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Review Article

Review On: Targeted Drug Delivery System

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ABSTRACT

The goal of a targeted drug delivery system is to deliver medication directly to the site of action. In contrast, conventional drug delivery systems, such as intravascular injections, distribute the medication through systemic circulation. Targeted delivery increases the concentration of the drug in the affected tissue, improving its efficiency while minimizing side effects. One of the key advantages of this technique is the potential for reduced dosage and fewer side effects. The development of targeted drug delivery systems has become a highly preferred and rapidly advancing field in the pharmaceutical industry. Transdermal devices, for example, enable the delivery of drugs across the skin barrier. The primary aim of such systems is to transport the drug specifically to the target site. The main intention of targeted drug delivery is to achieve the desired pharmacological and therapeutic effects by directing the agent to the diseased organ, without harming healthy tissues. This is especially beneficial in cancer treatment using chemotherapeutic agents.

INTRODUCTION

When biological and pharmacological factors contribute to the accumulation of a drug at a specific site, the process is referred to as *passive targeting*. This often occurs due to disease-related changes in tissue properties, such as in cancer, where abnormal vasculature allows drugs to accumulate in the affected organs. When nanosized particles are introduced into the body via the intravenous route, the immune system is immediately activated and releases opsonins, which can interfere with drug delivery. Approximately 99% of targeted drug delivery systems (TDDS) are pharmaceutical formulations designed to deliver medications directly to the site of disease or infection, thereby minimizing side effects and improving therapeutic outcomes. This targeted approach increases drug efficiency while reducing unwanted systemic effects. The therapeutic index of a drug—measured by its

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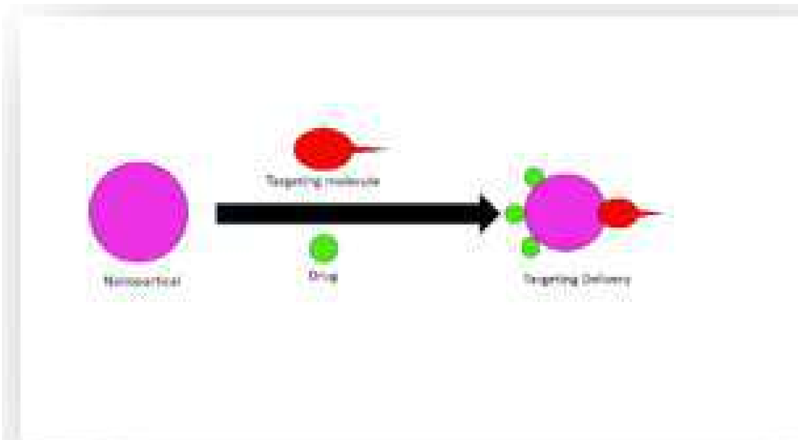
pharmacological response and safety—depends significantly on its ability to access and interact with specific receptors. Targeted or site-specific drug delivery is an especially promising strategy because it offers one of the most effective methods to enhance a drug's therapeutic index. In chemotherapy, for example, conventional drug administration often fails to effectively reach the tumor site, highlighting the critical need for targeted delivery systems.

