Review Article

Precision Medicine: The Role of Drug Carriers and Targets in Targeted Drug Delivery

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ABSTRACT

Targeted drug delivery, also known as smart drug delivery, is a treatment approach that involves administering medication to specific body parts, thereby increasing the drug concentration in those areas compared to others. Drug targeting employs two main strategies: passive targeting and active targeting. Drug delivery vehicles transport the drug to the targeted area, and an ideal delivery vehicle is designed to reach challenging sites such as the blood-brain barrier. The field of Nanomedicine, the medical application of nanotechnology, has recently advanced. Due to their minute size, nanoparticles used in Nano-drug delivery can enhance drug solubility and circumvent first-pass metabolism by the liver. This technology can also extend the drug's circulation time in the bloodstream, reducing plasma level fluctuations and minimizing side effects. Examples of nanotechnology-based drug delivery systems include polymer-drug conjugates and nanoparticles such as liposomes, quantum dots, and dendrimers. Other approaches involve coupling therapeutic agents with targeting ligands capable of identifying tumour-associated antigens.

Keywords: Targeted drug delivery, Targeting ligands, Nanotechnology.

INTRODUCTION

In ancient days, acute or chronic diseases are cured by delivering drugs through different dosage forms like tablets, capsules, creams, ointments, liquids, injectables, etc… Even now these systems are primary pharmaceutical products. However, these conventional dosage forms don't produce the maximum therapeutic response.

The targeted drug delivery system is advantageous when compared with the conventional delivery of drugs with improved bioavailability and absorption of drugs. A targeted medication delivery system delivers a specific dosage of a medicinal ingredient to a particular site in the body over an extended period. Maintaining the appropriate levels of tissue and plasma in the body aids in preventing the medication from causing harm to healthy tissue. The utilized carriers must be readily eliminated from the body or biodegradable.[1]

The delivery system should be easy to prepare, reasonably simple, reproducible, and economical. There are three key reasons why a targeted drug delivery system is better than a standard drug administration system. Compared to tailored drug delivery methods, conventional pharmaceuticals have lower solubility and greater drug instability. Conventional medications also need a huge volume of distribution, have a shorter half-life, and have poor absorption. The pharmacodynamic qualities of medications make up the third justification. When considering a targeted medication delivery system, conventional pharmaceuticals are less effective in terms of specificity and therapeutic index. The following design factors must be considered when putting into practice a targeted release system: the disease, the medication's qualities, its adverse effects, the drug's delivery method, the targeted site, and the drug.[2]

OBJECTIVES OF TARGETED DRUG DELIVERY:

To maintain the medication's safety, localization, and targeting while extending its effects on the diseased tissue. The medication needs to work specifically at a certain site, have the fewest possible side effects, and have a higher therapeutic index there without negatively interacting with other sites.[3]

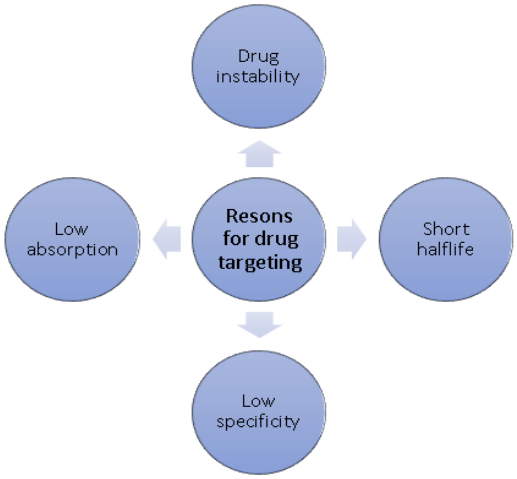

Figure 1: Reasons for drug targeting [4]

ADVANTAGES OF DRUG TARGETING [5]

- The drug administration procedure gets easier to follow.
- Focusing on a particular spot reduces the medicine's toxicity.
- A modest dosage can produce the required pharmacological effect.

- Prevent the effect of the initial pass.
- An increase in the drug's absorption from the application site.
- There was no peak or dip in plasma concentration as a result of drug targeting.
- Reduction of the dosing frequency.
- Reduction of the fluctuation in the circulating blood levels.
- No peak and valley plasma concentration.

