**EMERGING ASPECTS IN TARGETED DRUG DELIVERY SYSTEMS**

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**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 technique 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 in the body for a long time. To solve the issues with traditional drug delivery methods, TDDS is required. There are various carrier systems being utilized and researched.

**INTRODUCTION**

 Active pharmaceutical ingredients (APIs) are transported in the body using various techniques, formulations, technologies, and processes to provide the intended therapeutic effect. This process is known as drug delivery (DD) [1]. Drug delivery is referred to as "targeted drug delivery" (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 targeted drug delivery (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 its targeted body location (organ, cellular, and subcellular level of specific tissue). It is necessary to deliver the drug to its target tissue in the right amount and at the right time to elicit the pharmacological reaction in order to analyze drug use. By lowering the relative concentration of the medication in the remaining tissues, TDD releases medication to the target tissues. Therefore, in a "targeted drug delivery system," the medication is only supplied or displayed at the site of action and does not affect other organs, tissues, or cells in the body [5]. TDD aims to manage and control the therapeutic agent's pharmacokinetics, pharmacodynamics, particular toxicity, immunogenicity, and biorecognition. The ultimate objective is to lessen negative effects while increasing treatment effectiveness [6].

**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.

**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 as well as ability in the manufacture of drug delivery preparations.

5. Toxicity symptoms from drug deposition at the target site are possible.

**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 site of action at a dosage and pace that maximizes therapeutic effects while minimizing side effects, the effectiveness of drug-target interactions is compromised. In addition, simpler drug-administration procedures, decreased drug quantity, which reduces therapeutic costs, and the potential to sharply increase drug concentration in target compartments without adverse effects on nontarget compartments are promising benefits of TDD. Generally, drug targeting results in increased efficacy, modulated pharmacokinetics, controlled biodistribution, increased specificity of localization, decreased toxicity, reduced dose, and improved patient compliance. The limitations [11] of conventional drug delivery system are the reasons for TDD.

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| --- | --- | --- |
| **Limitations of Conventional Drug Delivery/** R**easons for drug targeting** |  |  |
| **Pharmacokinetic:*** Short half life
* High volume of distribution (Vd)
 | **Solution** | **TDD** |
| **Pharmacodynamic:*** Low specificity
* Low Therapeutic Index (T.I)
 |
| **Pharmaceutical:*** Low drug solubility
* Low drug stability
 |
| **Pharmacotherapeutic:*** High Dose
* Adverse effects
* Low patient compliance
 |

**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 should have 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 deliver 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.

**CONCEPTS OF TARGETED DRUG DELIVERY SYSTEMS**

 The first targeted delivery 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 access to normal cellular lining by minimizing therapeutic index 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].

**TYPES OF DRUG TARGETING**

Generally, drug targeting has been classified into different types such as

I. Passive and active targeting

II. Biological, physical, and chemical targeting

III. Local and systemic targeting

IV. Inverse, dual, double, and combination targeting

V. Location-based and disease-based targeting

**I.PASSIVE AND ACTIVE TARGETING**

**1.Passive targeting**

Passive targeting is drug delivery that targetssystemic circulation.As a result of the body's natural reaction to the physicochemical properties of the drug or drug delivery system, 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 reticuloendothelial systems (RES), particularly in the liver and spleen.

The body's defense immunological system is quickly triggered and releases opsonins if any foreign nanoparticle enters 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 approach are often well exploited for targeting of medicine to the hepatic system. Many of the colloidal systems are up taken by the RES vectors thanks to passive targeting. The macrophages of the RES system also play a crucial role in treatments of diseases like leishmaniasis, candidiasis, and brucellosis.

 Passive targeting [16] is based on the accumulation of drug(s) at areas targeting the site of interest, such as in the case of tumor tissue. NPs are used as carriers in passive targeting, and they are directed to enter blood vessels more at the disease site, which provides the opportunity for significant drug accumulation at the target.

**2.Active targeting**

This method uses modifications to the carrier system's surface to deliver the medicine to a specific spot rather than relying 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, active targeting is a specific ligand receptor-type interaction that follows extravasation and blood circulation [17]. It primarily 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-carrier 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 provision of drugs towards specific types of cells (tumor cells). It is also called cellular targeting. it represents targeting a specific cell type (s) within the tissue or organ. Ex. Specific delivery to kupffer cells of liver.

**Third-order targeting**

 It explains delivery to specific intracellular compartments in the target cells, e.g. lysosomes

**Fourth order targeting**

 Fourth order targeting is targeting of drug macromolecules (DNA and proteins)

**II.BIOLOGICAL, PHYSICAL,** **AND CHEMICAL TARGETING [18]**

**Biological targeting**

 Biological targeting allows localized agents to target areas through the use of antibodies (Abs), peptides, proteins, or other biomolecules that have bind with receptors, sites, or other biological targets in a specific manner and controlled manner. Gene expression can also be localized to target areas through the use of cells, tissue, or other specific promoters in vector systems.

