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Review on: Targeted Drug Delivery System

Purva Madhukar Ghumre[1]*, Shyam Suryakant Awate[2]*, Sanjay R. Arote[3], Mahadevan Raju Swamy[4], Shubhangi Pandurang Manwar[5], Yogesh Baban Zambare[6]

[1]*M. Pharm. student, Department of Pharmaceutics, [2]Associate Professor, Department of Pharmaceutics, [3]Assistant Professor, Department of Medicinal Chemistry, [4]M. Pharm. student, Department of Pharmaceutics, [5]Professor, Department of Medicinal Chemistry, [6]Associate Professor, Department of Medicinal Chemistry, [7]Principal,
Indrayani Vidya Mandir's Krishnarao Bhegade Institute of Pharmaceutical Education and Research, Talegaon Dabhade, Maval, Pune – 410507. India.

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ABSTRACT:

Giving more medication to one or a few body areas than to others is a treatment strategy known as "good drug delivery," often referred to as "targeted drug delivery." There are two frequently used ways for directing drugs to a specific organ or tissue: passive targeting and active targeting. Medication is either continually delivered by drug delivery vehicles or is limited to the target region. An ideal drug delivery vehicle would be able to flow over obstacles such as the blood-brain barrier. By delivering the medicine to the targeted site of action or absorption and blocking its release at any other non-target place, "drug targeting" is a revolutionary strategy to drug delivery. The delivery mechanism is designed to contain the medication intact and undamaged until it arrives and releases at the target location. Tailored drug delivery systems provide several advantages over standard ones, including increased pharmacological activity, less adverse effects, and lower administered dosage. The main goal of targeted drug delivery systems is to only administer therapeutic medications to diseased organs while avoiding negative effects on healthy organs. When utilizing chemotherapeutic medications to treat cancer, this is very critical. A targeted drug delivery system (DDS) transports drugs to certain tissues, organs, and cells using a range of drug carriers. Inadequate bio distribution, drug agglomeration, limited solubility, lack of selectivity, controlling drug release carrier, and natural tissue damage are among the problems that it is frequently meant to alleviate. Enhancing the pharmacological and therapeutic properties of conventional drugs is another goal. In this essay, we will discuss the method of delivering medicine with specificity.

Keywords: Targeted Drug Delivery System, Passive Targeting, Active Targeting, Blood Brain Barrier, Liposomes, Carbon Materials

INTRODUCTION:

DDS refers to the application of new technologies and biological polymer materials technology to deliver genes or drugs to particular body parts in line with the clinical demand timing and dose[1]. It can be designed to have controlled drug release, which minimizes toxicity and adverse side effects, limit drug degradation, increase bioavailability, allow targeting to specific cells, and reduce the overall amount of medication needed[2]. DDS medication research and development attempts to boost curative efficacy, decrease the influence of adverse reaction in patients, and simplify medicine administration by modifying the drug pharmacokinetic model and delivery methods. Innovative materials and technologies are used to achieve this[3]. DDS or drug delivery system, is the use and development of modern science and technology in pharmacy; it has become a key topic in the development and expansion of the industry[4].

Targeted drug administration, often referred to as smart drug delivery, is a method of giving a patient medicine so that the substance is concentrated in some parts of their body more than others[5]. The primary foundation of this delivery approach is nanomedicine, which uses nanoparticle-mediated drug delivery to address the drawbacks of conventional pharmaceutical administration[6]. These medication-loaded nanoparticles are designed to selectively target diseased tissue in the body, avoiding interaction with healthy tissue[7,8].

