Review Article



Targeted Drug Delivery Systems: A Promising Approach for Effective Treatment

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ABSTRACT

Targeted drug delivery systems have emerged as a promising approach to enhance the efficacy of treatments while minimizing side effects. By delivering therapeutic agents directly to the site of action, these systems can increase the concentration of drugs in specific tissues or cells, reducing exposure to healthy tissues. This review highlights the principles, advantages, and challenges of targeted drug delivery systems, including nanocarriers, dendrimers, liposomes, and other types of carriers. The article discusses various targeting strategies, such as passive and active targeting, and their applications in treating diseases like cancer, tuberculosis, and ocular disorders. Targeted drug delivery systems offer several benefits, including improved therapeutic index, reduced systemic toxicity, and enhanced patient compliance. However, challenges like rapid removal of nanocarriers from the body and potential toxicity need to be addressed. Further research is necessary to optimize targeted drug delivery systems and translate them into clinical practice.

Keywords: Targeted Drug Delivery, Nanocarriers, Drug Targeting, Cancer Treatment, Nanotechnology, Controlled Release.

1. INTRODUCTION

target is a specific organ, cell, or group of cells that needs to be treated for an acute or chronic disease ¹. Since Ehrlich originally proposed the "magic bullet" in 1906, the idea of targeted medications has existed. Although the concept's longevity is a clear sign of its popularity, the "magic bullet" is still difficult to apply in clinical settings ². For this purpose, a variety of biomaterials, mostly based on polymers or lipids, can be employed, providing a wide range of chemical options and the possibility of additional modification using nanoparticles 3. The nanoparticles exceptionally wide surface area offers a variety of options for adding functional groups to the surface 4. A single inhibition of one signalling pathway typically results in the overexpression of another signalling pathway, which causes drug resistance. Molecular targeted therapy has produced some results. Furthermore, diarrhoea, nausea, vomiting, rash, and fever are among the side effects that cancer patients may encounter when receiving targeted therapy 5.

Targeted drug delivery may provide maximum therapeutic activity by preventing degradation or inactivation of drug during transit to the target site. Meanwhile, it can also minimize adverse effects because of inappropriate disposition and minimize toxicity of potent drugs by reducing dose. An ideal targeted delivery system should be nontoxic, biocompatible, and biodegradable and physic chemically stable in vivo and in vitro. The preparation of the delivery system must be reasonably simple, reproducible and cost-effective ⁶. Delivering therapeutic compound to the desirable site is a major problem in treatment of many diseases. Conventional utilization of drugs is characterized by poor bio distribution, limited effectiveness, undesirable side effects, and lack of selectivity ⁷. Because of their theoretically high quantum yield, quantum dots are

most attractive options for use in solid-state quantum computation and diagnosis, drug administration, tissue engineering, catalysis, filtration, and textile technologies is the capacity to modify the size of quantum dots, which is beneficial for a variety of applications 8. Colon illnesses such ulcerative colitis, Crohn's disease, inflammatory bowel disease, and colon cancer can all be effectively treated by oral medication administration to the colon 9. The first concrete proof that the cell membrane has a bilayer lipid structure was provided by the microscope images and the likeness to the plasma lemma ¹⁰. Recent developments in innovative drug delivery systems have led to the targeted and sustained delivery of anti-cancer drugs using a variety of colloidal carriers, including liposomes, niosomes, microemulsions, nanoemulsions, microspheres, polymeric micelles ¹¹. To maximize regenerative procedures, targeted medication delivery systems have been developed. This keeps the body's necessary amounts of tissue and plasma drug stable, preventing the drug from harming healthy tissue 12. The process of administering medication to a patient in a way that accurately increases the drug concentration in specific body parts over others is known as drug delivery. The ultimate goal of any delivery method is to safely target, extend, and contain the medication in the diseased tissue. Both the active pharmacological components of a medicine and non-drug excipients are included in every dose form ¹³. To transport a treatment to a specific location rather than the entire body or organ, drug delivery directed distribution systems, also known as targeted drug delivery systems, combine a number of scientific fields, such as pharmacology, molecular biology, polymer science, and bioconjugate chemistry ¹⁴. The production of several nanoparticle kinds using chemical, physical, and biological processes was the main emphasis of this review 15. It is desirable to apply

especially important for optical applications. One of the

particles that exhibit superparamagnetic behaviour at room temperature for biomedical applications ¹⁶.

