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ADVANCEMENTS IN TARGETED DRUG DELIVERY SYSTEM: A REVIEW OF NOVEL APPROACHES AND CARRIER SYSTEMS

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Abstract

Targeted drug delivery systems have transformed pharmaceutical sciences by enhancing therapeutic efficacy, reducing side effects, and improving patient compliance. This review article explores the evolution of drug delivery systems, highlighting the importance of targeted approaches in disease management. We examine the principles, advantages, and limitations of various carrier systems, including liposomes, nanoparticles, monoclonal antibodies, niosomes, and quantum dots. These systems demonstrate potential in delivering drugs specifically to the site of action, minimizing toxicity, and enhancing therapeutic outcomes. The article discusses challenges and future directions in targeted drug delivery development, emphasizing the need for further research in nanotechnology and biomaterials. By understanding targeted drug delivery systems' potential, researchers and clinicians can develop more effective and safer treatments. This review provides insights into the current state of targeted drug delivery, highlighting its potential to revolutionize disease management. The development of novel carrier systems and approaches is crucial for improving therapeutic outcomes and patient quality of life.

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Introduction

Overview of Drug Delivery and Its Evolution

Drug delivery (DD) refers to the methods, formulations, technologies, and processes used to transport pharmaceutical substances within the body to achieve the desired therapeutic effect [1]. It involves strategies for administering medicinal compounds in both humans and animals to ensure therapeutic effectiveness. Recent advancements in drug delivery systems (DDSs) have increasingly focused on smart delivery, which emphasizes administering drugs at the right time, dosage, and target site with maximum safety and efficacy [2].

The development of novel drug delivery systems (NDDSs) has gained significant attention in recent years. These systems improve the therapeutic performance of both existing and new drugs by offering targeted, controlled, and sustained delivery while aligning with the actual drug demand [1].

As a growing field within pharmaceutical science, drug delivery now includes five generations of DDSs, with targeted delivery falling under the fourth generation [3]. Figure -1 illustrates the evolution of these generations. Over the past few decades, considerable research has focused on creating sustained or controlled DDSs. These systems aim to regulate the rate of drug release, reduce dosing frequency, and enhance efficacy compared to conventional delivery methods. One example of an NDDS is the bilayer tablet, which combines either two different drugs or two formulations of the same drug within a single dose. This design allows for sequential release such as immediate and sustained release or a combination of loading and maintenance doses [4].

Despite these advancements, certain challenges remain. Further refinement is needed in systems for delivering poorly soluble drugs, protein-based therapeutics, self-regulated

insulin, and targeted drug delivery systems (TDDSs). One particularly promising direction is targeted tumor delivery using nanotechnology-based DDSs [5]. Nanoparticle (NP)-based delivery systems offer the ability to control drug release, allowing drugs to remain active for longer periods and to respond to specific internal stimuli such as pH, light, temperature, or enzymes [6].

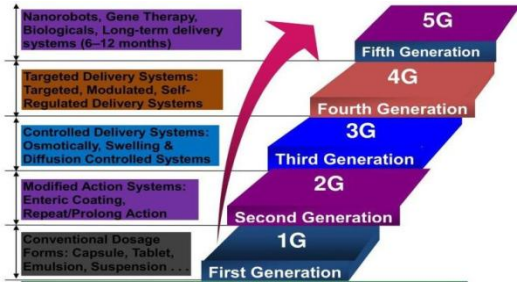

Fig 01: Generation of Drug Therapy Systems

TDDSs are where a drug is delivered to a specific location, rather than the whole body or organ, and combine diverse fields of science, such as polymer science, pharmacology, bioconjugate chemistry, and molecular biology. TDD is aimed at managing and controlling the pharmacokinetics, pharmacodynamics, a specific toxicity, immunogenicity, and bio recognition of therapeutic agents [7]. The end goal is improving treatment effectiveness while reducing side effects. TDDSs differ from conventional or traditional DDSs in that they Acquire site-specific release of drugs from a dosage form, while the former depends on drug absorption through biological membranes [8].

Why Targeted Drug Delivery Is Necessary? [9,10,11].

