

# EMERGING ASPECTS IN TARGETED DRUG DELIVERY SYSTEMS

## Abstract

In terms of a targeted medicine delivery system, Paul Ehrlich's "magic bullet" idea is a method that specifies the drug moiety straight into its specified bodily location. The Targeted Drug Delivery System (TDDS) is a cutting-edge method for pharmaceutical science innovation. Instead of delivering the drug to the entire body, it targets a specific cell, tissue, or organ through a carrier to achieve therapeutic effectiveness. It has created a number of cutting-edge techniques to treat fatal or chronic diseases in the body by delivering the drug to the right places for longer duration in the body. To solve the issues with traditional drug delivery methods, TDDS is required. There are various carrier systems being utilized and researched.

**Keywords:** Targeted Drug Delivery System, therapeutic effectiveness pharmaceutical science.

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## **I. INTRODUCTION**

Active pharmaceutical ingredients (APIs) are using a variety of methods, preparations, tools, and procedures to deliver the desired therapeutic outcome inside the body. Drug delivery (DD) is the term for this procedure [1]. DD is known as "targeted drug delivery"(TDD) (or "drug targeting"). Paul Ehrlich, a biologist, initially put up the idea of targeted medications in the form of the "magic bullet" concept in 1906 [2].

The theory of TDD which is unrelated to the mode and route of drug administration, explains drug accumulation within a target zone [3]. To overcome a specific adverse impact [4] of traditional medication distribution, targeted drug delivery is a technology that specifically specifies the drug moiety into the cellular, organ, and subcellular level of the particular tissue that is the target organ To produce the desired effect of pharmacological reaction, the medicine must be administered to its target tissue at the proper time and in the proper quantity. By lowering the relative medication concentration in the body's residual tissues, TDD releases medication to the target tissues. Therefore, in TDDS the medication is only supplied or displayed at the area of intervention and has no impact other organs, tissues, or cells in the body [5]. TDD seeks to regulate and control the therapeutic drug's pharmacokinetics, pharmacodynamics, specific toxicity, immunogenicity, and biorecognition. The ultimate objective is to lessen negative effects while increasing treatment effectiveness [6].

## **II. ADVANTAGES OF TDDS [7, 8]**

1. By transporting the active medicinal ingredient to its target place, toxicity is decreased.
2. A smaller dose of the drug can be used to get the desired effect.
3. Steer clear of first pass hepatic metabolism.
4. The dosage is lower than with traditional drug delivery systems.
5. Plasma concentration peaks and valleys were not produced by drug targeting.
6. A boost in the target site's medication absorption.

## **III. DISADVANTAGES OF TDDS [9]**

1. TDD systems are cleared quickly since drug clearance measures how quickly the active medication leaves the body.
2. Immune responses against intravenously given carrier systems are possible.
3. It might have inadequate localisation in tumor cells.
4. It calls for highly advanced technology for the formulation furthermore to expertise in creating drug delivery formulations.
5. Toxicity symptoms from drug deposition at the target site are possible.

## **IV. REASONS FOR DRUG TARGETING**

There are four reasons why TDDs are preferable to conventional DDs: standard delivery methods do not adequately administer medications with respect to their pharmacodynamic, pharmacokinetic, pharmaceutical, and pharmacotherapeutic properties. Drugs should be targeted to a specific area using optimal DD techniques in order to increase therapeutic effectiveness [10] as well as lessen the toxicity brought on by large doses and a

small therapeutic index. If a medicine is not administered to the a dose at the site of action and pace that maximizes therapeutic effects even minimizing side effects, interactions between drugs and their targets are less effective. TDD has several benefits, such as the ability to significantly increase drug concentration in target compartments without negatively affecting nontarget compartments, simpler drug delivery procedures, and decreased drug amount, which reduces therapeutic costs. The rationale for TDD is the shortcomings [11] of conventional drug delivery systems (CDDS).

<b>Limitations of CDDS/ Reasons for drug targeting</b>		
<b>Pharmacokinetic:</b> <ul style="list-style-type: none"> <li>➤ Limited half life</li> <li>➤ High volume of distribution (Vd)</li> </ul>	<b>Solution</b>	<b>TDD</b>
<b>Pharmacodynamic:</b> <ul style="list-style-type: none"> <li>➤ Reduced specificity</li> <li>➤ Reduced Therapeutic Index (T.I)</li> </ul>		
<b>Pharmaceutical:</b> <ul style="list-style-type: none"> <li>➤ Low drug solubility</li> <li>➤ Low drug stability</li> </ul>		
<b>Pharmacotherapeutic:</b> <ul style="list-style-type: none"> <li>➤ High Dose</li> <li>➤ Adverse effects</li> <li>➤ Low patient compliance</li> </ul>		

## V. IDEAL CHARACTERISTICS OF TARGETED DRUG DELIVERY [12]

1. TDD should be prepared in a straightforward, affordable manner.
2. It ought to be harmless, biocompatible, and degradable.
3. Target cells or tissues must possess homogeneous capillary distribution to limit medication delivery.
4. It must possess stable physicochemical properties both in vivo and in vitro.
5. Drug release has no impact on how well it works.
6. It should have the ability to administer a therapeutic dose of medication to the desired location.
7. The carriers that are employed for targeted drug administration must degrade naturally and be simple to remove from the body.