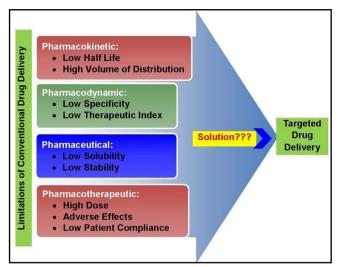


Figure 1: Need of Targeted drug Delivery System ¹⁷.

1.1 Properties Of Targeted Drug Delivery

- 1. It must be physicochemically stable both in vitro and in vivo, nontoxic, biodegradable, and biocompatible.
- 2. Target cells, tissues, or organs should get precise medication administration, and capillaries should be distributed uniformly.
- 3. Controllable and predictable medication release rate 18 .
- 4. Drug delivery shouldn't be impacted by drug release.
- 5. Therapeutic medication release amount.
- There is very little medication leaking while in transportation.
- 7. Compound ought to join a union ¹⁹.

1.2 Principles of Targeted Drug Delivery System: 20

The goal of targeted drug delivery is to minimize exposure to healthy tissues while delivering therapeutic medicines precisely to the site of action, such as sick tissues or cells. Targeted drug delivery systems use a variety of mechanisms to improve the specificity, accuracy, and efficacy of drug delivery, in contrast to systemic administration, which distributes medications throughout the body through the bloodstream. Targeted drug delivery is based on a number of fundamental ideas.

- The purpose of targeted medication delivery systems is to identify and attach to particular molecular targets that are either overexpressed or exclusive to sick cells or tissues. By limiting exposure to healthy tissues, this selective targeting enables the accurate delivery of therapeutic medicines to the disease site.
- Enhanced retention and accumulation of therapeutic agents within the target tissue can be achieved by

targeted drug delivery systems that take advantage of the distinct features of the diseased tissue microenvironment, such as altered cell surface receptors, aberrant angiogenesis, or increased vascular permeability.

 Therapeutic substances can be released in a regulated manner by targeted drug delivery devices, either in response to specific stimuli inside the target tissue or otherwise.

1.3 Advantages of Targeted Drug Delivery System:

- Targeted drug delivery improves the treatment's therapeutic index by reducing systemic toxicity and off-target effects by delivering therapeutic agents just to the site of pathology.
- 2. By creating an environment that is "friendlier" for proteins and peptides than the upper GI tract.
- 3. Preventing the stomach discomfort caused by oral NSAIDS use ⁹.
- Reducing excessive first pass metabolism of steroids.
- 5. Drugs used to treat rheumatoid arthritis, asthma, and angina are released gradually.
- Minimizing side effects when treating a variety of illnesses.
- 7. Targeted drug delivery systems maximize the effectiveness of therapeutic medicines in eliminating sick cells or tissues while avoiding exposure to healthy tissues by ensuring that they reach their intended target at therapeutic quantities ²⁰.
- 8. It is possible to avoid intermittent dosage.
- 9. Boost patient adherence.
- 10. Minimize variability both within and between patients.
- 11. To get the desired side effect, a lower dosage of the drug can be used.
- 12. There are no plasma concentration peaks or valleys.
- 13. Regulate the drug's release at a set pace ²¹.

1.4 Disadvantages of Targeted Drug Delivery System:

- The drug must be in solution before it reaches the colon for delivery to be successful, but the colon's fluid content is lower and more viscous than that of the upper gastrointestinal tract, which limits the use of poorly soluble medications.
- 2. Drug transfer across the mucosa into the systemic circulation may be restricted by the colon's tight junctions' lower surface area and relative tightness.
- Drug transfer across the mucosa into the systemic circulation may be restricted by the colon's tight junctions' lower surface area and relative tightness 9.



- 4. Produces quite little High dose frequency is caused by the body's quick medication removal.
- 5. The immune response may be triggered by the carrier of the targeted drug delivery mechanism.
- 6. The drug delivery method does not spend enough time in the tumor tissue ²⁰.
- Diffusion and redistribution of medications that have been released need administrative and manufacturing skills.
- 8. Drug release's redistribution and diffusion.
- 9. Targeted systems are cleared quickly.
- 10. It's challenging to keep the dosage form stable.
- 11. Formulation requires highly advanced technologies 21.