**Physical targeting**

 Systems that localize agents to target areas based on their size, composition, or other features are known as physical targeting systems. The goal of the physical targeting strategy is to alter the drug delivery systems physically from the outside in order to target them to a certain place. Some environmental factors, including as pH, temperature, light intensity, electric field, and ionic strength, alter in this form of targeting. To localize the drug carrier to a predetermined 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 or genetic material. This technique has great potential for gene and tumor targeting.

**Table 1: Physical Targeting Methods**

|  |  |  |
| --- | --- | --- |
| **Physical Targeting** | **Formulation System** | **Mechanism for Drug****Delivery** |
| Heat | Liposomes | Change in Permeability |
| Magnetic Modulation | Magnetically Responsive Microspheres Containing Ironoxide | Magnetic Field can retardfluid Flow of particles. |
| Ultrasound | Polymers | Change in Permeability |
| Electrical Pulse | Gels | Change in Permeability |
| Light | Photo responsive HydroGels Containing Azo Derivatives | Change in Diffusion Channels, Activated bySpecific Wavelength |

**Chemical targeting**

 Chemical targeting involves the localization of agents to targeted areas through the use of site-specific prodrugs, enzymes or chemical reactions. By the help of this the targeting of a vehicle or the controlled release or action of the agent can occur.**III.** **LOCAL AND SYSTEMIC TARGETING [19]**

**Local targeting**

 Locally targeted systems are noninvasive targeting strategies with the principal goal of delivering the drug to the local site for the management of local pathologies.

**Systemic targeting**

 With systemic targeting, delivery of such therapeutic systems occurs through an invasive route, such as intravenous administration of nanotechnological systems. Such systems deliver the drug via systemic circulation after distribution in the body. The major limitations of such systems arise from the adverse effects of the drugs in a specific tissue.

**IV.INVERSE, DUAL, DOUBLE, AND COMBINATION TARGETING [20]**

**Inverse targeting**

 The reticuloendothelial system will become saturated with the suppression of its defense systems if the normal action of the system is suppressed by a blank colloidal carrier to reduce its passive drug uptake, a technique known as inverse targeting.

 By preventing passive uptake of colloidal carriers by the Reticulo Endothelial system (RES), this method concentrates its effects at the point of action. 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 achieve inverse targeting, a significant amount of blank colloidal carriers or macromolecules, such as dextran sulphate, are pre-injected to block the RES' normal function. This strategy causes the RES to get saturated and the defensive system to become suppressed. This kind of targeting is a practical strategy.

 **Dual targeting**

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

**Double targeting**

 The term "double targeting" refers to a tactic that combines both temporal and spatial elements. While the temporal delivery entails managing drug release at the target site, the spatial delivery involves 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.**V.****LOCATION-BASED AND DISEASE-BASED TARGETING [21]**

 TDD with specific location-based strategies is a targeted delivery to specific cells, organs, and organelles. Intracellular targeting, gastrointestinal tract (GIT) targeting, brain targeting, and targeting the respiratory tract are some examples of location-based targeting.

Drug-loaded nanocarriers, proteins, Abs, and other intracellular delivery of pharmaceuticals ensure that the therapeutic effect is specifically delivered to the nucleus or particular organelles. Antiviral, antifungal, and antibiotic drugs are absorbed from particularly specific parts of the GIT in a method known as floating DD. To target the stomach/duodenum, small intestine, lymph nodes, and colon, various site-specific oral controlled-release methods have been created. While disease-based targeted delivery is a site-specific therapy targeting cancers and other treatable infectious disorders, polymer-based DDSs such dopamine-liposome conjugates show effective brain targeting with less degradation throughout circulation.

**COMPONENTS OF TARGETED DRUG DELIVERY [22]**

**Target**

 Target means specific organ or a cell or group of cells, which in chronic or acute condition need treatment by applying drug to the particular area.

**Carrier or marker**

 These are required for the effective transportation of drug to the pre-selected sites. They may be called as engineered vectors, which retain drug inside or onto them either via encapsulation and/ or via spacer moiety and transport or deliver it into the target cell. Carriers can be divided into soluble, cellular carriers, particle type.

 Soluble carriers are monoclonal antibodies, modified plasma proteins, peptides. Cellular carriers are better drug carriers due to their natural biocompatibility. They will encounter endothelial barriers and can rather easily invoke an immunological response.

 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. Among the cellular carriers are erythrocytes, serum albumin, antibodies, platelets, and leukocytes.

 Liposomes, lipid particles such as low-density lipoproteins (LDL) and high-density lipoproteins (HDL), polymeric micelles, nanoparticles, and microspheres are examples of particle type carriers. Lipoproteins and serum albumin-resealed erythrocytes are two examples of endogenous carriers. Triglycerides and cholesteryl esters make up the lipoproteins, which are encased in a phospholipid monolayer. They are nonimmunogenic because they must have the benefit of being endogenous. High-density lipoproteins (HDL), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), and chylomicrons are the four types based on densities into which they are divided.