## VI. CONCEPTS OF TARGETED DRUG DELIVERY SYSTEMS

The first TDD method was developed by Paul Ehrlich in 1906, along with the notion of medication delivery [13]. He coined the phrase "magic bullet" to describe the focused medicine delivery method. Targeted drug delivery prevents entry to the typical cellular lining by reducing T.I. in addition to releasing pharmacologically active medication to targeted target with optimal therapeutic concentration for desired pharmacological response [14]. The medication can target bacteria, viral, and intracellular locations. Targeted drug delivery maximizes the advantages of targeted drug administration by minimizing drug distribution in non-target cells while increasing greater and effective concentration at the targeted spot [15].

## VII. TYPES OF DRUG TARGETING

Drug targeting has generally been divided into several categories discussed below.

### 1. Passive and Active Targeting

- **Passive Targeting:** Passive targeting is drug delivery which targets systemic circulation. Due to the body's inherent processes, reaction to the physicochemical characteristics of the medication or DDS, drug targeting happens in this technique. Some colloid types constituted suitable substrates for passive hepatic medication targeting due to their capacity to be absorbed by RES especially in the spleen and liver. The body's defense immunological system is quickly triggered and releases opsonins if any foreign nanoparticle gets within the body through an intravenous route. These opsonins rapidly cover the nanoparticle's surface and direct it toward the liver and spleen, which are RES organs. Such a passive targeting strategy is frequently effective for targeting the hepatic system with medication. Passive targeting [16] is predicated on the drug(s) accumulating at the site of interest, such as tumor tissue, to target the site of interest. Nanoparticles (NPs) are employed in passive targeting as carriers.
- **Active Targeting:** This method uses modifications to the carrier system's surface to deliver the drug to a certain spot as opposed to rely on RES's natural absorption. Targeting systemic circulation through extravasation and the drug-carrier system is done by receptor-mediated targeting. It is predicated on the medication building up at the site of action through ligand-receptor interaction. It can be done by applying a coating made of bioadhesive, non-ionic surfactants, tissue antibodies (such as monoclonal antibodies), albumin proteins, or any particular cell, among other things. Thus, an example of a specific ligand receptor-type interaction is active targeting which follows extravasation and systemic circulation [17]. It is mostly depends on the biological contact between the ligands on NPs and the target cells. It is widely used in tumor targeting in cancer therapy. It is further classified as first, second, third and fourth order targeting.
- **First-order Targeting:** First order targeting involves restricting drug distribution from the drug-transporting system to the target site of action's capillary bed. It speaks of delivery to a tissue or organ that has been damaged. It primarily found in peritoneal cavity, pleural cavity, lymphatic cavity, organ compartmental targeting etc.
- **Second-order Targeting:** Second-order targeting includes the selective administration of medications towards certain types of cells (tumor cells). It is also called cellular targeting. It denotes concentrating on a particular cell type (or cell types) within the tissue or organ. Ex. Specific delivery to kupffer cells of liver.
- **Third-order Targeting:** It explains delivery to particular intracellular compartments, such as lysosomes, in the target cells
- **Fourth order Targeting:** Fourth order targeting is targeting of drug macromolecules (DNA and proteins)

## 2. Biological, Physical, and Chemical Targeting [18]

- **Biological Targeting:** Using peptides, proteins, or other compounds that act as antibodies (Abs) specifically and precisely engage with receptors, sites, or other biological targets, localized agents can target specific locations using biological targeting. Using cells, tissues, or other particular promoters in vector systems, gene expression can also be restricted to specific regions of interest.
- **Physical Targeting:** Systems that localize agents to target locations depending on those areas' size, make up, or other characteristic features are known as physical targeting systems. The goal of the physical targeting strategy is to alter the DD systems physically from the outside in order to target them to a certain place. In this type of targeting, pH, temperature, light intensity, electric field, and ionic strength all change. To direct the medication carrier to a certain area spot, minor and even specific cues like glucose concentration are employed. This strategy was shown to be very effective for both targeting tumors and cytosolic delivery of drugs. This technique has great potential for gene and tumor targeting.
- **Chemical Targeting:** Chemical targeting entails directing agents to specific locations using prodrugs that are site-specific, enzymes or chemical reactions. By the help of this the deliberate targeting of a vehicle or the agent's controlled release or action can occur.

