bacterial toxins, cytokines and enzymes in order to potentiate their cytotoxic effects.Recently human mAbs are developed as antitumor agent[.Adalimumab (HUMIRA) is the first human mAb approved for human use.(25)

3. Modified plasma proteins

Modified plasma proteins can be intelligent drug vehicle for drug transportation due to their solubility and having relatively small molecular weight. They can easily be modified by the attachment of different molecules like peptides, sugar and other ligands to transport the drug of interest makes them a suitable mode of drug delivery. In the case of liver cell targeting, extensive modification of protein backbones such as albumin have been carried out effective delivery of the drug.

4. Quantum dots

Optical characterization of quantum dots is usually done by UV-VIS and photoluminescence spectroscopy, which offer fast, non destructive and contactless option. The optical properties (fluorescence emission) of Quantum dots can be fine-tuned by the Quantum dots' size and is calculated using conventional techniques like scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM) or more preferably scanning tunneling microscopy (STM) and dynamic light scattering (DLS) studies. Besides these techniques, field flow fractionation was also successfully employed an excellent complement to characterization of water soluble quantum dots by the conventional tools.(26)

5. Microspheres and nanotechnology

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature and ideally having a particle size less than 200μm. This is the important approach in delivering therapeutic substance to the target site in sustained and controlled release fashion.(27)

Advantages of microspheres

They facilitate accurate delivery of small quantities of potent drug and reduced concentration of drug at site other than the target organ or tissue. They provide protection for unstable drug before and after administration, prior to their availability at the site of action. They provide the ability to manipulate the in vivo action of the drug, pharmacokinetic profile, tissue distribution and cellular interaction of the drug. They enable controlled release of drug. Examples: Narcotic, Antagonist, Steroid hormones.(28)

6. Lipoproteins

Lipid particles such as LDL and HDL containing a lipid and an apoprotein moiety is termed as natural targeted liposomes and its core can be used to incorporate lipophillic drugs and it does not require covalent bonding with the drug.(29) Modification at the level of glycolipid incorporation can be used to introduce new targeting moieties. The majority of the research on the use of LDL and HDL particles has been done and improved at the level of targeting the drugs to the liver.(30)

4. 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 thedose 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.A targeted drug delivery is coming towards as an advanced technique used in the treatment of lethal diseases. Targeted delivery of drugs, as the name suggested, is to assist the drug molecule to reach preferably to the desired site. The advantage of this technique has been the reduction in dose and side effects of the drug.

Delivery of drug molecule to reach its specific site is itself a difficult task in the complex cellular network of an organism. Finally, targeted drug delivery is coming forward as one of the brightest advanced techniquein the medical sciences in the diagnosis and treatment of couple of lethal diseases. It has crossed the infancy period and now touching height of growths in research and development in clinical and pharmaceutical fields. Many problems which appeared during thedevelopment of drug targeting strategies for clinical application for different types of therapies have been identified, analyzed and solved especially in the treatment of cancer

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