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Research Article

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ABSTRACT

Nanocarriers have become strong platforms that enhance efficacy and precision of drug delivery to address hundreds of years of issues that persist like low solubility, rapid clearance and off-target toxicity. Their nanoscaled size, controllable surface features and the capacity to accommodate various therapeutic loads facilitate improved bioavailability, regulated and sustained delivery, and site selective targeting through passive and ligand-mediated effects. The opportunities are especially pertinent in oncology, CNS disorders, infectious disease, and autoimmune diseases, where traditional therapies are likely to be unable to provide sufficient therapeutic indices. Nonetheless, the implementation of nanocarriers in clinical practice is limited by significant risks and ambiguities. The disadvantages that may be presented are immunogenicity, allergenicity, rapid clearance through reticuloendothelial system, organ accumulation over time, and nanotoxicological effects, which cannot be completely detected in the typical preclinical models. There are also the complexities of manufacturing, expensive cost of production, and the changing regulatory systems that act as major obstacles to mass production. The considerations concerning ethics and the patient, including fair access, disclosure of the long-term risks, and sound informed consent, are also essential. This review analyzes critically, the two-sidedness of risks and opportunities risk of nanocarrier-based drug delivery, which requires rational design, stringent safety testing, and collaboration across the interdisciplinary boundary. Nanomedicine can become better incorporated in personal and precision-focused treatment approaches by being properly balanced between innovation and adequate risk evaluation.

Keywords: Nanocarriers Nanotoxicology Targeted drug delivery Nanoparticle nanocarriers Personalized nanomedicine.

INTRODUCTION

Background of Drug Targeting

Traditional drug delivery techniques usually cause extensive distribution of the active compound, which causes suboptimal drug concentrations in the disease site and undesired side effects. [1] Conventional drug delivery techniques usually create a wide distribution of the active compound, which results in suboptimal drug concentrations in the disease site and unwanted adverse effects. The current molecular biology, receptor biology and pathophysiological insights have made it possible to identify disease-specific biomarkers, including overexpressing receptors, aberrant enzymes and altered microenvironment. [2] These biological biomarkers are availed of a chance of selective drug delivery with increased therapeutic index. With the ongoing development of precision medicine, drug targeting has become mandatory in enhancing the outcome of various diseases such as cancer, inflammatory diseases, infectious diseases, and neurological diseases. [3]

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Emergence of Nanocarriers in Targeted Therapy

Nanocarriers have transformed targeted therapy in that they provide very highly engineered mechanisms

that can deliver drugs in a site-specific and controlled way. Liposomes, polymeric nanoparticles, dendrimers, micelles, and inorganic nanocarriers have brought levels of control over pharmacokinetics and biodistribution never before seen by researchers, due to their ability to circulate through biological barriers, preferential accumulation in diseased tissues and release of drugs in a sustained or stimulus-responsive fashion. Physiological processes also used by nanocarriers include the increased permeability and retention (EPR) effect of passive targeting, and can be active targeting using ligands, antibodies, peptides, or aptamers. They have been at the frontline of the current drug delivery innovation due to their capacity to deliver several therapeutic agents, preserve sensitive molecules, and enhance solubility. [5, 6]

Objectives and Scope of the Review

The purpose of this review is to describe the principles of drug targeting strategies in detail with an emphasis on the emergence and use of nanocarrier-based delivery systems. [7] The review will provide critical and detailed analysis of drug targeting strategies and mechanisms, advantages and limitations of nanocarriers. It also gives an assessment of recent developments in stimuli-responsive systems, ligand-mediated targeting, and multifunctional platforms intended to be used as therapeutic and diagnostic (theranostic) tools. [8,9] Future regulatory challenges, translational barriers as well as future perspectives of nanocarrier-based targeted therapy are also covered in the scope. Through the combination of the core principles and recent findings, this review is aimed at helping researchers, clinicians, and formulators to advance toward the creation of the next-generation precision medicines.[10]

Fundamentals of Targeted Drug Delivery

Definition and Classification

Drug targeting is defined as the active and premeditated delivery of therapeutic agents to target tissues, cells, or molecular structures to improve the therapeutic activity and minimize systemic side effects. [11, 12] The concept involves the knowledge of biological barriers, disease microenvironment, and molecular markers that can be used to selective localization of drugs. More recent approaches include stimulus-responsive targeting and cell-mediated targeting, extending the range of classification, particularly enabling more specificity to a variety of pathological diseases.