Targeted drug delivery involves delivering a medicine to its desired site of action and releasing it there via either peripheral (control) or local (environmental) means[9]. Generally, medications are transported to the target site either passively or actively after being linked with a targeting moiety via covalent or non covalent methods[10]. Passive targeting aims to increase the ratio of medication reaching the target spot compared to the non target site by minimizing nonspecific interactions with non target organs, tissues, and cells[11]. By using ligands that bind to specific receptors that are overexpressed on target cells, active targeting allows drugs to be delivered to the intended location. The drug will either be internalized by the cells as a combined drug/carrier (CNT) complex, which is more effective, or it will be internalized by the cells on its own after being freed from the carrier by the environment or a peripheral trigger when it reaches the target location[12]. It has been shown that CNTs are capable of passing through cell membranes and internalizing via insertion and diffusion across lipid bilayers, as well as endocytosis and an endocytosis-independent mechanism. Their long, thin, tubular shape and high aspect ratio are the causes of this[13,14].

Targeting methods:

It is possible to achieve the ability of nanoparticles to concentrate in areas of primarily diseased tissue by using passive or active targeting approaches[15].

- **Passive targeting**

To achieve passive targeting, the therapeutic material is incorporated into a macromolecule or nanoparticle that passively migrates to the target organ[16]. The medication's circulation time and effectiveness in passive targeting are highly connected. This is accomplished by covering the nanoparticle[17]. PEG, or polyethylene glycol, is one of the substances that might make this happen. The inclusion of PEG makes the nanoparticle's surface hydrophilic, allowing water molecules to establish hydrogen bonds with the oxygen molecules on PEG[18]. The material's antiphagocytic qualities are derived from the formation of a hydration layer around the nanoparticle as a result of this interaction[19]. This property is provided to the particles by the hydrophobic contacts present in the reticuloendothelial system (RES), which permits the drug-loaded nanoparticle to stay in circulation for a longer period of time[20]. It has been found that smaller nanoparticles (between 10 and 100 nanometers) circulate systemically for longer periods of time, which might be related to this passive targeting mechanism[21].

- **Active targeting**

Actively targeted drug-loaded nanoparticles enhance the effects of passive targeting, making them more selective to a target site[22]. Several methods may be used to provide active targeting. Selectively targeting diseased tissue inside the body might be aided by knowing the kind of receptor on the cell that the medicine is meant to target[23,24]. Subsequently, researchers can facilitate the attachment of the nanoparticle to the matching cell by employing ligands specific to that cell type[25]. Effective active targeting has been found when transferrin is used as the cell-specific ligand[26]. The transferrin was coupled to the nanoparticle and was intended to target tumor cells that have transferrin-receptor mediated endocytosis mechanisms on their membrane[27]. It was shown that compared to non-conjugated nanoparticles, this tailored approach boosted absorption more[28]. Another cell-specific ligand that attaches to the integrin αvβ3 is the RGD motif[29]. This integrin is more highly expressed in malignancies and activated endothelial cells[30].

Targeted drug delivery system:

- **Liposomes**

Since the creation of viral vectors can be expensive and pose a risk to healthy organs, a variety of nano vectors have been explored as possible gene therapy vehicles[31]. Lipid bilayer membranes are the main component of liposomes, particularly nano-liposomes. Because buried liposomes release the pharmaceutical package slowly, phospholipid clearance in the circulation is comparatively sluggish. This effectively extends the half-life of medications[32].

- **Carbon Materials**

Nano diamonds, graphene/graphene oxide, and carbon nanotubes are typical examples of materials with carbon at the nanoscale. Single-walled carbon nanohorns (SWCNTs) have been shown to exhibit both in vitro and in vivo targeting and selectivity during cancer cell killing through molecular surface functionalization[33]. The use of materials at the nanoscale has attracted a lot of attention. It has been shown that materials at the nanoscale have a range of medicinal and diagnostic uses. Its diameter typically ranges from 10 nm to 1000 nm[34]. The medication is mostly composed of natural polymer materials and has been used extensively in the treatment of vascular disease, diabetes, and tumors[35]. In addition to reducing the drug's toxic and adverse effects, it can successfully prolong the drug's duration of action and enhance its therapeutic impact.