Conventional drug delivery systems often fall short in several areas, including their pharmacodynamic, pharmacokinetic, pharmaceutical, and therapeutic performance. These limitations, as highlighted in Figure-2, underline the growing importance of targeted drug delivery (TDD). By directing drugs specifically to the site of action, TDD not only enhances the therapeutic response but also minimizes harmful side effects that arise from using high doses or drugs with narrow therapeutic windows.

Traditional delivery methods like parenteral administration are invasive, oral routes are unsuitable for peptides and proteins, and topical formulations have restricted applications limited to surface-level treatment. Moreover, if a drug doesn't reach its intended site at the right concentration and time, its interaction with the target can be inefficient, increasing the risk of side effects while reducing therapeutic benefit.

TDD addresses these challenges by improving drug delivery precision. It offers several advantages, including simpler administration methods, reduced drug quantities—which lowers treatment costs and the ability to achieve high concentrations of the drug at the target site without impacting healthy tissues. Overall, targeted delivery enhances drug efficacy, modifies pharmacokinetics, improves distribution within the body, increases localization accuracy, lowers toxicity, reduces dosing frequency, and supports better patient adherence to treatment.

Figure 02: Limitations of Conventional drug therapy

Common Approaches of Targeted Drug Delivery

The basic approaches for targeting the drug to specific site based on different research outcomes 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 bio-environment to ensure a programmed and desirable bio-distribution

Properties of ideal targeted drug delivery

I. It should be nontoxic, biodegradable, biocompatible and physicochemical stable in- vivo and in-vitro
II. It should be capable to deliver the drug to target cells or tissue or organ and should have uniform capillary distribution.
III. It should release the dug in a controlled and predictable manner for a suitable period of time.
IV. It should efficiently maintain the drug concentration at the targeted site within the therapeutic window for prolong period of time
V. Minimal drug losses due to leakage of the carrier system should be ensured.
VI. Carrier used should be biodegradable or and get readily eliminated from the body without showing any toxic interaction.
VII. Its preparation should be easy or reasonably simple, reproductive and cost effective.

Basic Principles and Applications of Targeted Drug-Delivery Systems

The core principle of targeted drug delivery is to ensure that a high concentration of the therapeutic agent reaches the intended site of action while minimizing its distribution to non-target areas [13]. This selective delivery helps maximize therapeutic efficacy and reduce adverse effects caused by off-target interactions, excessive dosing, or drug accumulation in unintended regions.

Targeting also reduces unwanted interactions between the drug and various biological components that could otherwise hinder its access to the specific site of action, as illustrated in Figure-3 [14]. A targeted delivery system typically consists of three coordinated elements: the drug molecule, the target site, and a pharmaceutical carrier. The target may be a specific organ, cell, or group of cells usually associated with a chronic or acute pathological condition that requires therapeutic

intervention. The carrier is an engineered vehicle or molecular system designed to transport and releases the drug precisely at the preselected site [15].

An ideal drug-targeting complex should meet several criteria: it must be non-toxic, non-immunogenic, and biochemically inert, biodegradable, and biocompatible both in vivo and in vitro. Additionally, it should offer a predictable and controllable drug release profile, be easy and cost-effective to manufacture, and show reproducibility in preparation. Other important features include minimal drug leakage during circulation and the ability to be effectively cleared from the body after delivering its payload [12, 16].

Strategies of Drug Targeting

1. **Passive Targeting**: Drug delivery systems which are targeted to systemic circulation are characterized as Passive delivery systems. Passive targeting is achieved by incorporating the therapeutic agent into a macromolecule or nanoparticle that passively reaches the target organ. In passive targeting, the drug's success is directly related to circulation time [20]. In passive targeting, nanoparticles (NPs) act as drug carriers and naturally accumulate more at diseased sites by entering the nearby blood vessels. This targeted build-up is further enhanced by slow lymphatic drainage, a phenomenon known as the enhanced permeability and retention (EPR) effect [18].The ability of some colloid to be taken up by the Reticulo Endothelial Systems (RES) especially in liver and spleen made them ideal substrate for passive hepatic targeting of drugs.
2. **Inverse Targeting**: In this type of targeting attempts are made to avoid passive uptake of colloidal carrier by RES and hence the process is referred to as inverse targeting. To achieve inverse targeting, RES normal function is suppressed by pre injecting large amount of blank colloidal carriers or macromolecules like dextran sulphate. This approach leads to saturation of RES and suppression of defence mechanism. This type of targeting is an effective approach to target drug(s) to non-RES organs.
3. **Active Targeting**: Active targeting of drug-loaded nanoparticles enhances the effects of passive targeting to make the nanoparticle more specific to a target site. In this approach carrier system bearing drug reaches to specific site on the basis of modification made on its surface rather than natural uptake by RES. Surface modification technique include coating of surface with either a bioadhesive, non-ionic surfactant or specific cell or tissue antibodies (i.e. monoclonal antibodies) or by albumin protein. The process largely depends on how target cells interact with the ligands attached to nanoparticles (NPs). To achieve this, researchers have explored a wide range of ligands, such as proteins, polysaccharides, nucleic acids, peptides, and small molecules [6,18].