Passive Targeting

Passive targeting makes the use of natural biodistribution patterns and pathophysiology of the disease, especially tumors and inflamed tissues, which are typically leaky and have poor drainage to the lymphatic becoming the basis of passive targeting. [15] Passive targeting takes advantage of the Enhanced Permeability and Retention (EPR) effect, which is defined as leaky tumors with poor lymphatic drainage. Nanocarriers with the ideal size (usually between 10 and 200 nm) may be used in these diseases and incur higher concentrations of the therapeutic agent in these areas than the free drugs, which is particularly useful in oncology, infectious disease, and inflammatory disease. [18]

Active Targeting

Active targeting incorporates the functionalization of drug carriers with ligands that are selective targeting towards molecular markers expressed on the surface of diseased cells. [19] Such ligands can be antibodies, peptides, sugars, aptamers or small molecules which target receptors or antigens expressed on the surface of diseased cells. Active targeting through ligand receptor interaction improves the specificity of target cell uptake, facilitates intracellular drug delivery, commonly via endocytosis, and is part of the evolution of antibody drug conjugates (ADCs), targeted nanoparticles and receptor mediated delivery. [10, 20, 21]

Principles of Drug Targeting

The concepts of drug targeting have their basis on biological systems, physicochemical properties of drugs, and properties of delivery vehicles. Drug solubility, stability, pharmacokinetics, and biodistribution are carefully considered in the process of effective targeting. [22] Controlled release, functionalization of ligands, and morphological optimization of carriers are also considered. The eventual aim is to have the right drug, right dose, right place, and right time, hence, to achieve maximum therapeutic effect with minimal side effects. [25, 26]

Role of Nanocarriers in Enhancing Targeting Efficiency

The fact that nanocarriers can be tuned in terms of size, surface characteristics, drug-loading capacity, and penetrating biological barriers has made them invaluable in enhancing the efficiency of targeting. Surface modifications keep drug release controlled, increase time to circulate, and accumulate selectively in diseased tissues and ligands conjugated on surface facilitate active targeting of diseased cells. [5, 27] Surface modifications, including PEGylation, allow avoidance of immune clearance, and ligand conjugation assists active targeting to diseased cells. The pH, temperature, enzyme, or even magnetic field are also examples of stimuli that multifunctional nanoparticles can respond to to release therapeutic cargoes on demand, and they are underdeveloped in personalized and precision medicine. [28,29] Nanocarriers can also integrate therapeutic and diagnostic capabilities.

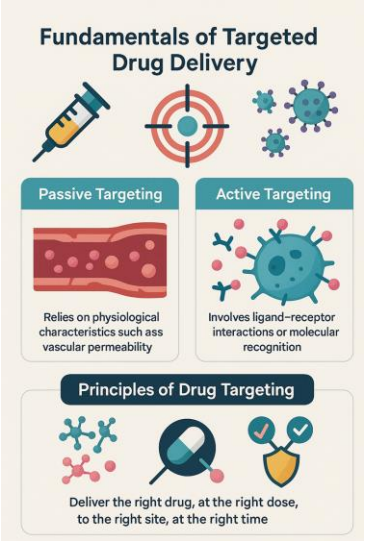

Figure 1: Fundamentals of Targeted Drug Delivery

Types of Nanocarriers in Targeted Delivery

Liposomes

Liposomes are vesicular nanoparticles that consist of lipid bilayers in the form of a spherical vesicle and that can contain an aqueous interior. Liposomes have structural versatility that enables both hydrophilic and lipophilic drugs to be incorporated which makes them widely applicable in targeted drug delivery by increasing drug solubility, increasing the length of circulation and decreasing systemic toxicity. Passive and active targeting to disease locations, e.g. in cancer and inflammatory diseases, is facilitated by surface modifications, e.g. PEGylation or ligand conjugation. The success of liposomal formulations and their safety profile is explained by the clinical validation of liposomal formulations, such as Doxil and Ambi some. [32]