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- **Metallic nanomaterials**

Metallic nanomaterials, such as nanorods and nanocrystals of silver and gold. have demonstrated the ability to cure the condition by producing localized hyper thermal heating using surface Plasmon relaxation and the absorption of incoming optical light[36]. influenced by the particle's size, shape, and potential for drift. Heterogeneity inside the tumor resulting from uneven blood artery architecture and impaired diffusion from a thick intercellular matrix is one issue with medication administration[37].

- **Semiconducting nanomaterials**

Recent years have also seen a great deal of interest in semiconducting nanomaterials for hyper thermal theranostics; these materials' architectures usually permit extensive electromagnetic field penetration into the interior volume of the particle[38].

- **Iron Oxide Nanocrystals**

Magnetic particles are distinguished from their metallic and semiconducting counterparts by the method of heating the particle[39]. To put it briefly, when external alternating magnetic fields are applied, hysteresis loss (Néel relaxation) or induced eddy currents cause the magnetic particles to heat up, leading to magnetic hyperthermia[40].

- **Nano micelles**

Polymer Nano micelle production is attributed to amphiphilic polymers with distinct hydrophobic and hydrophilic regions. The polymer self-assembles to form micelles in an aqueous solution. The process of drug release from nano micelles is determined by the kind and strength of interactions between the drug molecules and the core-forming polymer, as well as by the stability of the micelle[41].

Targeted drug delivery using divided dose system (TDDS) aims to minimize drug concentrations near target cells or tissues while increasing drug delivery to the site of action. Certain bioenvironmental factors also affect the therapeutic effectiveness of drugs[42]. These comprise, among other things, blood flow, tissues, receptors, co-enzymes, the structure of enzymes, and active and passive diffusion. Numerous factors influence the design of a delivery system: drug concentration, target site location, drug and carrier molecular weights, distribution, physicochemical properties of the molecules, particle size, physiological environment, pH, electrical field, and molecular surface characteristics like charge, shape, density, and stability[43]. Aside from other biological parameters, considerations include the rate of absorption of drug molecules through the gastrointestinal tract (GIT), their volume of distribution, metabolic rate, elimination rate, peak drug plasma concentration, half-life, pathological conditions, capillary wall permeability and structure, bioavailability, and toxic dose[44]. For TDDS therapy to be successful, target heterogeneity (tumor targeting), overexpression traits, and patient compliance are required for the therapeutic enhanced permeability and retention effect (EPR)[45]. In this industry, technology is evolving every day.

Characteristics of targeted drug delivery

- It ought to be inactive biochemically.
- It ought not to be immunogenic.
- In vitro and in vivo settings should result in physical and chemical stability.
- The medicine should release in a therapeutic amount.
- There should be very little medication leaking while in transport.
- It is recommended that carriers be biodegradable or easily removed from the body[46].

Review of Literature:

The distribution of medication throughout the body is achieved by the utilization of systemic blood circulation in conventional drug delivery techniques such intravascular injection or oral intake. Only a small portion of the drug actually reaches the affected organ or tissue when using most therapeutic medications. For instance, 99 percent of the drugs used in chemotherapy do not reach the tumor site. Targeted drug delivery reduces the relative concentration of the medication in the target tissues by getting it to those tissues[47].

The Control Workflow[SM] is a tactic used by targeted drug delivery (TDD) to assist lower systemic opioid consumption and provide effective pain management. The goal of this strategy is to provide low-dose TDD as a chronic pain treatment alternative. Patients need to get the right pain management after a thorough analysis of the benefits and drawbacks of different treatment options. The amount of medicine required to effectively manage chronic pain has significantly decreased, according to TDD. By outlining the process, we want to reduce the apparent barriers to TDD therapy[48].

The term "targeted drug delivery" describes a method of giving a patient medicine so that the substance is concentrated in specific parts of their body more than others. Research is now being conducted on a variety of pharmaceutical administration techniques in an effort to improve the therapeutic potential of the corresponding treatment and get around some of the drawbacks that classic dosage forms frequently provide. On the other hand, the way the new dosage forms interact with the cell microenvironment has received notice[49].