DISADVANTAGES OF DRUG TARGETING [6]

- A high dose of a medicine is produced by the body eliminating it quickly.
- An immunological reaction could be triggered by the targeted medication delivery system's carrier.
- The medication delivery mechanism is not kept long enough at the tumour site.
- The medications that are released and their subsequent redistribution.
- A high level of competence in this discipline is required for the development, storage, and administration of the targeted drug delivery system.

IDEAL CHARACTERATICS APPLIED FOR DRUG TARGETING[7]

- Carriers systems can be used to target drugs.
- The carriers are the mechanisms needed to deliver drugs that are entrapped to their intended locations.
- Without releasing the drug moiety into the non-target site, the carriers ensnared it and delivered it to the target site.
- Controllable and predicate rate of drug release.
- Drug release does not affect the drug action.
- Minimal drug leakage during transit.
- Therapeutic amount of drug release.

TYPES OF DRUG TARGETING

Drugs that are targeted to a particular area have a higher therapeutic efficacy and a lower level of toxicity.

Passive targeting:

Passive targeting refers to the process by which biological and pharmacological factors lead to the accumulation of drugs at specific sites in the body, such as in cancerous tissues. This can occur due to altered tissue characteristics in cancer, as well as the body's innate response to drug carriers. The Reticuloendothelial system (RES) plays a key role in this passive targeting strategy, which is effective in directing medication into the hepatic system. Additionally, the RES system's macrophages are essential for the treatment of certain illnesses.[8]

Active targeting:

Active targeting refers to a certain sort of interaction between ligand and receptor for intracellular localization, which happens only after extravasations and blood circulation. First-order targeting, which is defined as a restricted distribution of the drug carrier systems to the capillary bed of a predetermined target site, organ, or tissue (e.g., compartmental targeting in the lymphatic, peritoneal cavity, pleural cavity, cerebral ventricles and eyes, and joints), is one of the three levels of targeting that further categorize this active targeting approach. Second-order targeting is the delivery of medications selectively to certain cell types, such as tumour cells, and not to normal cells; an example of this would be the administration of pharmaceuticals to the liver's kupffer cells. [9]

Inverse targeting:

The goal of inverse targeting is to prevent the reticulum-endothelial system (RES) from passively absorbing the drug delivery mechanism. This procedure can be carried out by injecting large molecules of dextran sulphate or a blank drug delivery system to block the defence mechanism and saturate RES, hence reducing the normal absorption function of RES. When it comes to drug delivery to organs other than RES, inverse targeting is quite helpful. Balthasar and Fung targeted methotrexate to peritoneal tumours using an inverse targeting technique.[10]

Ligand mediated targeting

The receptor absorption of both manufactured micro-emulsions of low-density lipoprotein (LDL) particles coated in Apo proteins and naturally occurring LDL particles is necessary for this kind of medication targeting. [11]

Physical targeting

The goal of the physical targeting technique is to modify the drug delivery systems externally so that they can be directed to a certain location. The application of an electric field, variations in pH, and temperature are examples of physical changes. This approach has great potential for targeting genes and tumors.[12]

Dual targeting

With the dual targeting mechanism, the drug is delivered through a system where the carrier enhances the therapeutic efficacy of the entrapped drug by working in concert with it. For instance, the therapeutic impact of an antiviral medication loaded onto a carrier molecule having antiviral activity is increased.[13]

Double targeting

The term "double targeting" refers to a method that combines temporal and spatial elements. Targeting the drug to the intended location is known as spatial delivery, whereas managing the drug's release at the intended location is known as temporal delivery. A twofold targeting technique was used by Pitto-Barry et al. to direct an

anticancer medication laden with dendrimers to the tumour site.[14]

TYPES OF DRUG CARRIERS

Some of the more popular types of drug carriers include:

Nanotubes, Nanowires, Nanoshells, Nanopores, Gold nanoparticles, Nanocrystals, Nanobots, Polymeric micelles, Microspheres, Dendrimers, Quantum dots, Iron oxide particles, Niosomes, Liposomes, Ufasomes, Pharmacosomes, Virosomes, Cubosomes, Transferosomes.