Targeted Delivery: -

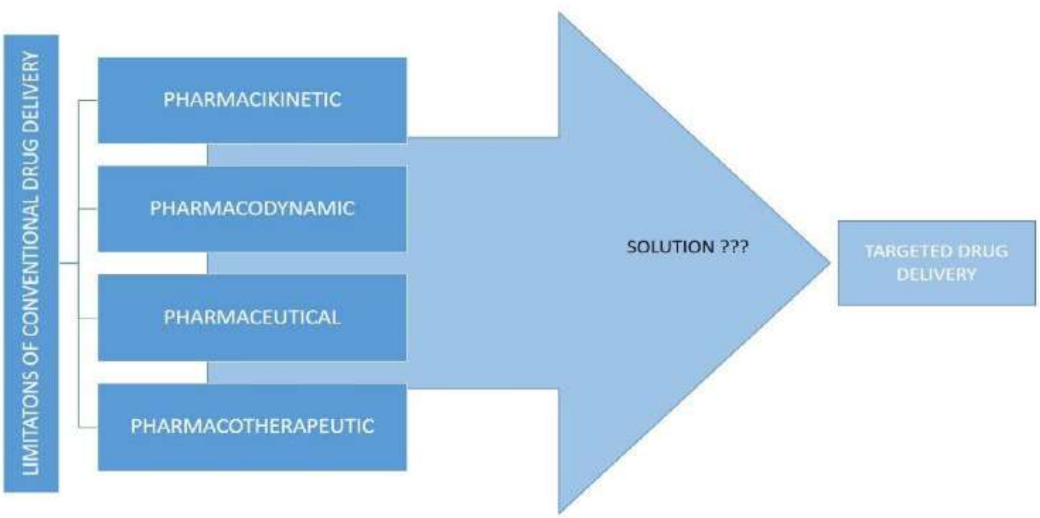
Reasons

1. Used in various treatment to prevent diseases.

2. Reduction of drugs side effects and fluctuations in circulating drug levels.



Limitations Of Conventional Drug: -



Stratergies Of Drug Targeting: -

Passive Targeting: -

Passive Targeting

Passive targeting generally refers to drug delivery systems that guide drugs into systemic circulation, with selective accumulation at specific sites based on physiological conditions. Certain colloids are readily taken up by the Reticuloendothelial System (RES), particularly in the liver and spleen, making them ideal candidates for passive hepatic targeting. This form of targeting exploits the body's natural mechanisms to localize drug delivery. For instance, Zhang et al. utilized salinomycin-loaded micelles for passive targeting in the suppression of breast cancer and cancer stem cells. This approach significantly improved the drug's bioavailability and reduced associated toxicity and side effects. Passive targeting primarily relies on the Enhanced Permeation and Retention (EPR) effect, a phenomenon observed in tumors and inflamed tissues due to leaky vasculature and poor lymphatic drainage.

Mechanism of Action – Passive Targeting:

Passive targeting leverages inherent physiological differences between healthy and diseased tissues. Nanocarriers (e.g., liposomes or nanoparticles) naturally accumulate in diseased tissues like tumors without needing a targeting ligand. This accumulation enhances the localized drug concentration and minimizes exposure to healthy tissues.

Active Targeting

Active targeting involves the use of specific ligands attached to the surface of drug carriers. These ligands bind to receptors overexpressed on the surface of target cells, enabling highly selective drug delivery. Common ligands include **bioadhesive agents, non-ionic surfactants, antibiotics, and albumin proteins**. For example, Zwicke et al. employed the folate receptor for the active targeting of anticancer drugs.

Levels of Active Targeting:

First-order targeting (Organ compartmentalization):
Drug carriers are localized to a specific organ or tissue based on the unique capillary structures of the target site.

Second-order targeting (Cellular compartmentalization):
Selective delivery of drugs to specific cell types, such as tumor cells, while sparing normal cells.

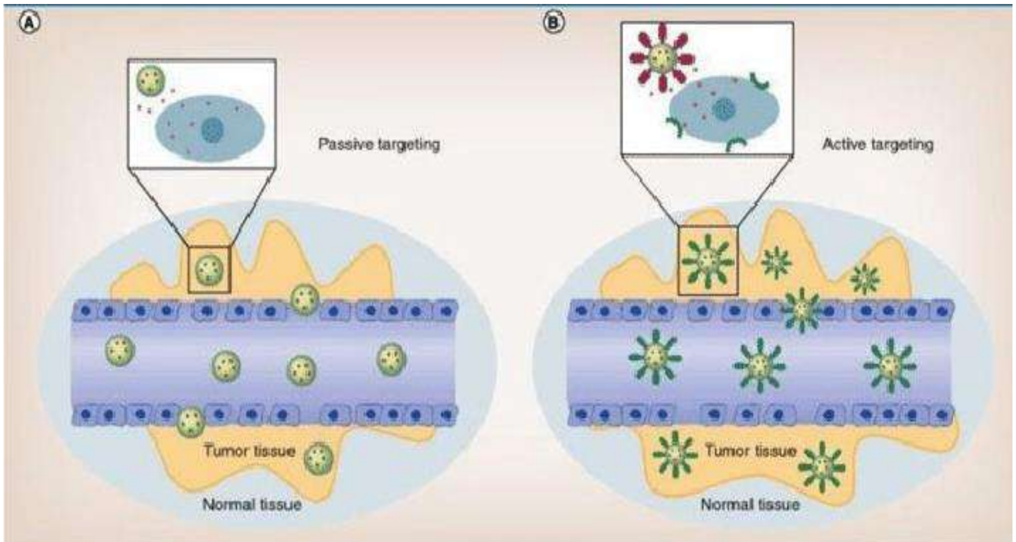
Third-order targeting (Intracellular organelle targeting):
Focused delivery to specific organelles (e.g., nucleus, mitochondria) within the target cells.