Polymeric Nanoparticles

Biodegradable and biocompatible polymers, including PLA, PCL, PLGA, or natural polymers, e.g., chitosan and alginate, are used in form of polymeric nanoparticles. They are very good platforms of hydrophilic and hydrophobic drug molecules because they have controlled and sustained release of drugs owing to its adjustable polymer matrices through stability, structural integrity, and easy functionalization capabilities [33, 34]. Targeted delivery of nanoparticles Polymeric nanoparticles can be considered attractive systems in cancer therapy, immunotherapy, and gene delivery based on their capacity to deliver small molecules, peptides, proteins, and nucleic acids. [35, 36]

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are carriers with a diameter below a micron composed of physiological lipids and solid at room and body temperature. They provide increased stability, regulated drug delivery and better biocompatibility.[37]. Small size allows SLNs to take advantage of the polymeric ones which incorporate drawbacks like toxicity or residual solvents, and surface modification facilitates use in active targeting. [38] Their size will allow them to be used to actively target tissues through the EPR effect, whilst surface modification allows their use in active targeting. Drugs that are not water-soluble, increase oral bioavailability and prevent the degradation of labile molecules are especially well suited to SLNs.[39]

Dendrimers

Dendrimers are monodisperse (highly branched) macromolecules, which have a central core, repeated basic units, and several functional groups on the surface. Their specific architecture enables a fine control of size, shape and surface chemistry. [40] Dendrimers can also accommodate drugs in the interior cavity or they can be conjugated to the surface groups and this enables high drug-loading capacities. Their conjugability with targeting ligands, as a result of being multivalent, increases receptor affinities to active targeting of dendrimers. [41] Dendrimers are also highly effective in delivering anticancer drugs, gene therapies and diagnostic molecules because of their remarkable structural uniformity and biological compatibility.[42]

Metallic Nanoparticles

Nanoparticles of metal are mainly gold nanoparticles, silver nanoparticles and iron oxide nanoparticles, which have unique optical, magnetic and physicochemical properties that render them useful in the treatment as well as diagnostic fields. Gold nanoparticles can be tuned in size and in surface chemistry and can be employed to deploy high drug-loading efficiency and

specificity in targeting photothermal therapy as well as magnetically guided drug delivery and magnetic imaging. [43] Magnetic iron oxide nanoparticles can be used to conduct magnetically targeted drug delivery and imaging. Peptides, antibodies or aptamers can be used to functionalize metallic nanoparticles and target them through receptor-mediated endocytosis, which provides high specificity in cancer therapy, biosensing and multimodal imaging. [44]

Micelles and Niosomes

Micelles and niosomes are carriers that are self-assembled by amphiphilic molecules. Micelles are made of surfactants which assemble into hydrophobic core and hydrophilic shell, which is ideal in solubilizing of hydrophobic drugs. Niosomes are non-ionic surfactant-based vesicles that form bilayers and are more stable and less expensive to prepare than liposomes, as well as increasing the solubility of drugs, extending their circulation and allowing targeted delivery using ligand functional groups. [45]Both are built on the principle of increasing drug solubility, extending the circulation of the drug and delivering it to a specific target site, both of which are more stable than liposomes and cheaper to make, which is why they have been functionalized with ligands. They are very convenient to prepare, biocompatible, and can prevent the destruction of encapsulated drugs; therefore, they are very useful in cancer treatment, dermatological delivery, and gene delivery. [46]