2. Types of Targeted Drug Delivery Systems:

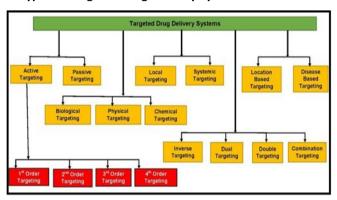


Figure 2: Types of Drugs Targeting ¹⁷.

2.1 Passive Targeting: 21,22

Passive targeting is the process by which pharmacological and biological variables contribute to the drug's accumulation at a certain location. Drugs can typically accumulate in these organs through passive targeting due to disease pathology or altered tissue characteristics in malignancy.

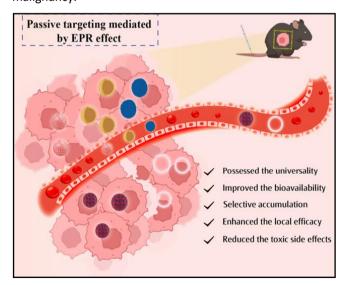


Figure 3: Mechanism and advantages of passive Targeting²³.

Normal blood arteries would only have pore sizes of about 6 nm, whereas cancer fenestrations created during angiogenesis are broader, with pore sizes ranging from 100 to 600 nm. Additionally, the interstitial spaces exhibit deficient permeability and leaky vasculatures, which enable a higher concentration of nanoparticles. The enhanced permeability and retention effect is the name given to this phenomena. The body's natural complex into a cell by endocytosis is what causes targeting. reaction to the drug's physicochemical properties.

2.2 Active Targeting:

Active targeting refers to the use of carriers or matrices designed to specifically target cells or tissues ²⁴. This method focuses on the drug because of the aim group's identity, which is connected to the target cells' receptors on the floor of the drug delivery device. The target group includes albumin protein, antibodies, and bioadhesive non-ionic surfactants ²⁵.

An intracellular localization including a specific ligandreceptor type interaction is referred to as active targeting. This only occurs following blood circulation and extravasations. This active targeting method consists of the following three targeting tiers:

- First order targeting, which includes compartmental targeting in lymphatics, the peritoneal cavity, numerous cavities, cerebral ventricles, the eyes, and joints, is the restricted delivery of drug carrier systems to the capillary bed of a selected target location, organ, or tissue.
- Second order targeting refers to the selective delivery of drugs to specific cell types, like cancer cells, rather than healthy cells, as is the case with the selective delivery of drugs to liver cells that are afflicted.
- 3. Third-order targeting involves delivering medication just to the intracellular location of specific cells ²⁶.

2.3 Inverse Targeting:

The goal of inverse targeting is to prevent the reticulumendothelial system from passively absorbing the drug delivery device. By injecting huge amounts of the blank drug delivery system or big molecules of dextran sulphated to make RES saturated and block the defence mechanism, this process can be accomplished by suppressing the normal absorption function of RES. When it comes to drug delivery to non-RES organs, inverse targeting is quite helpful. Targeting in reverse The biodistribution movement of the drug carrier system degenerates in inverse targeting ²².

Every time a mixed drug delivery system is injected into the body, opsonin triggers the RES system, which leads to a rapid and time-consuming biodistribution pattern. One possible strategy to get around the RES's absorption of mixed particles is inverse targeting. There are a few reportable strategies to stay away from the organs that are rich in RES. One method is to employ macromolecules like dextran sulphate or pre-inject blank mixture carriers into



the RES in greater quantities to saturate it. This approach is typically not advised in a clinical context since it is likely to induce RES since it would actually reduce the functions of RES. Altering the carrier's stiffness, hydrophilicity, surface charge, and scale is a further technique. Using a hydrophilic chemical substance to replace the carrier's surface deliquescent is one efficient technique. One effective way to reverse the targeting of the particles is to coat them with non-ionic surfactants, such as poloxamer 188. Retroviral targeting strategies can employ inverse targeting ²⁷.

2.4 Location-Based and Disease-Based Targeting:

TDD is delivered to particular cells, organs, and organelles via location-based techniques. Examples of location-based targeting include targeting the respiratory system, brain, gastrointestinal tract, and intracellular space. Pharmaceutical agents such as proteins, Abs, and drugloaded nanocarriers can be delivered intracellularly to guarantee that the therapeutic effect is delivered to the nucleus or organelles ²⁶.