## 3. Local and Systemic Targeting [19]

- **Local Targeting:** Local targeting is noninvasive targeting techniques whose main objective is to deliver the medicine to the affected area for the treatment of regional diseases.
- **Systemic Targeting:** With systemic targeting, such treatment systems are delivered by an intrusive method, such as intravenous NP injection. After being distributed throughout the body, such systems provide the medication via systemic circulation. The limitations of the systems result from pharmacological side effects in a particular tissue.

## 4. Inverse, Dual, Double, and Combination Targeting [20]

- **Inverse Targeting:** RES will become overflowing with the undermining its defense systems in the event that the usual action of the system is suppressed by a blank colloidal carrier to reduce its passive drug uptake, a technique known as inverse targeting. As passive uptake of colloidal carrier by RES is prevented in this sort of targeting, the procedure is known as inverse targeting. In order to accomplish inverse targeting, a substantial amount of blank colloidal carriers or macromolecules, such as dextran sulphate, are pre-injected to block the RES' normal function. The RES becomes saturated as a result of this method, and the defensive system will be suppressed.

- **Dual Targeting:** The carrier and the drug that is entrapped combine synergistically in the dual targeting mechanism's drug delivery method to increase the therapeutic effect of the drug. For instance, when an antiviral drug is loaded onto a carrier molecule having antiviral activity, the therapeutic efficacy is improved.
  - **Double Targeting:** Double targeting refers to a tactic that combines temporal and spatial elements. While the temporal delivery entails managing drug release at the target site, the spatial delivery entails targeting the drug to the target spot. Using a twofold targeting technique, for instance, one may direct a dendrimer-loaded anticancer medicine directly to the tumor.
  - **Combination Targeting:** Combination targeting offers direct approach to a target. It is a direct targeting method by the help of polymers, homing devices and some carriers having molecular specificity to deliver the drug to target sites.
5. **Location-Based and Disease-Based Targeting [21]:** Targeted distribution to particular cells, organs, and organelles is achieved with TDD using location-based specialized techniques. Location-based targeting includes, but is not limited to, intracellular, respiratory tract, brain, and gastrointestinal tract (GIT) targeting.

While disease-based targeted delivery is a site-specific therapy targeting cancers and other treatable infectious diseases, polymer-based DDSs, like dopamine-liposome conjugates, display good brain targeting with minimal degradation throughout circulation.

## VIII. COMPONENTS OF TARGETED DRUG DELIVERY [22]

1. **Target:** Target refers to a particular organ, cell, or collection of cells that require medical attention because to a persistent or severe disease by applying drug to the particular area.
2. **Carrier or Marker:** These are essential for the efficient delivery of drugs to the pre-selected locations. These are called as engineered vectors that carry or deliver the drug to the target cell while holding the drug within or on them using encapsulation, spacer molecules, or both. Carriers can be categorized into three categories: soluble, cellular, and particle type.

Soluble carriers are monoclonal antibodies, modified plasma proteins, peptides. Cellular carriers are better drug carriers due to their natural biocompatibility. Cancer therapy employs cellular carriers. They are the carriers already present in the body of a living thing and have the innate ability to transfer and move medicines from one location to another. Examples of particle type carriers include liposomes, lipid particles including low-density lipoproteins (LDL) and high-density lipoproteins (HDL), polymeric micelles, nanoparticles, and microspheres.