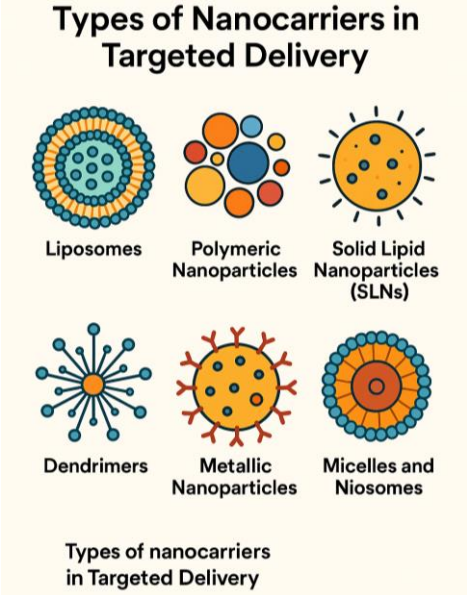

Figure 2: Types of Nanocarriers in Targeted Delivery

Table 1: Types of Nanocarriers in Targeted Delivery

Nanocarrier	Key Features	Applications	Targeting Capability
Liposomes	Phospholipid bilayers, biocompatible	Cancer, inflammation	Passive + Active
Polymeric NPs	Biodegradable polymers, versatile	Gene therapy, immunotherapy	Passive + Active
Solid Lipid NPs	Solid core lipids, high stability	Oral delivery, poorly soluble drugs	Passive + Active
Dendrimers	Branched macromolecules, high drug loading	Cancer, gene delivery	Active
Metallic NPs	Magnetic or optical properties	Imaging,	Active
Micelles	Self-assembled from surfactants	Dermatology, gene delivery	Active

Ligand-Based Active Targeting Strategies

Antibody-Drug Conjugates (ADCs)

The antibody-drug conjugates (ADCs) are a superior category of targeted therapeutics in which the specificity of monoclonal antibodies and cytotoxicity of small-molecule drugs come together in a hybrid form. ADCs are monoclonal antibodies coupled with a chemoattractive linker and a cytotoxic agent with three key components: the monoclonal antibody, a stable linker, and the cytotoxic agent. [47]The ADCs are designed to deliver cytotoxic agent in monoclonal antibodies with a selective overexpression to diseased cells, by contrasting healthy tissues with diseased ones. The connection chemistry is essential to make sure that

the drug is released upon internalization in the target cells. ADCs have proven to be highly successful in the oncology field, with approved agents like trastuzumab emtansine and brentuximab vedotin showing superior survival rates and less systemic toxicity. [48] Their modular structure has allowed the continuous refinement to achieve better specificity, stability and therapeutic effect.

Aptamers and Peptides

The aptamers and peptides are small and specific targeting ligands with high affinity and specificity to bind to cellular receptors, nucleic acid, or proteins. Aptamers are single-stranded oligonucleotides (DNA or RNA) produced by SELEX technology which has a number of benefits including low immunogenicity, easy production and high tissue penetration.[49]. Meanwhile, peptides are short chains of amino acids that are engineered to identify the receptor, adhesion molecules or integrins. The two types of ligands may be conjugated to nanocarriers or drug to allow receptor-mediated endocytosis and improve intracellular delivery. They are able to travel quickly through the tissue and tumor penetration is enhanced due to their small size unlike the antibodies. Aptamer-drug and peptide-nanoparticle conjugates are currently under development in cancer, cardiovascular and neurological therapies.[50]

Folate and Transferrin Receptors

The best studied ligand-mediated drug delivery targets are follate and transferrin receptors due to their overexpression in many cancer cells. Folate receptors also demonstrate a high affinity to folic acid and therefore transferrin receptors in fast-dividing cells are up-regulated, and therefore transferrin-conjugated carriers can take advantage of this non-neoplastic dependency to accumulate the drug target. [51] Transferrin receptors are also useful in the targeting of ovarian, breast and lung tumors as transferrin-conjugated carriers can take advantage of this biological dependency. Their inherent occurrence on cancer cells and low occurrence on normal tissues allows them to be ideal targets in the selective delivery of chemotherapeutics, gene therapies and imaging agents.[53]

Tumor and Organ-Specific Ligands

Tumor and organ specific ligands are tailored to identify distinctive biomarkers, receptors or microenvironmental clues that are expressed in a particular tissue or tumor type. Examples of such ligands are small molecules, peptides, carbohydrates, and expression proteins which are selectively bound to markers like integrins, prostate-specific membrane antigen (PSMA), matrix metalloproteinases (MMPs), or liver-specific asialoglycoprotein receptors.[54]. Targeted ligands are utilized to deliver drug to the brain, liver, lungs or kidneys after taking advantage of tissue-specific recognition pathways or microenvironmental cues. Tumor-specific ligands have been shown to increase the concentration in malignant tissue, circumvent biological obstacles, and increase the therapeutic penetration into hypoxic or stromal dense stromal areas in cancer therapy. Their application is applicable to accurate, localized therapy and off-target toxicity is minimized, and it facilitates the next-generation targeted delivery platforms.[55]