Nanotubes:

One kind of drug delivery device is a nanotube, which is a carbon hollow cylinder that is simple to fill and seal with the medication needed. Usually, they are employed to deliver the medication to the cancerous cell. Carbon nanotubes were used by Liu et al. to treat tumours in mice. Additionally, Mc Devitt et al. used radiolabeled carbon nanotubes functionalized with antibodies to target tumors. The structure of the nanotube was shown in Fig-2.[15]

Nanowires:

It is a very thin wire composed of either organic chemicals or metal. Because of its high surface area, the nanowire's surface can be modified to enable it to bind with particular biological molecules when it is placed into the body. It can be applied to the diagnosis and treatment of neurological conditions such Parkinsonism, seizures, and other disorders of the brain. Parkinson's and related conditions can be treated with this approach. Tumour localization and detection are further uses for it. The structure of the nanowires was shown in Fig-2.

Nanoshells:

New approaches to nanoparticles are called nanoshells, and they are made of a gold shell covering a hollow silica dielectric core. It can be applied therapeutically or for diagnostic purposes. Antibodies can bind to the surface of nanoshells, enabling them to conjugate specific regions, such cancer cells. The antineoplastic medication is effectively targeted by this method. The potential of nanoshells for cancer imaging and treatment was investigated. The structure of the Nanoshell was shown in Fig-2.[16]

Nanopores:

One strand of DNA molecules at a time can flow through their little openings. Permit very accurate and efficient DNA sequencing. This method has applications in biotechnology and genetic engineering. DNA translocations through graphene membrane Nanopores were reported.

Gold nanoparticles:

Scientists are using gold nanoparticles to create an ultrasensitive DNA and protein marker system that is linked to various cancer forms, including prostate and breast cancer. Gold nanoparticles were utilized to diagnose lung cancer. The structure of gold nanoparticles was shown in Fig-2.[17]

Nanocrystals:

Materials with a dimension of less than 100 nm and a single crystalline structure are known as nanocrystals. The dimensions of nanoparticles are less than 1000 nm, which sets them apart from nanocrystals. The significance of drug loading nanocrystals in cancer targeting and treatment was investigated. The structure of nanocrystals was shown in Fig-2.[18]

Nanobots:

One emerging technique for drug delivery systems is nanorobotics. They are a 10-9 m diameter nanoscale machine. Self-propelling tailored magneto-nanobots were created for deep tumour penetration. It was shown in Fig-2.[19]

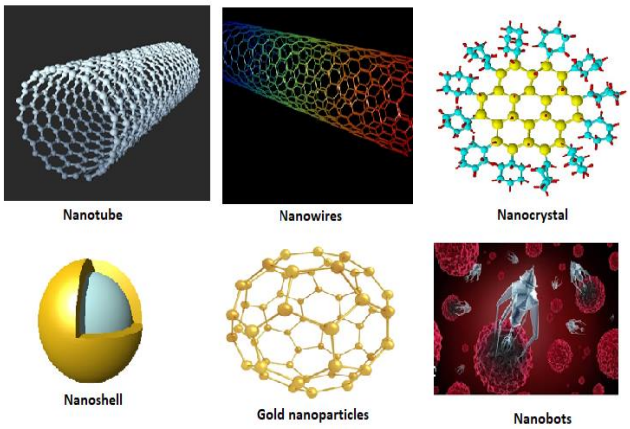

Figure 2: Structures of Nano carriers

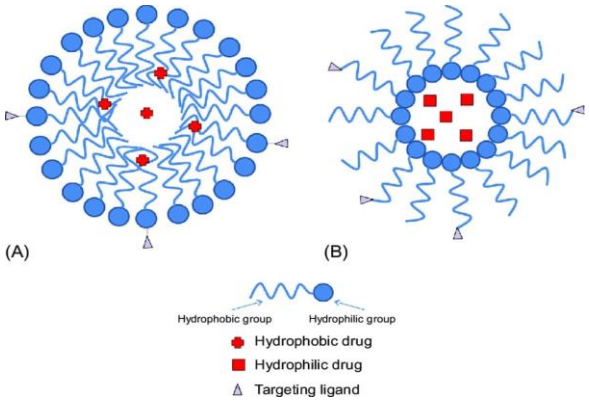

Figure 3: Structure of Polymeric micelles

Polymeric micelles:

In general, synthetic nanoparticles made of biodegradable nanomaterials are preferable due to the harmful effects that metal nanoparticles evoke. For the creation of nanocarriers, a range of biodegradable polymers are accessible, such as *Polylactic acid (PLA), *Poly (lactic-co-glycolic acid) (PLGA), *Polycaprolactone (PCL), as well as

their mixtures and/or modifications. These biodegradable polymers can be formed into micelles, a kind of self-assembling Nano vesicle with a hydrophilic outside and a hydrophobic interior that can hold poorly soluble medications. Polymeric micelles are shown in Fig-3.[20]