It's possible that targeted drug administration is an entirely realistic strategy for providing the patient the medication they need. The typical drug delivery technique includes the medicine being absorbed through a biological membrane, as opposed to the targeted unharness system, which releases the medication in a limitless amount form. Scientists, engineers, and chemists must work together to optimize the highly integrated pharmaceutical delivery system. The properties of the medicine, any side effects, the drug's distribution mechanism, the targeted website, and the patient's condition all had to be taken into account by the targeted release system when it was put into place[50].

The preference for customized medicine administration systems over conventional drug delivery systems arises from three main factors. Initially, there are medical justifications. Conventional drugs are less soluble and more unstable than customized drug delivery systems. Conventional drugs have low absorption, a shorter half-life, and a large volume of distribution required. These comprise its pharmacokinetic properties. The pharmacodynamic properties of drugs provide the third rationale. Standard medications are poor in therapeutic index and have insufficient specificity when compared to customized drug delivery systems. Tailored medicine administration systems are preferable than conventional drug delivery techniques because of these features[51].

A method that delivers a certain amount of medication to a particular diseased area of the body over an extended period of time forms the basis of a targeted drug delivery system. Because it aids in the maintenance of the appropriate levels of tissue and plasma in the body, there is thus a decreased possibility that the medicine may damage healthy tissue. The medication delivery system is highly integrated, thus in order to optimize it, chemists, engineers, and scientists must work together. When implementing a targeted release system, the following design variables need to be taken into account: the medicine, the targeted site, the drug's delivery technique, the disease, the medication's characteristics, and its side effects[52].

Products made with this kind of delivery system are prepared with consideration for the unique properties of the target cells, the kinds of markers or transport carriers that convey the medication to specific receptors and ligands, and physically altered components. Targeted drug delivery systems should ideally have confined drug distribution to specific cells, tissues, or organs, uniform capillary distribution, and be both immunogenic and biochemically inert (non-toxic). They should also be physically and chemically stable both in vitro and in vivo. The release of the medication should not impede its intended effects and the rate of release should be controlled and constant. It should be okay for there to be some drug leakage during transit in addition to the therapeutic dose of medication release[53].

Known as a smart drug delivery system, TDDS is a discrete, self-contained drug delivery system that is used to target, localize, and extend the damaged locations. The idea behind drug targeting is to deliver the medication via a carrier to a particular location of action known as the "magic bullet" (Muller RH. and Keck CM., 2004)[54]. These are naturally non-toxic and biodegradable. For instance, Magnetic Microspheres (Amit Chandna et al., 2013)[55]. Liposomes (Navneet Kumar Verma and Asha Roshan, 2015)[56], Dendrimers (Madaan K et al., 2014)[57], Lipoproteins (Mina Nikanjam et al., 2007) [58], Nanoparticles (Rajesh Singh and James W. Lillard Jr. 2009) [59], Liposomes (Mina Nikanjam et al. 2007)[58], Liposomes (Mina Nikanjam et al. 2007)[59], etc. A broader variety of applications in the field of TDDS is demonstrated by this scientific correlation. Through biological membrane absorption, the system aims to regulate the pharmacokinetics, pharmcodynamics, immunogenicity, toxicity, and bio-recognition of active components inside the body. Pharmacodynamics: low therapeutic index, low specificity; pharmacokinetics: low half life; pharmacotherapeutics: high dose; low patient compliance; toxic effects; etc.; pharmaceuticals: low solubility; low stability; etc. (Vyas SP. and Khar RK., 2008)[60].

Objectives:

- To Study of Targeted drug delivery system.
- Ligand receptor-mediated interaction
- Principles and Applications of Targeted Drug-Delivery Systems

Research Methodology:

Overall, as evidenced by the large database of diverse studies that are available for research, the science of site-specific or targeted medication administration has grown more perceptive and intelligent with the advancement of scientific technology. With the clinical field using all these strategies and state-of-the-art technologies, future therapies and diagnostics will enter a new era. Many problems have been identified, investigated, and overcome throughout the development of drug targeting strategies for clinical use for many types of therapy, especially with reference to cancer treatment. A number of these preparations are currently being commercialized after moving through the clinical testing or trial stages. The secondary data used in this research study was obtained from reliable websites, books, newspapers, journals, and the internet. The research design of the study is mostly descriptive in nature.