Table 2: Ligand-Based Active Targeting Strategies

Ligand Type	Example Ligands	Target Cells/Tissues	Use Cases
Antibodies	Trastuzumab	HER2+, EGFR+ cancer cells	ADCs in oncology
Aptamers	AS1411	Tumor	Targeted RNA/DNA delivery
Peptides	RGD, TAT	Integrins	Tumor
Folate	Folic Acid	Folate receptor-overexpressing	Ovarian, breast, lung cancers
Transferrin	Transferrin	Transferrin receptor+	Brain

Applications in Disease Management

Cancer Targeting

The goal of cancer targeting is to increase specificity towards accumulation of therapeutic agents in tumor tissues and reduce their contact with healthy tissue. Passive targeting through the EPR effect and active targeting through ligand receptor interactions are some of the strategies that have become necessary because tumors are heterogeneous [56]. Small molecule, peptide or antibody functionalized nanocarriers target overexpressed receptors including HER2, EGFR, folate receptors and integrins. Also, systems that respond to tumor microenvironment make use of pH, enzyme, or hypoxia to trigger local drug release. [26,57] These systems enhance therapeutic precision, surmounting multidrug resistance and decreasing systemic toxicity. The targeting of cancer has enabled the development of new chemotherapy, immunotherapy, gene delivery, and theranostics, which allows the provision of more effective and personalized treatment of cancer.[58]

Central Nervous System (CNS) Disorders

Targeted drug delivery in the CNS disorders aims at by-passing the blood-brain barrier (BBB) which is a highly selective barrier limiting entry of most therapeutics. Nanocarriers can also be utilized to target brain penetration and some of the ligands used to include transferrin, lactoferrin and peptides including TAT or

angiopep-2 have been shown to target neurons, glial cells or pathological sites in diseases like Alzheimer disease and Parkinson disease and epilepsy and in gliomas. [59,60]Some of the ligands that have been used to deliver to the brain include; transferrin, lactoferrin, peptides like TAT or angiopep-2, and nan Stimuli-responsive systems also permit local biochemical stimuli-controlled release to enhance improved neurootherapeutics. [61] Targeting With nanocarriers, more effective neurootherapeutics may be achieved by enhancing BBB crossing and improving neuronal specificity.

Infectious Diseases

In infectious disease, targeted drug delivery is suggested to increase the concentration of antimicrobials at the target site and decrease systemic toxicity, whereas it is expected to decrease resistance development. Nanocarriers enhance the solubility, stability and diffusion of antimicrobial agents into infected tissues or intracellular vesicles in which pathogens are hiding. [6,62] Ligand-functionalized carriers can be used to target microbial surface molecules, infected macrophages or biofilm matrices. Tuberculosis, HIV, fungal infections, and bacterial biofilm systems that have been targeted have been employed include liposomes, solid lipid nanoparticles, and polymeric nanoparticles. [63] Control release, increased immune modulation, and more effective eradication of persistent pathogens can be achieved using systems that have been targeted. Nanocarrier-based strategies are beneficial in solving the problems in antimicrobial therapy by enhancing the localization of therapy.

Autoimmune and Inflammatory Diseases

Autoimmune and inflammatory diseases are targeted therapy that aims at delivering anti-inflammatory and immunosuppressive agents to the inflamed tissues without general immunosuppression. The increased vascular permeability and high levels on adhesion molecules in the inflamed areas allow nanocarriers to selectively accumulate in those areas [64]. Targeting with ligands also improves delivery to activated immune cells, tissue-producing cytokines or inflamed joints as in rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease. Targeted nanomedicine can result in improved disease control and long-term safety by improving the therapeutic efficacy of corticosteroids, biologics, or nucleic acids by changing immune responses in a more precise way. [1,65] By changing immune responses in a more precise way, therapeutic efficacy of corticosteroids, biologics, or nucleic acids encapsulated in nanocarriers is improved and potentially leads to better disease control.

