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Review OnTargeted Drug Delivery System and Its Carriers as Drug Targeted to A Specific Organ

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Abstract:

Targeted delivery combined with controlled drug release has a pivotal function in the future of personalized medicine. Target drug delivery system is one of the most considerable novel approach towards drug delivery system. Targated drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the ultimate tissues thus enhancing therapeutic index and bioavailability at site specific-delivery .Now a days various carrier systems which includes liposomes, niosomes, aquasomes,pharmacosomes, dendrimers, nanoparticles, microspheres, solid lipid nanoparticles, resealed erythrocytes etc. are utilized in target drug delivery system which provide site specific drug delivery.Drug targeting is the principle by which the distribution of drug in organism is maneuverer in manner such that its major fraction interacts exclusively with the target tissue at the cellular and subcellular. The present review deals with the Targeted drug delivery system its advantages, disadvantages, need of Targeted drug delivery system, Types, drug targeted to a specific organ such as Brain, kidney, heart, colon and respiratory tract and research update on Targeted drug delivery system. Various drug carriers which can be used in this advance delivery system are Niosomes, Liposomes, Nanoparticles, Monoclonal Antibodies.

Keywords: Targated Drug Delivery system(TDDS),Drug carriers, Liposomes, Niosomes, Nanoparticles, Blood Brain Barrier (BBB), Immunoglobulin (lg).

Introduction:

Targeted drug delivery system (TDDS) is a type of smart drug delivery system which is incredible in delivering the drug to a patient. This traditional drug delivery system is done by the absorption of the drug across a biological membrane.Targeted drug delivery system is based on a Method that provides a certain quantity of a therapeutic Agent for a extended period of time to a targeted Diseased place within the body.This helps maintain the required plasma and tissue drug levels in the body.(1)The concept of designing targeted delivery system has been originated from the Paul Ehrlich, who was a microbiologist. Drug delivery and targeting systems under development aim to decrease drug deprivation and prevent dangerous side effects and enhance the availability of the drug at the disease site. Targeted drug delivery method accumulation of pharmacologically active moiety atdesired target in therapeutic concentration at the same restricting its access to regular cell lining, thus minimizing

therapeutic index. The drug can be targeted to intracellular sites, virus cells, bacteria cell and parasites using different scientific techniques have proven highly effective. The minimum distribution of the parent drug to the non target cells with higher and effective concentration at the targeted site certainly maximize the benefits of targeted drug delivery.(2)

General concept of Targeted drug delivery systems

The Ideal drug delivery system delivers drug to the location of action throughout the period of treatment. The concept of targeted delivery is fabricated for delivery of drug in tissues by decreasing the level of medication in other parts of tissues. As a result of this, drug is localized on targeted site resulting to achieve maximum efficacy of the drug. It show result localised drug on targeted site and achieving maximum efficacy of the drug.(3)Targeted drug delivery is the most important goal of pharmaceutical research and development amount of work has been concentrated worldwide in thepast two decades on the research and development ofdrug with improved site-specificity, that is, targeted drug delivery system.(4) Target means particular organ or a cell or group of cells, which in chronic or acute condition need treatment.(5)

Applications of targeted drug delivery system :(6)

- Targeted drug delivery can be used to deal with many diseases, which includes cardiovascular diseases and diabetes. However the most important application of targeted drug delivery is to treat cancerous tumours.
- Liposomes can be used as drug delivery for the treatment of Tuberculosis. The liposome delivery System allows for better microphage penetration and better buildsa concentration at the infection site.

The Need for Targeted Drug Delivery :(7)

The need for TDD over conventional DSs is fourfold: unsatisfied peformance of drugs in terms of pharmacodynamic, pharmacokinetic, pharmaceutical, and pharmacotherapeutic functions with conventional delivery as shown in Figure 2.

Figure 1: The need for Targeted Drug Delivery

Properties of Targated Drug Delivery: (8)

- It should be nontoxic.
- Should be biodegradable.
- Should be biocompatible.
- Should be physicochemical stable invivo and invitro condition.
- Carrier used must be biodegradable or readily eliminated from the body without any problem.
- Therapeutic amount of drug release.
- Minimal drug leakage for the duration of transit.
- Predictable and Controllable and rate of drug release.
- Drug release should not affect the drug delivery.