Targeted medication delivery is a tactic that, while preventing access to the nontarget site, distributes therapeutic agents to the target location in a selective and preferred manner. Using a "ligand" to help the therapeutic moieties find their way to the target tissues is an appealing strategy for this goal[61]. The mechanism of action of ligand-targeted chemotherapy is to exploit antigens or receptors that are either naturally expressed on tumor cells or overexpressed in them relative to normal tissues. This makes it possible to administer the anticancer medication just to the tumor tissue, protecting normal tissues from the medication's negative effects. These ligands might include small molecules, like low-density lipoprotein (LDL), peptides and proteins, like transferrin or antibodies, or small substances, like folate or carbohydrates. There are a number of important parameters that influence the choice of ligand that targets the therapeutic molecule (Fig. 1A)[62].

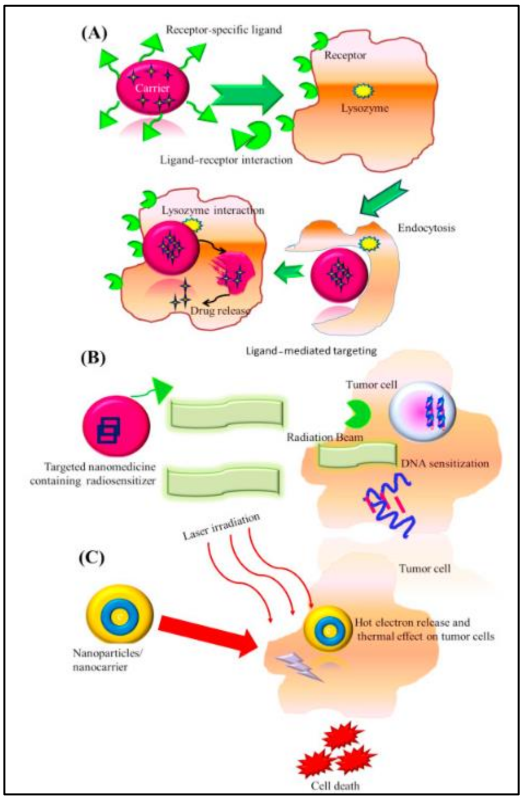

Figure 1: Schematic representation of (A) ligand receptor-mediated interaction, (B) radiotherapy, and (C) photothermal therapy.

Basic Principles and Applications of Targeted Drug-Delivery Systems

The basic principle of drug targeting is to provide a high concentration of medicine at the targeted location while lowering its concentration in the nontargeted region. This strategy aids in optimizing the therapeutic effects of the drug by minimizing the side effects caused by nontarget concentrations, higher doses, and multitarget interactions[63]. Drug targeting includes a pharmaceutical carrier, a targeting location, and coordinated drug behavior, as shown in Figure 2. Additionally, it lessens the medication's unwanted interactions with bioenvironmental factors that affect the drug's ability to reach the intended body locations[64]. The specific organ, cell, or group of cells that the medication will interact with and that need to be treated for an acute or chronic illness is known as the target[65]. In order for the loaded medication to be carried toward predefined sites in an efficient manner, a mechanism or molecule known as the carrier is required. A drug-targeting combination should be as safe, nonimmunogenic, biochemically inert, biodegradable, biocompatible, and physicochemically stable as possible, both in vivo and in vitro. It should also leave the body as soon as possible, have very little drug leakage while in route, and release the medication in a controlled and predictable manner. Additionally, it should be relatively simple, affordable, and repeatable to make[66].