Mechanism of Action – Active Targeting:

Ligands on the nanoparticle surface bind to specific receptors expressed on target cells. This receptor-ligand interaction facilitates internalization of the drug-loaded nanoparticles through endocytosis. As a result, intracellular drug concentration increases, enhancing therapeutic efficacy.

Ligands used in active targeting include:

- Proteins
- Polysaccharides
- Nucleic acids
- Peptides
- Small molecules



Comparison of passive targeting and active targeting: -

Aspect	Passive transport	Active transport
Definition	Drug delivery that relies on natural physiological properties like the Enhanced Permeability and Retention (EPR) effect	Drug delivery using specific ligands that bind to receptors on target cells.
Concentration gradient	High concentration to low concentration	Low concentration to high concentration
Specificity	Low specificity as drug accumulation	High specificity due to molecular targeting
Drug targeting	Moderate with some accumulation in non-targeting tissue	High with minimal effect on healthy cells
Side effect	High risk of side effect and toxicity	Lower side effect due to precise targeting
Application	Suitable for solid tumors and inflamed tissue	Ideal for targeted cancer therapy, gene therapy.
Examples	Liposomes, nanoparticles	Antibody drug conjugation, immunoliposomes

Recent Approaches in Targeted Drug Delivery Systems (TDDS)

Transdermal Approach

The transdermal drug delivery system (TDDS) offers a non-invasive method of administering medication through the skin, allowing it to reach systemic circulation. These systems can be designed for either passive diffusion or active delivery. In the case of passive diffusion, the drug moves from a region of higher concentration on the skin's surface to a lower concentration in the bloodstream. This approach ensures controlled drug release and enhances patient compliance. The design of transdermal systems can incorporate both passive and active targeting mechanisms to improve drug localization and therapeutic efficiency.

Folate Targeting

Folate targeting exploits the high affinity of folic acid for folate receptor proteins, which are often overexpressed in certain cancer cells. This strategy involves conjugating the drug molecule with folic acid, forming a folate-drug complex that selectively binds to folate receptors on target cells. Upon receptor binding, the complex is internalized into the cell, facilitating targeted drug delivery and minimizing off-target effects. Folate-mediated targeting has shown promising results in enhancing the specificity and potency of anticancer therapies.

Brain-Targeted Drug Delivery

Delivering drugs to the brain is particularly challenging due to the presence of the blood-brain barrier (BBB), a selective permeability barrier that restricts the entry of most therapeutic agents. Brain-targeted drug delivery systems utilize ligands or carrier molecules that can cross the BBB, either by forming prodrugs or using receptor-mediated transport pathways. In such systems, the drug is chemically modified or conjugated to a ligand that allows it to bypass or cross the BBB, delivering therapeutic effects directly to the central nervous system (CNS). Alternative strategies include nasal delivery or using nanocarriers capable of transcytosis**.**

Liposomes

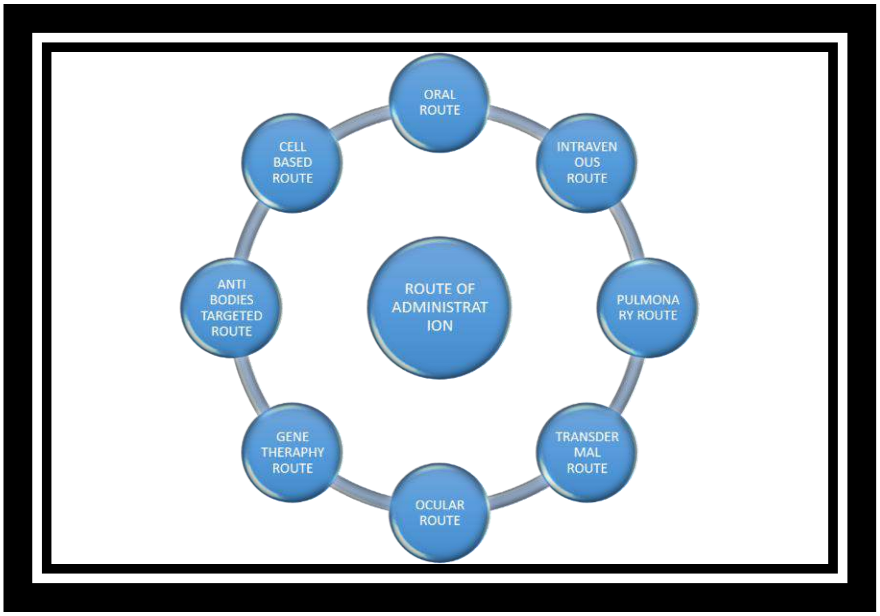
Liposomes are spherical vesicles composed of one or more phospholipid bilayers, capable of encapsulating both hydrophilic and lipophilic drugs. Ranging from nanometers to micrometers in size, they are biocompatible, biodegradable, and non-immunogenic. First introduced by Alec D. Bangham in 1965, liposomes have gained considerable interest due to their versatility in drug delivery. They enhance the therapeutic index of drugs by improving solubility, prolonging circulation time, and minimizing toxicity. Currently, liposomes are widely used in delivering anticancer agents, antibiotics, and vaccines.