This active targeting approach can be further classified into four different levels of targeting which are

- First-order targeting involves directing the drug carrier system to a specific organ, tissue, or capillary bed at the intended site. Examples include targeting the lymphatic system, peritoneal cavity, pleural cavity, cerebral ventricles, eyes, or joints.
- Second-order targeting focuses on delivering drugs selectively to specific cell types, such as tumor cells, while sparing normal healthy cells. For instance, targeting Kupffer cells in the liver is a common example.
- Third-order targeting goes a step further by delivering the drug directly to a specific location inside the targeted cells. This is often achieved through receptor-based, ligand-mediated mechanisms that allow the drug complex to enter the cell via endocytosis [17].
- Fourth-order targeting is sometimes nominated for drugs targeting macromolecules, such as DNA and proteins [19].

4. **Dual Targeting**: In this approach, the carrier molecule itself possesses therapeutic activity, thereby enhancing the overall effect of the drug. For instance, a carrier with intrinsic antiviral properties can be loaded with an antiviral drug, resulting in a synergistic therapeutic effect from the drug carrier conjugate.
5. **Double Targeting**: This approach combines both temporal and spatial targeting methodologies for drug delivery. Spatial targeting involves directing the drug to specific organs, tissues, cells, or even subcellular compartments, while temporal targeting focuses on controlling the rate and timing of drug release at the target site.

Fig 03: Types of Targeted drug delivery

Carriers for Targeting Drugs

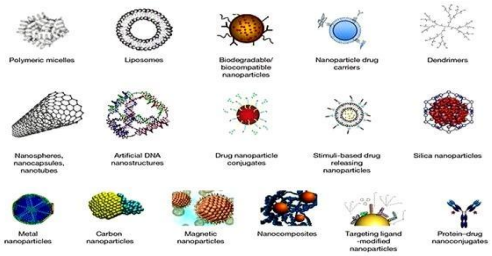

Fig 04: Carriers for Targeting Drugs

Liposomes

Liposomes were initially identified in early 1965 by Alec D. Bangham, and the term is derived from the Greek language, where lipo refers to “fatty” composition and soma denotes “body” or “structure.” Liposomes are comparatively small in dimension, typically ranging from 50 nm to several micrometers in diameter. They are spherical vesicles in which an aqueous interior is fully surrounded by one or more phospholipid bilayers. These structures possess a distinctive capability to encapsulate both fat-soluble (lipophilic) and water-soluble (hydrophilic) substances.

Lipophilic compounds are embedded within the bilayer membrane,as we can see in the figure-5 while hydrophilic agents are enclosed within the aqueous core. Due to their compatibility with biological systems, biodegradability, minimal toxicity, and ability to carry both hydrophilic and lipophilic drugs while enabling targeted delivery to tumor tissues, liposomes have gained significant attention both in research and in commercial drug delivery applications. Numerous investigations have focused on liposomes with the aim of minimizing drug toxicity and/or directing therapies toward specific cells [21].