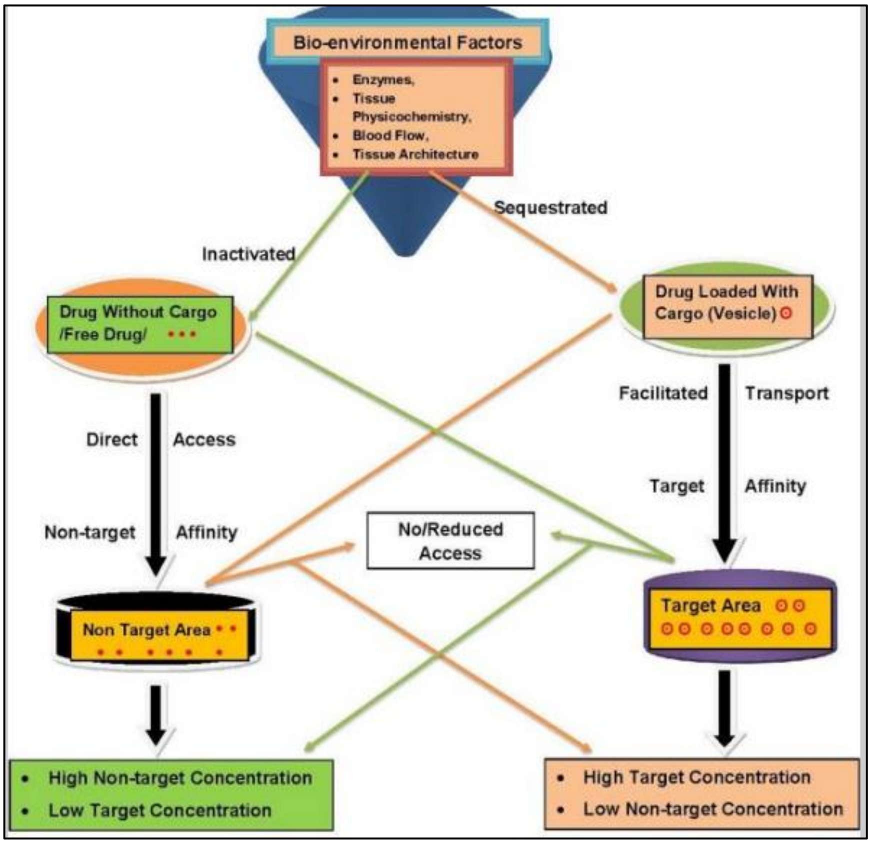

Figure 2: Principles of drug targeting.

Strategies for drug targeting

A variety of pharmacological targeting strategies are depicted in Figure 3, including:

Passive targeting

Passive targeting is a term used to describe drug delivery strategies that attempt to distribute the medicine into the systemic circulation. Figure 3 shows how the drug delivery system or the medication's physicochemical properties cause the body to react, trapping the drug until it reaches the intended region and generating passive targeting[67]. Zhang et al. used salinomycin passive targeting micelles to reduce breast cancer and stem cells.

Active targeting

By identifying the target group and connecting it to the drug delivery system's surface through receptors in the target cells, this technology targets the drug. Target group examples include bioadhesive nonionic surfactants, albumin protein, and antibodies[68]. The three types of active targeting are: First-order targeting (targeting organs), Second-order targeting (targeting cells), and Third-order targeting (targeting intracellular structures) (refer to Figure 4). Zwicke et al. exploited the folate receptor as an active target for anticancer drugs.

Figure 3: Different strategies for drug targeting.