**COMMON APPROACHES OF TARGETED DRUG DELIVERY** **[23]**

 The basic approaches for targeting the drug to specific site based on different research may be categorized broadly in to followings, though there are number of effective and successful strategies used in drug targeting.

I. Controlling the distribution of drug by incorporating it in a carrier system

II. Altering the structure of the drug at molecular level

III. Controlling the input of the drug into bioenvironment to ensure a programmed and desirable biodistribution

**DIFFERENT PHARMACEUTICAL CARRIERS USED FOR DRUG TARGETING [24-31]**

**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. Its exceptional capacity to entrap substances that are both hydrophilic and lipophilic. While hydrophilic molecules can be confined in the aqueous center, hydrophobic or lipophilic molecules are injected into the bilayer membrane. Liposomes have gained popularity both as an exploratory system and commercially as a drug delivery method due to their biocompatibility, biodegradability, low toxicity, ability to capture both hydrophilic and lipophilic medicines, and capacity to simplify site-specific medication administration to cancer tissues.

**Niosomes**

 Niosomes are one of the novel drug delivery systems of encapsulating the medicament in a vesicular system. The vesicle composed of a bilayer of non-ionic surfactants and hence the name niosomes. The niosomes are very small, and microscopic in size (in nanometric scale). Although being structurally similar to liposomes, they have several advantages over them,

**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. By using host-guest interactions and covalent bonding (prodrug method), these nanostructured macromolecules have demonstrated their prospective capacities for entrapping and/or conjugating the high molecular weight hydrophilic/hydrophobic entities. Despite their wide range of uses, their toxicity problems prevent them from being widely used in biological systems.

**Monoclonal antibodies**

 Monoclonal antibodies (mAB) are single type of immunoglobulin that are identical and are directed against a specific epitope (antigen, antigenic determinant) and are produced by B- cell clones of a single parent or a single hybridoma cell line. A hybridoma cell line is formed by the fusion of one B-cell lymphocyte with a myeloma cell. Some myeloma cell synthesize single mAB antibodies naturally. Derivation from a single B-cell clones and subsequent targeting of a single epitope is what differentiates monoclonal antibodies from polyclonal antibodies. Polyclonal antibodies are antibodies that are derived from different cell lines. They differ in amino acid sequences. **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.

**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.

**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.

**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.

**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.

**Gold** **nanoparticles**

Scientists have developed an ultrasensitive detection technology for DNA and protein markers linked to the presence of several cancer types, such as breast and prostate cancer, using gold nanoparticles.

**Ufasomes**

Unsaturated fatty acid vesicles known as ufasomes are made from fatty acids and an ionic surfactant (soap) in the presence of cholesterol. 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.

**Pharmacosomes**

 Pharmacosomes are a neutral molecule which carries both positive and negative charges and possesses both hydrophilic and lipophilic characters with an optimum ratio of polyphenol with phospholipids in form of a complex. The drug is conjugated to the lipoidal complex by electrostatic force or by forming a hydrogen bond. 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.

**Virosomes**

 Virosomes are unilamellar vesicles that are used as medication delivery devices. They are made of phospholipids. To help with recognition and targeting of the virosomes to the target place inside the body, the surface of virosomes contains sites to which the virus-derived glycoproteins are attached.

**Cubosomes**

 Drug delivery devices with a nanostructure called cubosomes are made from certain lipids. They are described as cubic-shaped liquid crystalline nanoparticles that are safe for injection.

**Nanocrystal**

Nanocrystals are particles of material that are less than 100 nm in size and have a single crystalline structure. Nanoparticles are smaller than 1000 nm in size, while nanocrystals are smaller than that.

**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.

**Polymeric micelles**

 A core-shell structure is a defining characteristic of polymeric micelles. They are composed of a hydrophilic shell and a hydrophobic core in a di-block structure. A biodegradable polymer that serves as a reservoir for an insoluble medication often makes up the hydrophobic core. As long as they are not poisonous to cells and can be released by the kidneys, non- or poorly biodegradable polymers can be employed. If a water-soluble polymeric core is utilized, it is chemically conjugated with a hydrophobic medication to make it hydrophobic. The physical stability of the micelles as well as drug release may be affected by the viscosity of the micellar core. The biodistribution of the micelle is mainly dictated by the nature of the shell which is also responsible for micelle stabilization and interactions with plasma proteins and cell membranes. The micelles can contain functional groups at their surface for conjugation with a targeting moiety. Polymeric micelles are mostly small (10–100 nm) in size and drugs can be incorporated by chemical conjugation or physical entrapment. For efficient delivery activity, they should maintain their integrity for a sufficient amount of time after injection into the body. Most of the experience with polymeric micelles has been obtained in the field of passive targeting of anticancer drugs to tumors.

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

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