Types of TDDS:

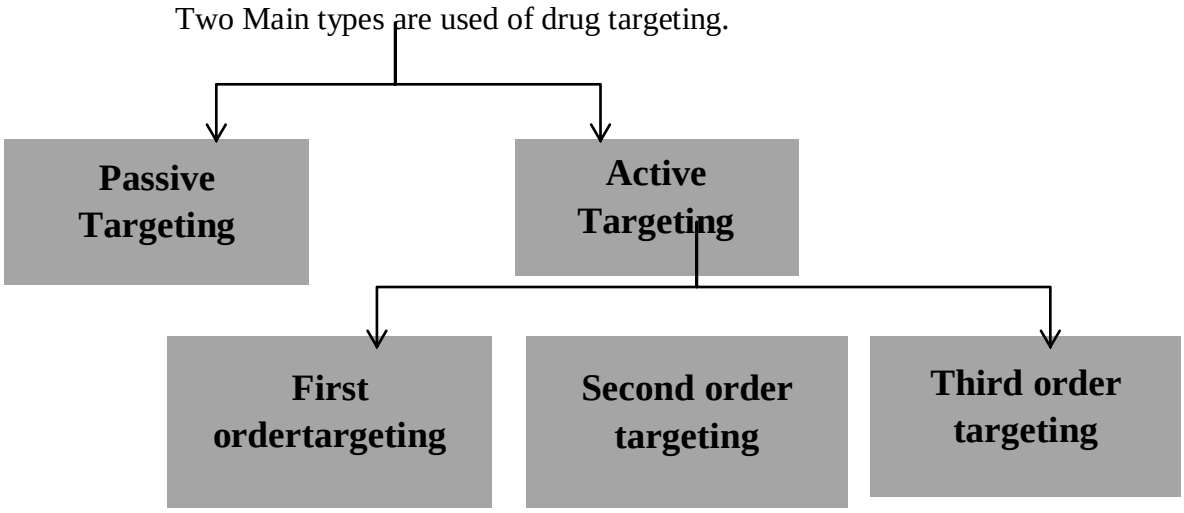

Figure 2: Type of Targeted drug delivery systems.

Passive Targeting:

This is based on the accumulation of drugcarrier System at a particular site which includes anti-cancerous drug explanation can be attributed to pharmacological elements of the Disease. Hence, in case of cancer treatment the size and surface properties of drug delivery nano-particles must Be controlled particularly to avoid uptake through the Reticulo-endothelial system (RES) to maximize circulate times and targeting ability.The bottom line is called passive targeting as misnomer that is simple drug delivery system through blood circulation.Other example for passive targeting is the ability of anti-malarial drugs to be targeted for the treatment of microbial infections such ascandidiasis and brucellosis.(9)

Active Targeting :

Active targeting includes specific modification of a drug/drug carrier nano systems with active agents having selective affinity for recognizing and interacting with a particular cell, tissue or organ in the body.Such an approach is based on specific interactions such as lectin-carbohydrate, ligand-receptor, and antibody-antigen. In case of cancer, it is achieved by conjugating the nanoparticle to a targeting component that provides preferential accumulation of nanoparticles in the tumor-bearing organ,totumor, individual cancer cells, intracellular organelles, or specific molecules in cancer cells.(10)

This active targeting approach can be further classified into three different levels of targeting which are:

1. **First order targeting** refers to limited 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 ligand mediated entry of a drug complex into a cell by endocytosis.(11)

Table No.1: Advantages and Disadvantages of Targated Drug Delivery system.

Sr.No	Advantages [12]	Disadvantages [13]
1.	Increases the patient compliance.	Difficult to Maintain stability and uniform release rate of drugs within the dosage form.
2.	It targets diseased tissue or particular parts of the body with out affecting healthy tissue.	Skilled people are required to handle and control the delivery to the site of action.
3.	Dose durations can be manageable due to uniform drug effect at target site.	Complex Manufacturing processes, administration and storage need advanced techniques.
4.	Drugs are released in a controlled way for an extended period of time.	Rapid clearance of drugs is needed to avoid side effects.
5.	Small dose of drug is effective to produce the desired effect.	Expensive.