A model for this kind of targeting is floating DD, where antibacterial, antifungal, and antiviral drugs are absorbed from extremely particular GIT areas. stomach/duodenum, small intestine, lymph nodes, and colon are the targets of several site-specific oral controlledrelease systems. While disease-based targeted delivery is a site-specific treatment that targets tumors and other infectious diseases that can be targeted, polymer-based DDSs, such as dopamine-liposome conjugates, exhibit efficient brain targeting with less degradation throughout circulation ²⁷. Using nano-DDSs to combat infections may offer a workable substitute for antibiotic treatment. It is a novel idea to design nano-vaccines with enhanced cellular responses and sophisticated targeting. Targeting specific and specialized infections to ensure their persistence within cells is being developed. One of them is functionalizing NPs with antibacterial substances 28.

2.4 Tumor Targeting:

One of the main obstacles in tumor treatment is the delivery of anticancer medications to tumors selectively without damaging the body's normal tissues. Prodrugs' synthesis and monoclonal antibody-based targeting of particular enzymes provide a great deal of freedom in experimental design ²⁸. Chemotherapy, Radiotherapy can work in treatment of cancer against tumor cells ²⁹.

2.5 Brain Targeting: 30

For a range of therapeutic substances, particularly neuropeptides, this general and methodical administration technique can offer a sustained release localized effect. They assist in taking advantage of the unique characteristics of the blood-brain barrier and offer site-specificity or site-enhanced targeting of the therapeutic ingredient by employing a sequential method for drug metabolism.

2.6 Combination Targeting:

The combination targeting approach for site-specific protein and peptide delivery has molecular specificity, just as double targeting. The latter offers direct access to the intended location ²¹. Compared to monotherapy using a single agent, combination treatments including two medications with distinct mechanisms of action have shown reduced morbidity and a higher chance of achieving clinical remission ³¹.

3. Different types of carriers applied for drug Targeting:

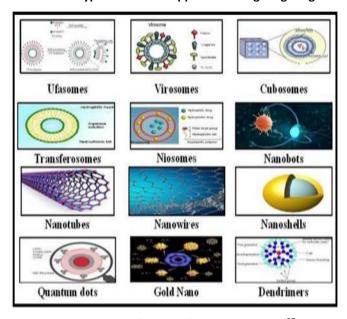


Figure 4: types of carriers for drug targeting ²⁷.

3.1 Nanocarrier:

It is hoped that the use of nanocarriers would help address the challenges and problems associated with traditional drug delivery methods, including their nonspecificity, adverse effects, burst release, and destructive destruction of sizable populations of healthy cells. In addition to offering preferential accumulation at the target region, nanocarriers increase the bioavailability and therapeutic efficacy of medications 32. Only a small number of the numerous nanocarriers that have been created recently have clinical approval for the delivery of chemicals due to their motivated effects at the targeted areas, particularly anticancer medicines. A nanocarrier's particles range in size, with those between 10 and 100 nm providing the best physicochemical properties. When compared to the same crude extract preparations, the primary benefits of canonization are increased absorbency, less adverse effects and dosages, and improved solubility of medicinal plants. Scientists are using gold nanoparticles to create an extremely sensitive technique for detecting DNA and protein markers linked to the existence of various cancer types ²¹. Nanocarriers can passively target tumors and inflammatory regions by altering their surface, such as via PEGylation, which takes advantage of fenestrated vasculature and raises medication concentrations at the tumor location 33.



3.2 Dendrimers: 27

Dendrimers, a new class of polymer compounds, are named after the Greek word "dendron," meaning "tree" and meros "part" 34,35. Dendrimers can carry both hydrophilic and hydrophobic drugs because of their hydrophilic surface and hydrophobic core ³⁶. Dendrimers are monodisperse, highly branching, symmetrical macromolecules that are nanometers in size 32. Dendrimers are three-dimensional branched nano polymers with internal cavities, many branches, and a core ³⁷. While the exterior groups influence the solubility and chemical behaviour of these polymers, the core and interior units determine the environment of the nanocavities and, in turn, their solubilizing capabilities. Attaching targeting ligands to the dendrimers' external surface affects their targeting efficacy, whereas functionalizing the dendrimers with polyethylene glycol chains increases their stability and defence against the Mononuclear Phagocyte System (MPS)³².