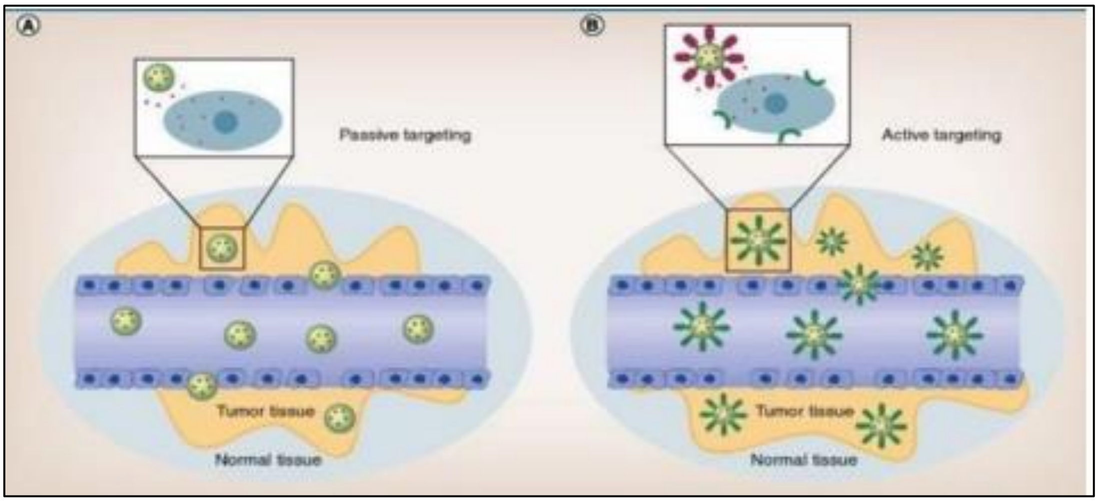

Figure 4: Mechanism of passive targeting and active targeting.

Inverse targeting

Preventing the reticulum-endothelial system (RES) from passively absorbing the drug delivery mechanism is the aim of inverse targeting[69]. To carry out this method, huge molecules of dextran sulfate or a blank drug delivery system can be injected. This will saturate RES and disable its defensive mechanism, hence decreasing its normal absorption function[70].

Ligand mediated targeting

This type of medicine targeting requires the receptor absorption of both naturally occurring low-density lipoprotein (LDL) particles and artificial micro-emulsions of LDL particles coated in Apo proteins[71]. In order to serve as a "homing device" for the drug and carrier, his approach employs ligands as carrier surface group(s) that may be used to precisely direct the carrier to the pre-designated site(s) that include the appropriate receptor units. Most carrier systems are colloidal in nature, and they may be accurately functionalized by a variety of physiologically relevant molecular ligands, including antibodies, oligosaccharides,

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polypeptides, viral proteins, and fusogenic residues. Drug carriers can preferentially approach the right target and deliver the medication because the ligands provide them with specificity, identification, and these other attributes[72].

Table 1: Examples of Ligands

Ligands	Target	Tumour target
Folate	Folate receptor	Overexpression of folate
Transferrin	Transferrin receptor	Overexpression of transferrin receptor
Galactosamine	Galactosamine receptors on hepatocytes	Hepatoma

Physical targeting

By altering the drug delivery systems externally, the physical targeting approach aims to route the drugs to a specific region. Physical changes include temperature, pH fluctuations, and the introduction of an electric field[73]. It has been demonstrated that this technique works very well for both targeting tumors and delivering genetic material or encapsulated medications directly into the cytosol, variations in the environment's pH, temperature, light intensity, electric field, and ionic strength[74].

Table 2: Physical Targeting Methods[75]

Physical Targeting	Formulation System	Mechanism of Drug Delivery
Heat	Liposome	Change in Permeability
Magnetic Modulation	Magnetically Responsive Microspheres Containing Iron oxide	Magnetic Field can retard fluid flow of particles
Ultrasound	Polymers	Change in Permeability
Electrical Pulse	Gels	Change in Permeability
Light	Photo Responsive Hydro Gels Containing Azo Derivatives	Change in Diffusion Channels, Activated by Specific Wavelength

Dual targeting

By collaborating with the entrapped drug, the carrier increases the therapeutic efficacy of the drug, which is administered using a device that uses the dual targeting mechanism[76].

Double targeting

The term "double targeting" refers to a method that combines temporal and geographical elements. Targeting the medicine to the intended location is known as spatial delivery, whereas managing the drug's release at the intended location is known as temporal delivery[77].