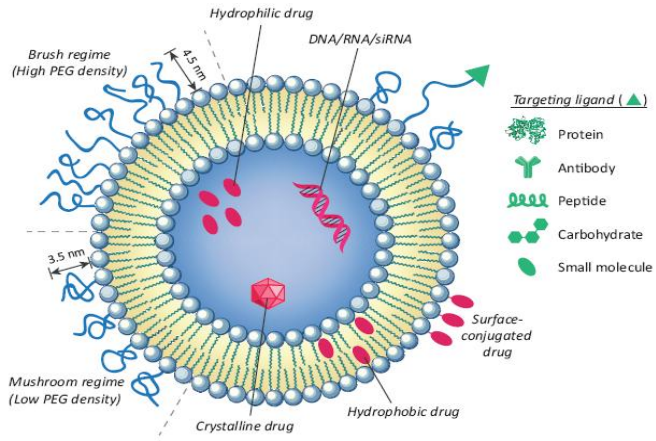

Fig 05: Liposomes for Drug Delivery

Advantages

- Suitable for delivery of hydrophobic (e.g. amphotericin B) hydrophilic (e.g. cytrabine) and amphipathic agents.
- Liposome increases efficacy and therapeutic index of drug (actinomycin-D).
- Liposomes help to reduce the exposure of sensitive tissue to toxic drug.
- Suitable to administer via various routes.

Disadvantages

- Production cost is high.
- Leakage of encapsulated drug during storage.
- Low solubility.

Nanoparticles

Rolland et. al., (1989) designed a site specific drug delivery system consisting of poly metacryclic nanoparticles. The main goal in designing nanoparticles as a delivery system are to control size of particle, surface characteristics and discharge of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen[22, 23].

Advantages

- Nano particles control and prolong release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.
- They offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.
- Polymeric nanoparticles can be easily incorporated into other activities related to drug delivery, such as tissue engineering.

Disadvantages

- Physical handling of nano particles is difficult in liquid and dry forms.
- Small size & large surface area can lead to particle aggregation.

Monoclonal Antibodies

Monoclonal antibodies may exhibit monovalent specificity, attaching exclusively to a single epitope (the portion of an antigen recognized by the antibody). In comparison, polyclonal antibodies interact with multiple epitopes and are generally produced by various antibody-secreting plasma cell populations. Bispecific monoclonal antibodies can also be bioengineered, enabling one monoclonal antibody to target two distinct epitopes, thereby broadening therapeutic applications. It is feasible to develop monoclonal antibodies that bind selectively to nearly any appropriate substance; such antibodies can then be employed for its identification or isolation. This property has become a valuable resource in biochemistry, molecular biology, and medical research. Clinically, monoclonal antibodies are now utilized for both the detection and treatment of various diseases [24].

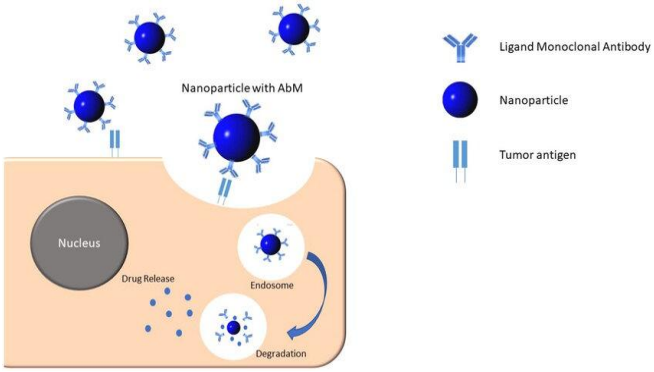

Fig 06: Monoclonal Antibodies

History

- In the early 1900s, Paul Ehrlich introduced the term “magic bullets”, suggesting that a compound could be designed to selectively target disease-causing organisms and deliver a toxin specifically to them.
- By the 1970s, scientists knew that the B-cell cancer multiple myeloma caused the production of a single type of antibody called a paraprotein
- In 1975, Köhler and Milstein demonstrated the clonal selection theory by fusing normal and cancerous cells, creating the Hybridoma technology. This achievement earned them the 1984 Nobel Prize.
- In 1986, the first FDA-approved monoclonal antibody-Orthoclone OKT3 (muromonab-CD3)-was introduced to help prevent kidney transplant rejection.

Applications [25]

Monoclonal antibodies are widely used as diagnostic and research reagents. They are used in diagnostic kits such as ELISA, Immuno fluorescence to diagnose various diseases.