Carriers of Targated Drug Delivery system:

1.Liposomes:

Liposomes are the firstto be explored as drug delivery vehicles. The first description for liposomes was given by British haematologist Alec Bangham and his colleagues in 1965 as swollen phospholipids system.Liposomes are sphere-shaped vesicles consisting of natural (Biodegradable) or synthetic bilayers of phospholipids. Because of the amphiphilic nature of phospholipids. (14) The liposomal formulations are targeted to deliver the essential drug combinations to the body. The sub-microscopic foams generated through encapsulation technology are carried out in the method of liposomes, which encapsulate numerous materials.The main aim of any treatment employing drug is not only to increase the therapeutic index of the drug but also to minimize its side effects. As a novel drug delivery system, liposomes and their use have been significantly used by pharmaceutical manufacturers in the field of medicine.Liposomes provide reduction in toxicity of the encapsulated agents.(15)

Advantages of liposomes:(16)

1. Increased efficacy and therapeutic index of drug.
2. Reduce the toxicity.
3. Enhanced activity against extracellular pathogens.
4. Help to reduce the exposure of sensitivetissue to toxic drug.
5. Improvement and control over pharmacokinetics and pharmacodynamics.

Disadvantages of Liposomes: (17)

1. Short half-life.
2. Low solubility.
3. Fever stable.
4. Production cost is high.
5. Oxidation of phospholipids may occur.

2. Niosomes :

Niosomes are formations of vesicles by hydrating mixture of cholesterol and non-ionic surfactants. Niosomes are non-ionicsurfactant vesicles obtained on hydration of syntheticnon-ionic surfactants, with or without incorporation of cholesterol or other lipids. These are formed by self assembly of non-ionic surfactants in aqueous medias spherical, unilamellar, multilamellar system and polyhedral structures in addition to inverse structures which appear only in nonaqueous solvent.(18)Niosomes are one of the best among these carriers. Niosomes behave in vivo like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolicstability.Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. It can also be used as vehicle for poorly absorbable drugs to design the novel drug delivery system.(19)

Advantages of niosomes: (20)

1.Niosomes are biodegradable and non-immunogenic.

2.Niosomes are osmotically active and chemically stable.

3. surface formation and modification are very easy because of the functional groups on their hydrophilic heads.

4.They have long storage time compared to liposomes.

5.they have high compatibility with biological systems.

Disadvantages of niosomes: (21)

1. Physical instability.
2. Entrapped drug can leak.
3. Time consuming.
4. Aggregation of drug molecules.
5. Hydrolysis can lower the shelf life of encapsulated drug.

3. Nanoparticles:

Nanoparticles are solid, colloidal particles consisting of macromolecular substances that vary in size from 10 nm to 1000 nm, which are formulated by natural, synthetic, and semi synthetic polymers.

Nanotechnology can deliver drug molecules to target sites without damaging healthy cells.Nanoparticles have specific material characteristics because of Sub microscopic size and additionally provide practical implementations in a extensive variety of fields such as engineering, drug delivery, nanomedicine, environmental indemnification, and catalysis, as well as target diseases including cancer and cardiovascular diseases (CVD),skin diseases, liver diseases, and many others. (22). Nanoparticles can mimic or regulate biological processes (e.g., infection, tissue engineering, , etc.). These devices include, however are not restricted to, functionalized carbon nanotubes, nanomachines, nanofibers, self-assembling polymeri nanomembranes, and nano-sized silicon chips for drug, protein, nucleic acid or peptide transport and release, and biosensors and laboratory diagnostics (23).

Advantages of Nanoparticles: (24)

1. Excellent bioavailability.
2. Improve stability of pharmaceutical.
3. Enhanced and high drug content.
4. Site specific drug targeting.
5. Controlled drug release.

Disadvantages of Nanoparticles: (25)

1. It is expensive.
2. Productivity more difficult.
3. Limited drug loading.
4. Require skills to manufacture.
5. Reduce ability to adjust the dose.