Microspheres:

Spherical tiny particles with a size range of 1–1,000 µm are what are referred to as these. The size-based definition can occasionally be unclear because spheres larger than 1,000 µm are nonetheless frequently referred to as microspheres. These particles have several potential uses, including flow indicators, the biological sciences, and the medical profession. They can also be used as carrier materials for purification. The most basic process for producing non-polymeric microspheres involves forming spheres in an aqueous medium, drying them thereafter, and, if necessary, sending them to be seeded. The mechanism was explained in Fig-4.[21]

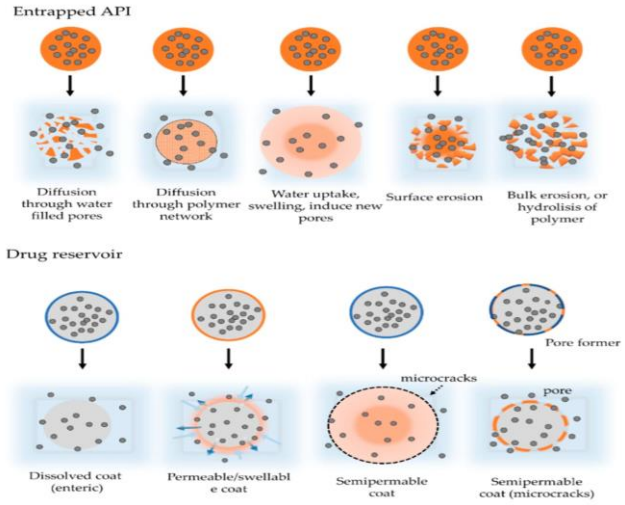

Figure 4: Mechanism of Microspheres

Dendrimers:

Dendrimers are nanoscale, three-dimensional, branching polymeric structures. Drugs can be covalently bonded on dendrimers or physically entrapped in them through non-covalent interactions. Dendrimers surface modification allows for control over drug entrapment and release.

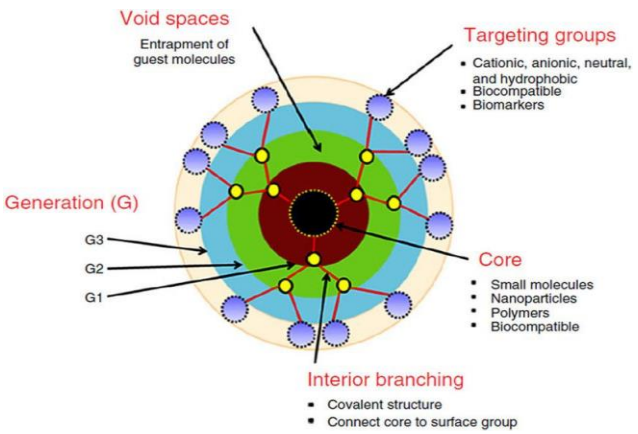

Figure 5: Structure of Dendrimers

Targeting ligands attached to dendrimers can functionalize their surface, increasing the efficiency of their targeting. The ability of dendrimers to entrap hydrophilic or hydrophobic molecules with high molecular weight, as well as their high surface to volume ratio, which makes them suitable carriers of gene therapy, make them extremely promising for usage in biomedical applications. Additionally, they improve many medications' oral bioavailability, stability, and solubility. The structure is shown in Fig-5.[22]

Quantum dots:

An inorganic semiconductor nanocrystals, quantum dots have a typical size of up to 10 nm. The most common types of quantum dots are carbon- and cadmium-compound-based, and they have optical, electrical, and fluorescent characteristics. Because of their special optical characteristics, which come from quantum and other processes, quantum dots can not only deliver drugs but also be used to visualize cancer cells. Quantum dots utilized in biomedicine usually comprise of a coating and a core, where the coating acts as a protective layer and allows the surface to be functionalized with different ligands, hence giving the dots their water solubility. The core provides the system with optical features.