- Enumeration of human lymphocyte subpopulations, anti-CD3 identifies all mature
- T lymphocytes, anti-CD4 identifies helper T lymphocyte subset, and anti-CD8 identifies cytotoxic T lymphocyte subset.
- **Immuno Suppression**: anti-CD3 depresses T cell function and anti-CD4 induces tolerance.
- Passive immunization: High titre antimicrobial human monoclonals can passive protection.
- **Blood Grouping**: anti-A monoclonal provides a more reliable standard reagent than conventional anti sera.
- **Diagnosis in Cancer**: Monoclonal anti-T acute lymphocytic leukaemia (ALL) allows differentiation from non TALL.
- **Imaging**: Radioactive anti-carcino embryonic antigen used to localize colonic tumours or secondary metastases by scanning.
- **Treatment of Cancers**: monoclonal antibody is coupled to a strongly-radioactive atom, such as Iodine-131 to aid in killing the target cancer cells.
- **Purification of Antigen**: Isolate antigen from mixtures by monoclonal affinity← chromatography.

Niosomes

A niosome is a vesicular system based on non-ionic surfactants, functioning similarly to liposomes. They are primarily produced through the incorporation of cholesterol as a stabilizing agent, although other excipients may also be utilized. Compared to earlier emulsion formulations, niosomes exhibit greater permeation efficiency. While they share structural resemblance to liposomes by possessing a bilayer membrane, the distinct components used in their preparation enhance their stability, allowing niosomes to provide several advantages over liposome [26]. Niosomes can be classified based on the number of bilayers present (such as MLV or SUV), their size (for example, LUV or SUV), or according to the drug delivery method employed (e.g., REV, DRV). Below is an outline of the different types of niosomes. These vesicles are generally grouped either by their dimensional range or by the number of bilayer membranes (SUV, LUV) and (MLV, SUV), or alternatively by the technique used for drug incorporation (e.g., DRV, REV) [27].

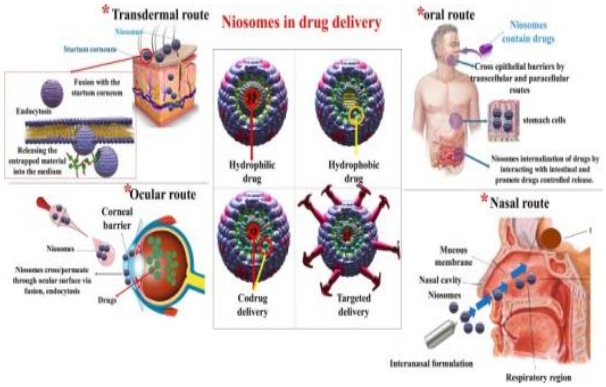

Fig 07: Drug Delivery of Niosomes

Advantages [21]

- **Controlled drug release** – Acts as a drug depot, releasing medication slowly.
- **High stability** – Osmotically active, stable, and increases drug stability.
- **Enhanced therapeutic performance** – Prolonged circulation, targeted delivery, and protection from biological degradation.
- **Biodegradable & safe** – Surfactants are biocompatible, biodegradable, and non-immunogenic.
- Improved drug absorption – Better oral bioavailability and enhanced skin penetration.
- **Multiple administration routes** – Suitable for oral, parenteral, and topical use.
- **Simple storage** – No special handling or storage needed for surfactants.
- **Versatile drug loading** – Can carry hydrophilic, amphiphilic, and lipophilic drugs.
- **Controlled delivery in non** - aqueous systems – Can regulate drug release via emulsification in non-aqueous phases.

Disadvantages

- **Physical instability** – Prone to aggregation and fusion, affecting vesicle size uniformity.
- **Drug leakage** – Entrapped drugs may leak, reducing effectiveness.
- **Limited shelf life** – Hydrolysis of encapsulated drugs shortens storage stability.

Quantum Dots

A quantum dot is a semiconductor nanostructure that restricts the movement of conduction band electrons, valence band holes, or excitons (paired conduction band electrons and valence band holes) in all three spatial dimensions. This confinement can arise from electrostatic fields (produced by external electrodes, doping, strain, or impurities), the presence of an interface between distinct semiconductor materials (e.g., in core–shell nanocrystal systems), the exposure of the semiconductor surface (e.g., semiconductor nanocrystals), or a combination of these factors. Quantum dots hold particular importance for optical applications owing to their theoretically high quantum efficiency. The capability to adjust the size of quantum dots offers benefits for various uses, making them one of the most promising materials for solid-state quantum computing, medical diagnostics, drug delivery, tissue engineering, and catalysis, filtration, and textile technologies [28].