Cardiovascular Targeting

Cardiovascular targeting aims at the delivery of therapeutics to diseased heart or vessel tissues to treat diseases like atherosclerosis, myocardial infarction, thrombosis and hypertension. Nanocarriers that are endothelial ligand functionalized, plaque and inflamed vascular functional groups allow a local deposition of drugs at the pathology site. Stimuli-reactive carriers triggered by shear stress, oxidative stress or enzymatic activity will also promote the localization and controlled release of drugs. [66] Stimuli-dependent carriers can also be used to release drugs to a specific location in a precise manner, through stimuli-specific carriers (VCAM-1 ligands, fibrin-binding peptides, platelet-specific markers, etc.). The targeted strategies lead to cardiovascular outcomes by enhancing the adhesion of drugs at vascular lesions, better plaque stabilization, and decreased systemic adverse effects**.** [9, 67]

Table 3: Applications in Disease Management

Disease Area	Targeting Method	Nanocarriers	Therapeutic Goal
Cancer	EPR effect + Ligand binding	Liposomes, polymeric NPs, gold NPs	Tumor
CNS Disorders	Receptor-mediated	Dendrimers, polymeric NPs, liposomes	Cross BBB, neuron-specific delivery
Infectious Diseases	Biofilm targeting, macrophage uptake	SLNs, polymeric NPs	Antimicrobial precision
Inflammatory Disorders	Endothelial targeting	Liposomes, micelles	Reduce systemic immune suppression
Cardiovascular Diseases	VCAM-1, fibrin, platelet ligands	Magnetic NPs, peptide-tagged liposomes	Vascular site-specific therapy

Benefits of Targeted Nanocarrier Systems

Enhanced Bioavailability

One of the main benefits of targeted and nanocarrier-based systems of drug delivery is enhanced bioavailability. A lot of therapeutic agents are poorly water soluble, fast metabolized or unstable in biological fluids, which causes suboptimal absorption and minimal clinical efficacy. Nanocarriers, including polymeric nanoparticles, liposomes, micelles, and solid lipid nanoparticles, enhance drug solubility propensity, prevent premature degradation, and promote absorption by oral, parenteral, transdermal, and mucosal routes of delivery. [6, 68] Optimizing particle size, surface charge, and hydrophobic-hydrophilic can be used to enhance the

absorption of drugs through oral, parenteral, transdermal, and mucosal routes. Increased bioavailability is not only associated with less dosage requirements but also with more predictable pharmacokinetic characteristics, which are additive to excellent therapeutic outcomes.[69]

Reduced Systemic Toxicity

Targeted drug delivery can considerably minimize the effects of systemic toxicity since it selects therapeutic agents to deliver them in the disease site at the minimal possible amount of exposures to normal tissues. The use of conventional chemotherapy, antibiotics, and immunosuppressants tends to cause serious adverse effects because they are indiscriminately distributed. Nanocarrier-based delivery systems are used to overcome this drawback and achieve controlled release, protection of healthy organs against excessive drug concentration, and receptor-specific uptake and subsequent intracellular delivery, which further minimizes off-target effects. Targeted systems enhance patient compliance, increase the therapeutic index and permit the use of potent therapeutic agents that would be otherwise intolerable in their free form by reducing systemic toxicity.[71]

Controlled and Sustained Drug Release

One of the main advantages of nanocarrier-based delivery is controlled sustained drug release, which allows maintaining stable therapeutic levels of drugs during a significant amount of time. Nano systems formed by polymers, lipid nanoparticles and hydrogel derived carriers are designed to deliver drugs slowly by diffusion, erosion or stimuli-response under pH, temperature, or enzyme conditions. [72,73] This decreases the frequency of dosing, minimizes intermittent plasma drug levels and eliminates stimuli or toxicity of drugs in peaks. In chronic diseases like cancer, diabetes, cardiovascular disorders, autoimmune diseases among others, sustained release formulations have long-term therapeutic effects and enhanced adherence to treatment. Further, controlled release enhances improved pharmacodynamic response, and decreases the chances of drug resistance.[74]