The quantum-dot core may be composed of cadmium compounds such as

*Cadmium selenide (CdSe)

*Cadmium sulphide (CdS)

*Cadmium telluride (CdTe)

These quantum dots have shown notable results as drug carriers. The structure of Quantum dots is explained in Fig-6.[23]

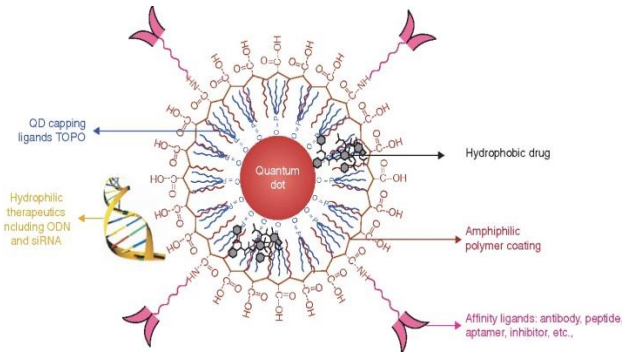

Figure 6: Structure of Quantum dots

Iron oxide particles:

Because of their biocompatibility, comparatively low toxicity, and the property known as "supramagnetism," which allows them to randomly change the direction of magnetization in response to temperature changes. Iron oxide nanoparticles are frequently employed as medication carriers and contrast agents. Magnetic resonance can be produced in iron oxide nanoparticles by self-heating or an external magnetic field. The RES will absorb and remove bare iron oxide nanoparticles since

they have a tendency to aggregate. By covering the nanoparticles with stabilizing nanomaterials like PEG, gelatin, or chitosan, this problem can be solved. Additionally, surface functioning can aid in the release of drugs in response to certain stimuli. Zanganeh et al. recently revealed an iron oxide nanoparticle advantage that was previously undiscovered. They discovered that pro-inflammatory macrophage polarization in tumour tissues can be employed to prevent the growth of tumours using ferumoxytol, an iron oxide nanoparticle currently licensed by the FDA and used to treat iron deficiency anaemia. The mechanism of iron oxide particles was explained in Fig-7.[24]

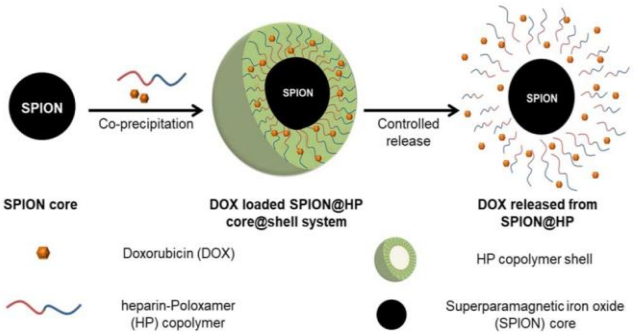

Figure 7: Mechanism of Iron oxide particles

Niosomes:

Non-ionic surfactant vesicles known as Niosomes can entrap both lipophilic and hydrophilic drugs. Because phospholipids are naturally occurring, Niosomes are more stable than liposomes. Niosomes are useful in the targeting of antiviral, anti-inflammatory, antibacterial, antifungal, and antineoplastic medications. Liu et al. developed and assessed a novel daunorubicin (DNR) noisome delivery system intended to treat acute myeloid leukemia (AML). To target the analgesic and anti-inflammatory impact on the pain site, Ahmed et al. produced piroxicam Niosomes. The structure of Niosomes is explained in Fig-8.[25]

Liposomes:

Liposomes are phospholipid vesicles made up of distinct aqueous regions enclosed by lipid bilayers. Liposomes have a few characteristics that make them attractive options for drug delivery systems. These self-assembling nanocarriers may carry substantial pharmacological payloads and are readily customizable and biocompatible. Drugs and/or imaging agents that are hydrophilic or lipophilic can be entrapped by liposomes in the aqueous core and lipid membrane, respectively. Additionally, they are typically regarded as having an excellent safety profile. The structure of Liposomes was explained in Fig-8.[26]

Ufasomes:

Unsaturated fatty acid vesicles, or Ufasomes, are a dispersion of fatty acid and an ionic surfactant (soap) in the presence of cholesterol. Ufasomes work well as carriers for medications meant for topical use. The stratum corneum, the skin's outermost layer, is thought to be the primary barrier preventing medication penetration. Because ufasomes are made of lipid membranes that may adhere to the skin, they can be used as DDS to solve this issue. The structure of ufasomes was explained in Fig-8.[27]