Applications of Nanoparticles: (26)

1. Nanoparticles for Gene delivery.
2. Tumor targeting using Nanoparticulate delivery system.
3. Nanotechnology in Medicine Application: Cell Repair
4. Nanoparticles for drug delivery into the brain.
5. Nanotechnology in Medicine Application: Anti-Microbial Techniques.
6. Nanoparticles for Opthalmic Delivery.

4. MonoclonalAntibodies:

Monoclonal antibodies (mAbs) are through far the most important class of therapeutic proteins and a key driver in the biopharmaceutical growth.Monoclonal antibody technology are continuing to adapt to increase drugs with increasingly advanced safety profiles, with the identity of recent drug targets being one key barrier for new antibody development. Monoclonal antibodies are immunoglobulins (Ig) of which there are five classes (IgA, IgD, IgE, IgG and IgM)(27).monoclonal antibodies are a mixture of homogenous antibody molecules with afinity towards a specific antigen, often generated using a hybridoma through fusing a B-cell with a single lineage of cells containing a definite antibody gene (28).

Application of monoclonal antibodies: (29)

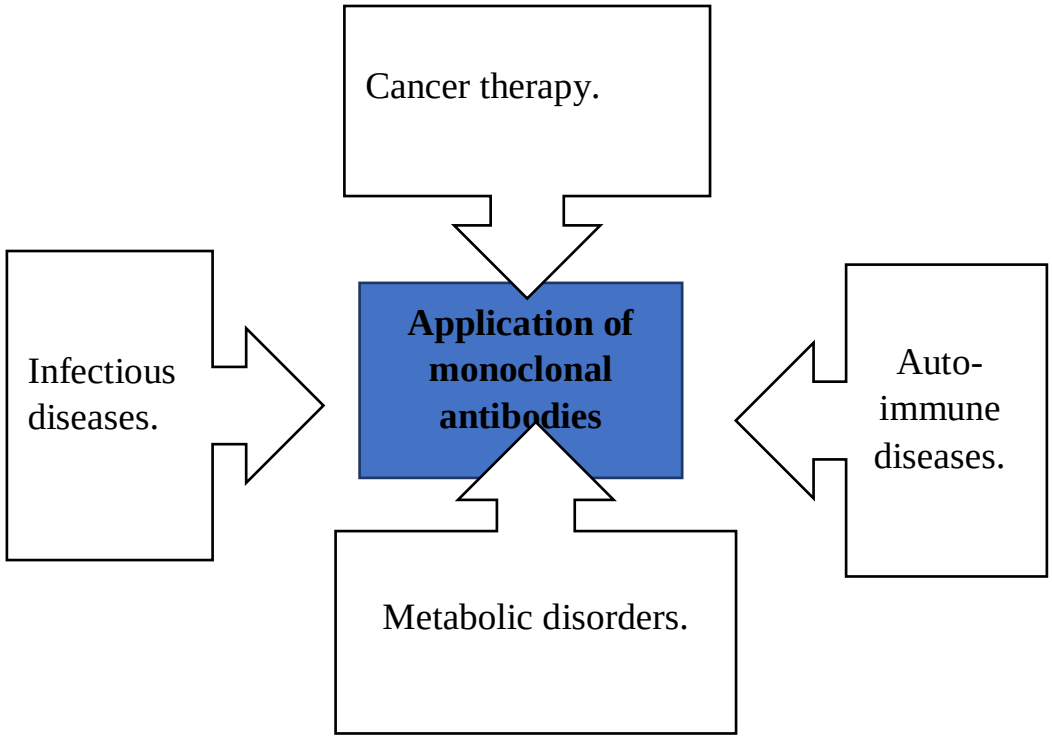

Figure 3: Application of monoclonal antibodies.

Organ BasedTargated drug delivery system :

1. Brain:

In the central nervous system, targeted action can be completed by direct administration of the drugs in to the CNS . Blood brain barrier can considerably impair the impact of the large number of drugs (e.g. antibiotics, antineoplasticagents).Presently, numerous techniques with enhanced pharmacodynamics effects, have been developed for the treatment of brain disorders (30). Brain-targeted drug delivery research is an active, rich and multidisciplinary studies area, and this special issueobjectives to give the modern state of the art in the field.