Micelles

Polymeric micelles are nanoscale carriers formed by the self-assembly of amphiphilic block copolymers in aqueous solutions. Typically consisting of 50–200 monomer units, micelles have a hydrophobic core that can encapsulate poorly water-soluble drugs, and a hydrophilic shell that provides stability in the bloodstream. Their small size enables prolonged circulation and enhanced permeability. Functionalization of micelle surfaces with ligands enables receptor-mediated endocytosis, significantly increasing the cellular uptake of drugs, particularly in cancer cells. Micellar systems are a promising tool in overcoming solubility, bioavailability, and toxicity issues associated with many therapeutic agents.

Route Of Administration: -

The main routes of administration available for drug therapies oral route, intravenous route ,transdermal route ,subcutaneous route , cell based , gene therapy , pulmonary route etc.



11. Intravenous (IV) Route

Intravenous administration involves injecting the drug directly into the bloodstream, ensuring immediate systemic distribution. This route is ideal in emergency situations due to its rapid onset of action. Targeted IV delivery is often achieved using nanocarriers such as **liposomes, nanoparticles**, and **antibody-drug conjugates**. Administration is typically through a superficial vein via bolus injection or continuous infusion using a catheter. The ability to control the infusion rate also enables sustained drug delivery, making it suitable for drugs requiring precise dosing.

2. Oral Route

Oral administration remains the most commonly used and convenient route, especially for long-term management of chronic diseases. However, the harsh gastrointestinal environment—marked by acidic pH and digestive enzymes—poses challenges for certain drugs, particularly protein-based therapeutics. Nanoparticles, polymeric micelles, and **enteric-coated capsules** are being developed to protect drugs and enhance absorption in the GI tract. Although it has limitations in delivering drugs to specific organs, oral delivery is still preferred due to its ease and patient compliance, prompting continuous innovation in stimuli-responsive and controlled-release formulations.

3. Pulmonary Route

Pulmonary drug delivery involves administering medications directly into the lungs using **inhalers or nebulizers**. Traditionally used for respiratory conditions like asthma and chronic obstructive pulmonary disease (COPD), this route is now being explored for systemic drug delivery. The lungs offer a large surface area and rich blood supply, allowing for rapid absorption of therapeutics into the bloodstream.

4. Transdermal Route

The transdermal route delivers medications across the skin barrier using patches or topical formulations. This non-invasive approach allows for controlled and sustained release of drugs into systemic circulation. The rate of absorption is influenced by skin thickness, drug properties, and the formulation used. Transdermal delivery reduces first-pass metabolism and improves patient adherence.

5. Gene Therapy Route

Gene therapy introduces genetic material (DNA or RNA) into cells to treat or prevent diseases. It can be executed through two major approaches:

- **In vivo**: Genetic material is delivered directly into the patient using viral or non-viral vectors.
- **Ex vivo**: Cells are harvested from the patient, genetically modified in vitro, and then reintroduced into the body.

Gene therapy is increasingly being used in **oncology, genetic disorders**, and **neurological conditions**, offering highly targeted therapeutic action.

6. Nanoparticle-Mediated Delivery

Nanoparticles serve as carriers for drugs, improving stability, solubility, and targeted delivery. These nano-carriers can bypass biological barriers and localize to specific tissues, particularly tumors, through enhanced permeation and retention (EPR) or ligand-mediated mechanisms. Nanoparticle-mediated systems are instrumental in overcoming drug resistance, especially in oncology, where metastasis often becomes unresponsive to conventional therapy.