3.3 Nanowires: 27

It is a very thin wire composed of metal or other organic materials. Because of its large surface area, the nanowire 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 brain disorders such parkinsonism, seizures, and others. Parkinson's disease and related conditions can be treated with this technology. Additionally, it can be utilized to locate and detect malignancies. Fluorescent zinc oxide nanowires were employed by Hong et al. to image cancer cells with molecular targeting.

3.4 Quantam dots:

The motion of conduction band electrons, valence band holes, or excitons (bound couples of conduction band electrons and valence band holes) in all three spatial directions is restricted by a semiconductor nanostructure known as a quantum dot ³⁸. Quantum dots have unique optical and physical properties that make them ideal for diagnostic applications ³⁹. Electrostatic potentials, the existence of a semiconductor surface, an interface between various semiconductor materials, or a combination of these may be the cause of the confinement. Because of their theoretically high quantum yield, quantum dots are especially important for optical applications ⁴⁰. One of the most attractive options for use in solid-state quantum computation and diagnosis, drug delivery, tissue engineering, catalysis, filtration, and textile technologies is the capacity to modify the size of quantum dots, which is beneficial for a variety of applications. These blood-borne conjugates entered the tumor cells, moved to the perinuclear area, bound HER2 on cell membranes, and extravasated into the tumor 41.

3.5 Liposomes:

The first drug delivery system to be identified was liposomes. As seen diagrammatically in Fig. 5, they are vesicles with an aqueous core surrounded by a hydrophobic

lipid bilayer ³². liposomes can contain both hydrophilic drugs in the aqueous compartment and hydrophobic drugs inside the lipid bilayer 42. Targeted liposomes have been developed with ligands on the surface to help in their detection and binding to specific cell receptors (such as the folate receptor) 43. Liposome-encapsulated and liposomedelivered drugs have highly improved pharmacokinetic characteristics with a high therapeutic index, which is the ratio of the amounts of a therapeutic agent that produce toxicity to the levels that produce a therapeutic benefit. In addition to their anti-cancerous properties in vitro and in vivo, liposomes also have a fat metabolic function and reduced toxicity ²⁷. A cell-like membrane structure, excellent biocompatibility, minimal immunogenicity, protection of the active ingredient or medication, prolonged half-life, decreased toxicity, enhanced efficacy, and more are just a few of the many benefits that liposomes offer as carriers 44. They act as carriers for a variety of drugs ⁴⁵. Liposomes have numerous applications in dermal and transdermal medication administration, including targeted delivery to skin structures 46.

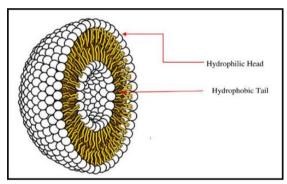


Figure 5: Structure of Liposomes 47

3.6 Nanotubes:

One kind of drug delivery device is a hollow, cylindrical carbon tube called a nanotube, which is simple to fill and seal with the necessary medication ²⁷. They are typically employed to deliver the medication to the cancerous cell. Carbon nanotubes were used by Liu et al. to target the tumor in mice. Additionally, Mc Devitt et al. used radiolabeled carbon nanotubes functionalized with antibodies to target tumors ⁴⁸.

3.7 Niosomes:

Niosomes are better than liposomes in terms of stability, large-scale manufacture, and sterilization. A niosomal formulation is also a self-assembly method that traps hydrophilic and/or hydrophobic active components in these vesicles by building a variety of hydrophilic moieties and molecules with a hydrophobic alkyl group ⁴⁹. Usually, lipid compounds like cholesterol are used to keep niosomes stable ⁵⁰.

4. Applications of Targeted drug delivery system:

 Drug delivery via liposomes can be utilized to treat illnesses such as tuberculosis. Skin chemotherapy is the conventional treatment for tuberculosis (TB), although



it is not very effective. This could be because the chemotherapy does not reach a high enough concentration at the infection site. Better microphage penetration and concentration building at the infection site are made possible by the liposome delivery mechanism ²².