Barriers in brain targeted drug delivery:(31)

1. Blood-Brain Barriers
2. Blood-Cerebrospinal Fluid Barrier
3. Blood-Tumor Barrier

common administration route for brain-targeted drug delivery: (32)

- **Intranasal administration** has currently been explored through researchers because it reaches the brain, bypassing the BBB via the olfactory bulb.
- **Intracranial route**for brain-targeted drug delivery is to enhance intracranial viral vector delivery in non-human primates (NHPs).
- **Intraperitoneal administration**for drug delivery into the brain.
- **Intravenous administration** for brain-targeted drug delivery.

2. Kidney:

The main functions of the kidney are the maintenance of from the bloodstream, the secretion of hormones, and multiple homeostatic controls including the acid-base regulation of the blood.The kidney is a vital organ that filters blood and eliminateextra fluid and waste products. Drugs for treating kidney diseases are frequently limited through tolerability and extra-kidney safety concerns. The majority of kidney- specific delivery system target the proximal tubular cells and can make contributions in the treatment proximal tubular cells and can contribute in the treatment of renal diseases including kidney transplantation, ureteral obstruction, diabetes, proteinuria (33).
Nanoparticles , polymers ranging from 1 to 100 nm, have been shown great potential in increasing the targetability and potency of treatments for chronic kidney diseasesand Acute kidney injury. Nanoparticles therapy can focus on passive or active delivery routes.Nanoparticles size, shape, and surface chemistry, the particles' interactions with various regions of the kidney can be exactly controlled, main to improved dosing efficiency and decreased damage to outlying cells (34).

3. Heart:

The cardiovascular system plays a main role in health and disease in the body, and any deregulation in the cardiovascular system can result in cardiovascular diseases, which includes atherosclerosis, myocardial infarction and microvascular disease (35). Traditionally small molecules are used to treat cardiovascular system diseases. Examples of generally used drugs include atorvastatin, metoprolol, valsartan and ezetimibe. These drugs are commonly available in oral drug delivery systems and are used in the chronic control of the disease. Liposomal delivery systems Liposomes are vesicle based systems generally utilized in drug delivery system. . A main purpose for the formulation into liposome for small molecules has traditionally revolved across the improvement of oral bioavailability. Also the nanomaterialsare used to treat cardiovascular system diseases such asnanoparticles, nanofibers, carbon nanomaterials(36).

4. Colon:

Colon drug delivery system refers to targeted delivery of drug into the lower GI tract, which occurs usually in the large intestine (i.e. colon).
Targeted drug delivery into the colon is especially suitable for local treatment of numerous bowel diseases which includes ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs . Targeted drug delivery to the colon to make sure that direct treatment on the disease site, at lower dosing and less systemic side effects (37).
Approaches for colonic drug delivery :[38]

1. Prodrug approaches
2. pH dependent approach
3. pressure-controlled release system
4. osmotic system
5. polysaccharide based delivery system.

5. Respiratory Tract :[3]

Targeting drugs on the respiratory tract has been attempted with bronchodilators and anti-inflammatory steroids for the effective control of asthma.Drug delivery through the respiratory tract has been used for local and systemic effects.The nasal or pulmonary route of drug administration delivers therapeutic agents to the diseased region. Therapeutic index can be obtained for the treatment of respiratory diseases when drugs are administered directly to the respiratory tract. Drug delivery to lungs can be carried out through Aerosols, nebulizers, metered dose inhalers , dry powder inhalers.
These systems are used for the following purposes:

1. Enhancement of bioavailability.
2. Rapid onset of action.
3. Better patient compliance.
4. Avoid hepatic first pass metabolism.
5. Peptide and proteins drug moieties.

Conclusion:

Targeted drug delivery is now developing fast due to its potential to deliver drugs at specific sites. This causes injection of a lower amount of dose as well as a significant decrease in side-effects that were more pronounced earlier because of the inefficacy of any drug delivery system to deliver drugs at the specific site of action. Also first pass metabolism is avoided in the TDDS. The application of nanotechnology in drug delivery has particularly enhanced the delivery of drugs. There are numerous nanoparticles that have been approved for clinical use and, although they are still in their development stages, they hold the key to the future of drug-targeting. Several other approaches have also been developed with similar results. 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. They all outline the bright future of targeted drug delivery.

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