Table 01: Pros and Cons of QDs [29]

Pros	cons
Superior Optical Properties: QDs exhibit high brightness, strong fluorescence, and resistance to photobleaching, making them excellent for bioimaging and tracking drug delivery in real time.	Limited Biodegradability: Unlike lipid-based systems (liposomes) or polymeric nanoparticles, QDs are not easily biodegradable, potentially leading to bioaccumulation and long-term toxicity.
High Surface-To-Volume Ratio: QDs, small size allows them for a high drug-loading capacity and surface modification with targeting ligands, enhancing specificity toward diseased tissue.	Toxicity Concerns: Many QDs contain heavy metals (e.g., lead, cadmium), which can be toxic to cells and tissues, limiting their clinical translation.

Tunable size and emission wavelength: By adjusting the size and composition of the QDs, the emission wavelength can be precisely tuned, enabling multiplexed imaging and tracking of multiple drugs.	Potential immunogenicity: Some QD formulations can trigger immune responses, making them less favorable for systemic administration.
Enhanced stability: QDs are more chemically stable, preventing degradation and ensuring longer circulation times compared to some organic dyes.	Complex functionalization: Modifying QDs for targeted delivery and biocompatibility requires sophisticated surface engineering, increased cost, and complexity.
Multifunctionality: QDs can be conjugated with various biomolecules (peptides, antibodies, or drugs) to achieve targeted drug delivery, imaging, and therapy in a single platform.	Lower Drug Encapsulation Efficiency: QDs, compared to liposomes or polymeric nanoparticles, may have lower drug-loading capacities, depending on the surface chemistry and drug-binding methods.
Potential for Theranostics: The dual capability of QDs in diagnostics (imaging) and therapy makes them promising for personalized medicine applications.	Regulatory Challenges: Due to their toxicity and long-term safety concerns, QDs face strict regulatory scrutiny, delaying their approval for clinical use compared to traditional drug delivery systems.

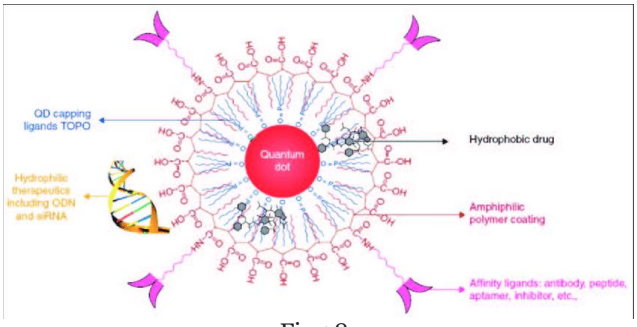

Fig 08:

Discussion

Targeted drug delivery systems have transformed pharmaceutical sciences by improving therapeutic efficacy, reducing side effects, and enhancing patient compliance. Novel carrier systems like liposomes, nanoparticles, and monoclonal antibodies have shown promise in delivering drugs specifically to the site of action.

Advantages

- Improved pharmacokinetic and pharmacodynamic properties
- Enhanced therapeutic efficacy
- Reduced side effects

Limitations and Challenges

- Complexity of designing and manufacturing
- Potential toxicity and biocompatibility concerns
- Regulatory hurdles

Potential Applications:

- Cancer treatment
- Infectious diseases
- Chronic diseases

Future Directions:

- Personalized medicine
- Theranostics
- Combination therapies

By addressing the challenges and limitations, targeted drug delivery systems can play a critical role in improving human health.

Conclusion

Targeted drug delivery systems have revolutionized the field of pharmaceutical sciences, offering improved therapeutic efficacy, reduced side effects, and enhanced patient compliance. The development of novel carrier systems, such as liposomes, nanoparticles, monoclonal antibodies, niosomes, and quantum dots, has shown promise in delivering drugs specifically to the site of action, minimizing toxicity, and improving therapeutic outcomes. Despite the challenges and limitations associated with these systems, the potential benefits of targeted drug delivery make it an exciting and rapidly evolving field. Further research and development are needed to overcome the existing challenges and to fully realize the potential of targeted drug delivery systems in improving human health. With continued advancements in technology and our understanding of disease biology, targeted drug delivery systems are poised to play a critical role in the future of medicine.

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Conflicts of Interest

The authors declare no conflicts of interest.

Author Contribution

Both are contributed equally

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