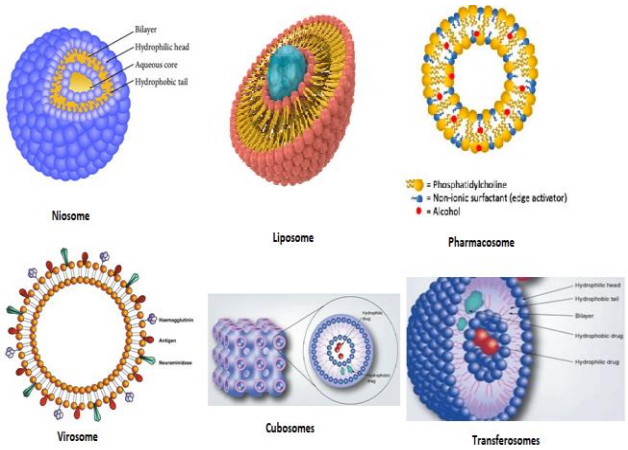

Figure 8: Structures of Vesicular drug delivery systems

Pharmacosomes:

Pharmacosomes are neutral molecules with both hydrophilic and lipophilic properties, carrying both positive and negative charges. They have an ideal ratio of polyphenol to phospholipids in the form of a complex. By creating a hydrogen bond or by using electrostatic force, the medication is conjugated to the lipoid complex. The words "pharmakon," which means drug, and "soma," which means carrier, are the roots of the word "Pharmacosomes." The medication may conjugate to the lipoidal complex as hexagonal aggregates or micelles. The structure of Pharmacosomes is explained in Fig-8.[28]

Virosomes:

Virosomes are unilamellar vesicles made of phospholipids that are used as medication delivery vehicles. To help with virosome recognition and targeting to the intended site inside the body, virus-derived glycoproteins are coupled to specific spots on the virosome surface. Using erythro-magneto-HA-virosomes a novel platform for the treatment of brain malignancy were created. The structure of virosome was explained in Fig-8.[29]

Cubosomes:

Drug delivery systems called Cubosomes are nanostructured and made of specific lipids. They are defined as injectable liquid crystalline nanoparticles with a cubic structure. To stabilize phytantriol-based Cubosomes and enable the delivery of macromolecular therapies to the brain. The structure of Cubosomes was explained in Fig-8.[30]

Transferosomes:

One such innovative vesicular medication delivery method is Transferosomes. Transformers are particularly "ultra-flexible," self-optimizing, and self-regulating. The

surfactant has been employed as edge activators because vesicular membranes, which have an inner aqueous core surrounded by a complex lipid bilayer with unique characteristics, contain "edge activators." In order to effectively enter the skin, they must squeeze through pores that are five to ten times smaller than their diameter. By doing this, the medication will stay intact after entering the skin and prevent the vesicle from completely rupturing. The structure of Transferosomes was explained in Fig-8.[31]

Table 1: Marketed Formulations:

Carrier	Active substance	Therapeutic use	Brand name
Nanoparticles	Aprepitant	Nausea and vomiting	Emend®
	Iron sucrose	Iron deficiency	Venofer®
	Paclitaxel	Metastatic breast cancer	Abraxane®
	Iron gluconate	Iron deficiency	Ferrlecit®
	Doxorubicin	Hodgkin lymphoma	Doxil®
Nanocrystals	Paliperidone	Schizophrenia	Invega®
	Fenofibrate	Lipid disorders	Trigilde®
	Morphine sulphate	Brain stimulant	Avinza®
	Sirolimus	Immunosuppressant	Rapamune®
	Tizanidine HCL	Muscle relaxant	Zanaflex®
Microspheres	Naltrexone	Alcohol dependence	Vivitrol®
	Octreotide	Acromegaly	Somatuline®
Liposomes	Amphotericin b	Fungal infections	Ambisome®
	Mifamurtide	Osteosarcoma	Mepact®
	Bupivacaine	Anaesthetic	Exparel®
	Morphine	Pain relief	Depodur®

CONCLUSION

A novel method called "drug targeting" aims to deliver drug molecules to a particular organ or place within the body. The drug's negative effects were decreased as a result of this delivery method's reduction in dosage. Several delivery mechanisms, including liposomes, Transferosomes, gold nanoparticles, lysosomes, Cubosomes, chromosomes, and nanotubes, are employed in medication targeting. In the treatment of several cancers, including brain, breast, prostate, and colon cancers, the targeted drug delivery system plays a critical role. Drug targeting is making progress these days to address issues with traditional drug delivery methods.

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