Important Properties Influencing Drug Targeting

Three broad categories may be used to categorize the general features impacting drug targeting: drug, carrier, and in vivo environment properties. Table 3 summarizes these categories[78].

Table 3: Properties Influencing Drug Targeting[79]

Properties related to	Important Properties/ Characteristics
Drug	Concentration, Particulate location and Distribution Molecular Weight, Physiochemical properties, Drug Carrier Interaction
Carrier	Type and Amount of Excipients Surface Characteristics, Size, Density
In Vivo Environment	PH, Polarity, Ionic Strength, Surface Tension, Viscosity, Temperature, Enzyme Field

Need of targeted drug delivery[80]

An organ, cell, or collection of cells suffering from an acute or chronic sickness can be treated with a customized medicine delivery system. One of the special molecules required for the effective transportation of a loaded medication to a predetermined site is the drug carrier[81]. The drug delivery system must be biodegradable and able to exit the body with ease and without creating any problems[82]. The purpose of this system is to deliver a prescribed dosage of medicine to the body's intended administration location. This will help to prevent any medication-induced damage to healthy tissue by maintaining the body's required plasma and tissue drug levels[83].

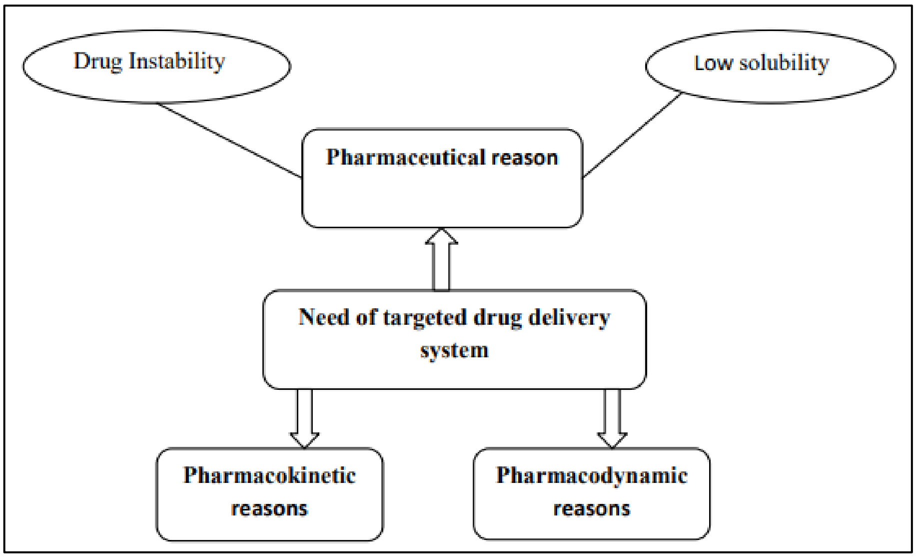

Figure 5: Need of targeted drug delivery[84]

Conclusion:

To transport medication molecules to a specific organ or location inside the body, a revolutionary approach known as "drug targeting" is used. This technique of administration resulted in a decrease in the dose and consequently the side effects of the drugs. Medication targeting makes use of a variety of delivery systems, including as liposomes, transferosomes, gold nanoparticles, niosomes, cubosomes, virosomes, and nanotubes. The targeted drug delivery system is essential for treating a variety of malignancies, such as those of the brain, breast, prostate, and colon. Targeted drug delivery is now developing swiftly because of its capacity to deliver drugs to specific areas. Medication delivery systems are ineffective at precisely the correct location, which leads to injections of lower amounts and a notable decrease in side effects that were more apparent before. The use of nanotechnology in medication delivery has particularly enhanced the distribution of medicines.

Abbreviations: -

TDD: - Targeted drug delivery

LDL: - Low-Density Lipoprotein

RES: - Reticulo Endothelial System

CNTs: - Carrier Nanoparticles

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