## IX. DIFFERENT PHARMACEUTICAL CARRIERS USED FOR DRUG TARGETING [23-31]

- 1. Liposomes:** Liposomes are typically quite small, with diameters ranging from 50 nm to several microns. One or more phospholipid bilayers completely encapsulate the aqueous core of these spherical vesicles. It can entrap substances that are both hydrophilic and lipophilic. Liposomes are biocompatible, biodegradable, low toxicity, ability to capture both hydrophilic and lipophilic drugs, and capacity to deliver drugs to cancer tissues.
- 2. Niosomes:** The self-assembling vesicles known as niosomes are constructed of nonionic surfactants and have either a unilamellar or multilamellar shape. Lipids, such as cholesterol, are typically added to niosomes to stabilize them. The vesicles are among the greatest nano-carriers for drug and gene delivery systems because of their stability, affordability, and bioavailability. Anti-cancer medications for conditions like breast cancer, brain tumors, and prostate cancer use drug-loaded niosomes.
- 3. Pharmacosomes:** Pharmacosomes are covalently linked amphiphilic complexes of phospholipid and a drug with an active hydrogen atom. Pharmacosomes have emerged as an alternative prospect because they have a distinct benefit over other traditional vesicles. Their small size, amphiphilic nature, and drug encapsulation in vesicles increase the time the drug spends in systemic circulation, decreases toxicity, and enhances cell wall transfer and solubility of weakly water soluble molecules.
- 4. Ufasomes:** Ufasomes, or unsaturated fatty acid vesicles, are formed in the presence of cholesterol from fatty acids and an ionic surfactant (soap). Ufasomes are effective drug carriers for topical medications. The stratum corneum, the skin's outermost layer, is thought to be the greatest impediment to medication penetration. Because ufasomes are made out of a lipid membrane that can adhere to skin, this issue can be solved by employing them as DDS.
- 5. Transferosomes:** In addition to an edge activator, transferosomes are vesicular carrier structures that are specifically designed to feature at least one internal aqueous compartment that contains a lipid bilayer around it. A lipid bilayer surrounds the aqueous core to create ultra-deformable vesicles with the ability to regulate. Edge activator improves the vesicle membrane's ability to deform, and when combined in the right ratio with the right amount of lipid, it makes transferosomes more pliable and capable of greater penetration. The use of edge activators makes hydrophobic medicines more soluble, thus improving the drug's ability to be trapped. In addition to large molecular weight pharmaceuticals, it can also deliver low molecular weight medications entrapment.
- 6. Virosomes:** Virosomes are reconstituted viral envelopes that can be used as vaccinations and delivery systems for macromolecules into cells. Virosomes are composed of phospholipid bilayer vesicles with a spherical or unilamellar shape with a mean diameter between 120 and 180 nm. Since virosomes are nontoxic, nonautoimmunogenous, biocompatible, and biodegradable, attempts have been made to employ them as adjuvants or antibodies.

- 7. Cubosomes:** Cubosomes are square and rounded self-assembling, cubic-latticed, nanostructured, thermodynamically stable particles. Due to their characteristics, these are regarded as adaptable systems that can be administered in a variety of ways, including orally, subcutaneously, and parenterally. Cubosomes are three-dimensionally arranged as honeycomb structures made of two internal aqueous channels separated into two curved bicontinuous lipid bilayers that can be utilized by a range of bioactive compounds, like peptides, proteins, and chemical medicines. Due to the relative insolubility of the lipid that forms the cubic phase in water, cubosomes can be easily included due to the fact that they are nearly stable at any dilution level, into product compositions.
- 8. Dendrimers:** Dendrimers, which are highly branched, monodisperse macromolecules, are an emerging new class of polymeric structures. The physical and chemical characteristics of pharmacological molecules are more significantly impacted by these materials' structures. They have a large number of functional groups and an empty interior cavity, which contribute to their high solubility. Despite their wide range of uses, their toxicity problems prevent them from being widely used in biological systems.
- 9. Nanoparticles(NPs):** Nanoparticles are defined as particulate dispersions or solid particles having a size between 10 and 1000 nm. The medication was dissolved, encased, confined, or connected to a matrix of nanoparticles. The different types of NPs include fullerenes, quantum dots, super paramagnetic NPs, solid lipid NPs, polymeric NPs, gold NPs, nanostructured lipid carriers, etc.
- 10. Monoclonal Antibodies (MAbs):** The use of MAbs, which are glycoproteins having the ability to bind an antigen to a specific epitope, in therapy has increased recently. In comparison to tiny molecules, MAbs provide better target selection, which reduces toxicity by binding to non-targets. MAbs are a desirable choice for the development of innovative medicines and molecular targeted therapies against a wide range of disorders because of their selectivity and adaptability.
- 11. Polymeric Micelles (PM):** A core-shell structure is a defining characteristic of polymeric micelles. The hydrophobic region of the block copolymer makes up the inner core of PM, which are built up of a core and shell structure. The hydrophilic block of the copolymer serves as the outer shell, protecting the poorly water-soluble medication from the aqueous environment and stabilizing the PM against in vivo identification by the RES. PM are hence self-assembling nanoparticles constructed from amphiphilic block polymers. It has a number of benefits, including its physicochemical characteristics to target tumor using a passive targeting process known as the increased permeability and retention (EPR) effect. Drugs can be included into PM because they are tiny (10-100 nm) and can be chemically or physically conjugated.

## X. CONCLUSION

A novel strategy called drug targeting aims to deliver medication molecules to a particular place or organ within the body. The dosage and consequent adverse effects of the medications were decreased as a result of this delivery technique. Drug targeting uses a variety of delivery mechanisms, including liposomes, transferosomes, gold nanoparticles, niosomes, cubosomes, virosomes, and nanotubes. In the treatment of numerous cancer types,



including colon, prostate, breast, brain, and esophageal cancer, the targeted medication delivery system is crucial.

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