Site-Specific Drug Action

Site-specific drug action guarantees that therapeutic agents act their effects at the target site and in this manner approach clinical maximization and systemic minimization. Nanocarriers do this by passive targeting, e.g. the EPR effect, or by active targeting, e.g. with ligands that bind overexpressed receptors or tissue-specific biomarkers.[67]. Stimuli-responsive mechanisms are then activated at the target site under response to local stimuli (acidic pH, overexpressed enzymes or hypoxic environments). Therapeutic precision in pathologies like cancer, neurodegenerative diseases, inflammatory diseases, and organ-specific diseases is made more precise with the use of site-specific action. The degree of targeting promotes individualized treatment and enhances the overall safety and effectiveness of treatment.[75]

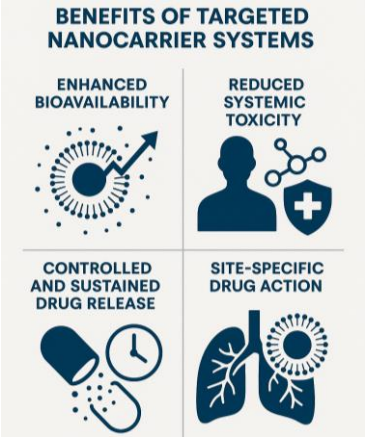

Figure 3: Benefits of Targeted Nanocarrier Systems

Risks and Limitations

Immunogenicity and Hypersensitivity Reactions

The targeted and nanocarrier-based drug delivery systems are limited by immunogenicity and hypersensitivity reactions. Various nanomaterials, proteins, and polymers, in particular, and metallic particles can trigger the immune system, which in turn reacts by production of antibodies, activation of the complement cascade, or release of cytokines. These immune reactions may interfere with therapeutic activity by accelerating drug clearance, or result in reactions at one extreme in mild allergic symptoms, and at the other extreme, severe anaphylaxis [69]. Several techniques to reduce immunogenicity (such as PEGylation), however, may be overcome by repeated dosing, causing anti-PEG antibody to develop. The immune-nanocarrier interactions and surface chemistry optimization are therefore necessary to reduce the hypersensitivity and provide safe and long-term usage. [76]

RES Clearance and Biodistribution Challenges

The reticulo endothelial system (RES) which mostly involves macrophages in the liver, spleen, and lymph nodes has a significant role to play in the removal of nanocarriers in circulation. The quick absorption of the therapeutic agent by the RES diminishes the dose of the therapeutic agent that is reaching the required target thereby decreasing the efficacy of treatment. The clearance of particles by RES depends on factors such as particle size, surface charge, hydrophobicity, and protein binding. [77] Even though methods like PEGylation, ligand functionalization and biomimetic surface coating are used to extend the circulation time, biodistribution is still very difficult to achieve. The immune evasion versus efficient target recognition balancing is of significant concern to reach maximum therapeutic efficiency and overcome the premature clearance barriers.

Scale-Up and Cost Issues

Although the experimental results of most nanocarrier-based targeted delivery systems have been very promising in preclinical testing, numerous challenges are observed in the scale-up and manufacturing of such systems at an industrial level. When the laboratory processes are replaced with the industrial ones, reproducibility of the particle size, drug loading, surface modification, and lot-to-lot consistency become challenging. Advanced methods of synthesis can be expensive in terms of equipment, purity of materials used and environmental considerations, which increase the cost of production. Also, complicated purification and quality control processes also increase the cost of manufacturing further. These obstacles restrict mass clinical access particularly in low- and middle-income areas. Hence, cost-effective, scalable and standardized technologies in production are crucial to the wider clinical translation.[78]

Long-Term Toxicity and Biocompatibility Concerns

The safety of clinical use of nanocarrier systems has been a basis of serious consideration on long-term toxicity and biocompatibility. Certain nanomaterials can be deposited in the body in organs like liver, spleen or brain causing chronic inflammatory response, oxidative stress or tissue damage. Examples of these include release of ions or formation of reactive species by the metallic nanoparticles and degradation of polymeric or lipid carriers into metabolites with unclear long-term outcomes. Also, the long-term exposure to targeting ligands or coating of surfaces can change immune reactions or cellular activities. Nanocarriers also need to be experimented on in vivo, long-term toxicity tests, and other standardized biocompatibility tests in order to guarantee that they do not pose a threat to the body during their lifecycle.