7. Cell-Based Delivery

This approach uses living cells—such as **stem cells** or **immune cells**—as carriers for therapeutic agents. These cells can home in on disease sites, making them effective for targeted delivery. **Receptor-mediated endocytosis** facilitates the internalization of therapeutic agents once cell surface receptors recognize specific ligands, enabling highly specific intracellular drug delivery.

Applications of TDDS

1. Cancer Therapy

Targeted drug delivery plays a crucial role in oncology by minimizing damage to healthy cells while maximizing drug concentration at tumour sites.

- **Gene Therapy**: Alters or replaces defective genes within cancer cells.

- ○ Approaches include:
- ▪ Gene replacement
- ▪ Gene editing
- ▪ Suicide gene therapy
- ▪ Immunotherapy enhancement

- **Nanoparticles**: Various nano-carriers such as liposomes, polymeric nanoparticles, and metallic nanoparticles are used to enhance delivery and reduce toxicity.

2. Neurodegenerative Diseases

Neurodegenerative disorders involve the gradual breakdown of nerve cells. Targeted delivery across the blood-brain barrier (BBB) using ligands, nanocarriers, or gene therapy enhances the effectiveness of treatment for diseases like Alzheimer's and Parkinson's.

3. Cardiovascular Diseases

TDDS can deliver drugs directly to affected cardiac tissues, increasing efficacy while minimizing systemic exposure. Approaches include:

- Nanoparticles for drug encapsulation
- Liposomes and micelles for controlled release

4. Autoimmune and Inflammatory Diseases

Site-specific delivery of **immunosuppressants** helps in treating inflammation while reducing systemic immune suppression. This targeted strategy lowers the risk of generalized immunosuppression and enhances therapeutic outcomes.

5. Pulmonary Diseases

In diseases such as **asthma**, **COPD**, and **cystic fibrosis**, TDDS using inhaled nanoparticles or gene carriers offers localized treatment with improved efficiency and fewer side effects.

Advantages of Targeted Drug Delivery Systems

1. Improved drug efficiency and efficacy
2. Reduced systemic side effects
3. Enhanced bioavailability
4. Decreased development of drug resistance
5. Improved therapeutic index
6. Enhanced patient quality of life
7. Potential for personalized and combination therapy

Disadvantages of Targeted Drug Delivery Systems

1. Rapid clearance of drug carriers from circulation
2. Immune reactions against delivery vehicles
3. Inadequate accumulation in target tissues or tumours.
4. Potential for diffusion and off-target distribution
5. High manufacturing and development costs
6. Challenges in ensuring stability and reproducibility of the delivery system

CONCLUSION: -

Targeted Drug Delivery Systems (TDDS) represent a transformative innovation in the field of pharmaceutical science, offering a refined approach to therapy by concentrating drug action precisely at the site of disease. By ensuring localized delivery, TDDS increase therapeutic efficacy while significantly minimizing systemic side effects. This strategic localization is particularly valuable in complex treatments such as cancer chemotherapy, where the distinction between healthy and diseased tissue is critical. Techniques like transdermal systems, folate receptor targeting, liposomal formulations, and nanoparticle-mediated carriers have demonstrated substantial improvements in drug bioavailability, stability, and solubility. These systems address long-standing challenges in traditional drug delivery, such as poor absorption, high toxicity, and rapid drug clearance, while enhancing patient compliance and quality of life. The development of TDDS has been greatly accelerated by advancements in nanotechnology, material science, and biomedical engineering. These multidisciplinary contributions have enabled the creation of intelligent, responsive delivery systems with high specificity and controlled release profiles. The impact spans a wide array of diseases, including oncological, neurological, infectious, autoimmune, and genetic disorders. Despite their immense potential, TDDS are not without limitations. Concerns such as high production costs, complex scalability, immune system interactions, and regulatory challenges must be addressed for widespread clinical adoption. However, continuous research and innovation are paving the way for overcoming these barriers. Looking forward, the future of TDDS is undeniably promising. With ongoing progress, these systems are poised to become a cornerstone of personalized medicine, offering tailored therapies that are more effective, safer, and patient-centric. As the pharmaceutical landscape evolves, targeted drug delivery is set to redefine how we treat disease—moving from generalized approaches to highly precise and individualized care.

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