- 2. Used as a vaccine adjuvant.
- 3. In intracellular targeting.
- 4. In DNA delivery, and in oligo nucleotide delivery ²¹.
- 5. Drug delivery via liposomes may be utilized to treat tuberculosis. Chemotherapy is the conventional treatment for tuberculosis (TB), although it isn't usually very effective. This could be because the chemotherapy doesn't reach a high enough concentration at the infection site online ²⁵.
- Also used for ocular medication delivery system treatment ⁵¹.
- 7. Ocular drug delivery one of the major challenge is to maintain and obtain a therapeutic level at the site of action for desired period of time⁵².
- 8. Standards: Particle sieves and particle counting equipment are calibrated using monodisperse microspheres.
- 9. To alter viscosity, thickening agents are added to paints and epoxies ⁵³.
- 10. Numerous illnesses, including diabetes and cardiovascular conditions, are treated using targeted drug administration. Regenerative medicine has been created to treat a number of illnesses. Recently, a few regeneration approaches for treating heart problems have been developed ⁵⁴.
- 11. Stem cell treatment also makes use of targeted medication delivery. By establishing a microenvironment prior to myocardial infarction, this therapy aids in the regeneration of myocardium tissue and restores the contractile function of the heart ⁵⁵.
- 12. Stem cell-based therapies hold great potential as novel therapeutic agents for the regeneration and repair of injured or damaged tissues. They are essential for the growth, development, upkeep, and repair of our brains, bones, muscles, nerves, blood, and skin, among other organs ⁵⁶.
- 13. Nanoparticles are widely utilized to deliver drug molecules that are difficult to dissolve and have low bioavailability when taken orally. It has been observed that using nanoparticles to improve pharmacokinetic characteristics, reduce toxicity, and increase oral bioavailability can help several drugs ⁵⁷.
- 14. Nanoparticles include liposomes, dendrimers, micelles, polymer nanoparticles and inorganic nanoparticles which can carry remedial medicines or imaging examinations and deliver them to target point 58.

- Enhancing targeting, which is achieved by modifying AuNPs' surface targeting ligands to more accurately target specific cells, tissues, or biological molecules ⁵⁹.
- 15. Nano drug delivery systems can maintain drug release and avoid drug degradation resulting in great potential to improve drug therapy ⁶⁰.
- 16. Nanosponges have the ability to selectively distribute drugs and target cancer cells ⁶¹.

5. Types of conventional drug delivery: 62

In a traditional drug delivery system, the medication is formulated into an appropriate form.

- 1. Solid dose forms: powders, tablets, and capsules
- Doses in liquid form: Monophasic: elixirs and syrups Biphasic: Emulsions and Suspensions.
- 3. Powders

6. Causes of using the targeted drug delivery systems: 63

A targeted drug delivery system may be used for a number of reasons, such as:

- 1. Low drug stability.
- 2. Ineffective medication absorption.
- 3. The medication's brief half-life.
- 4. The drug's extensive dissemination volume.
- 5. Low specificity for drugs.
- 6. The drug's limited therapeutic index.

7. Future Perspectives of Targeted drug delivery System:

Because nanoparticles have demonstrated superior antitumor effects on various tumor types, research on nanodrugs has grown increasingly comprehensive and indepth in recent years 23. The most modern methods for colon drug delivery, including multi-particulate systems, 3D printing, microsystems, and nanosystems, were thoroughly covered in this article ⁶⁴. Theoretical mathematical models of prediction, technology for evaluating these events, the effect of the medicine at the tissue/cellular level, and the idea of controlled release of specific drugs at the troubled areas have not yet been fully developed ⁶⁵. Computer-aided drug design is another significant turning point that deserves recognition because it provides a great deal of opportunity for the creation of such innovative and cuttingedge systems ⁶⁶. Encouraging investment in nanorobotics research, fostering multidisciplinary collaborations, and establishing safety and efficacy standards through regulatory bodies are crucial steps 67. Targeted drug delivery is a method of delivering a drug to a patient in a manner that increases the concentration of the drug in certain parts of the patient's body relative to others ⁶⁸. Compared to traditional approaches, computer-aided drug design helps design and develop medications and delivery systems more accurately and with higher quality while using fewer time and resources ⁶⁹.



CONCLUSION

Targeted drug delivery systems hold great potential for improving treatment outcomes by delivering therapeutic agents directly to the site of action. By leveraging advances in nanotechnology and biomaterials, these systems can enhance the efficacy of treatments while minimizing side effects. The development of targeted drug delivery systems requires a deep understanding of the underlying biology of diseases and the properties of nanocarriers. Further research is necessary to overcome the challenges associated with targeted drug delivery, such as rapid removal of nanocarriers from the body and potential toxicity. With continued advancements in targeted drug delivery, it is likely that these systems will play an increasingly important role in the treatment of various diseases, improving patient outcomes and quality of life.

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