Regulatory and Approval Challenges

The barriers to the translational research of targeted nanomedicines to clinical practice are regulatory and approval challenges. Nanocarriers possess complicated physicochemical characteristics, multifunctional designs, and distinctive biodistribution profiles, which is not comparable to standard drugs, and the assessment of regulation is more challenging. Various agencies like the FDA and EMA demand a lot of characterization, safety profiling, pharmacokinetics and manufacturing consistency data. Nevertheless, uniform standards on nanomedicines remain in developmental stages and hence ambiguity in the approval requirements. Also, it is frequently required that approval be obtained through long-term safety demonstration, as well as strict enforcement of quality control by regulatory bodies. Stronger regulatory frameworks, standardized world guidelines and certified tools of analysis are needed to open up the clinical adoption of nanocarrier-based targeted therapies.

Recent Advances and Smart Nanocarriers

Stimuli-Responsive Nanocarriers

Smart or intelligent delivery systems (also referred to as stimuli-responsive nanocarriers) are designed to release therapeutic agents based on a response to particular internal or external stimuli. Examples of internal triggers are pH changes, redox gradients, enzyme activity and hypoxia, which are frequently seen in tumors or inflamed tissues. Drug release can also be controlled using high spatial and temporal precision by external stimuli like temperature, magnetic fields, ultrasound and light. These nanocarriers can improve targeting accuracy significantly because the drug will be activated only at the sites of the disease, which reduces the systemic exposure and has a positive effect on the therapeutic result. They have the potential to be used in the treatment of cancer, inflammatory disorders, and precise medicine due to their dynamic responsiveness.

Dual and Multi-Targeted Systems

Dual and multi-target systems combine several targeting ligands, pathways or therapeutic agents into one carrier nanoparticle in order to increase their efficacy in complex diseases. These systems overcome the drawbacks of single-targeted strategies which include tumor heterogeneity, drug resistance and multi-factorial pathophysiology. These platforms maximize the specificity of binding and uptake in cells by incorporating both passive and active targeting or by applying multiple ligands (e.g. antibody + peptide). Multi-functional systems have the capability to co-deliver chemotherapeutics, immunomodulators, RNA molecules or imaging agents and by doing so can achieve a synergistic therapeutic outcome. They can control a wide

array of disease pathways and make them especially useful in oncology, neurodegenerative diseases and chronic inflammatory diseases.

Hybrid Nanocarriers and Theranostics

In hybrid nanocarriers, two or more types of nanomaterials, including lipids, polymers, metals or inorganic structures are incorporated to form multifunctional platforms that are more stable, can load more drug and target specific tissues. This is exemplified by lipid polymer hybrid nanoparticles, polymer coated liposomes, and metal lipid hybrid. These systems take advantage of the positive properties of each class of material, enhancing biocompatibility, circulation time and controlled release characteristics. Theranostic hybrid nanocarriers extend this to incorporate therapeutic factors such as diagnostic markers such as contrast dyes, fluorescent markers or imaging metals. Such twin-ability allows up-to-date tracking of biodistribution, treatment response, and disease progression to put hybrid theranostic systems in the vanguard of personalized medicine.

CRISPR and Gene Editing Delivery

Gene editing technologies based on CRISPR-mediated methods need to have a highly efficient and safe delivery mechanism to transfer gene-editing systems, including Cas nucleases, guide RNA, or donor DNA, to target cells. Nanocarriers offer an alternative method of viral vectors, which is less viral and is safer, loads more easily, is less immunogenic, and can be produced on scale. Lipid nanoparticles (LNPs), polymeric carriers, gold nanoparticles, and exosomes are extensively studied to use as CRISPR delivery systems since these can encapsulate and protect the nucleic acid. Specific nanocarriers can also increase the delivery to a particular tissue using nanocarriers so that gene correction can be highly specific and the off-target effects reduced. These developments are hastening the curative power of the genetic disease, cancer, and regenerative medical treatment with the help of gene editing.

Regulatory and Ethical Considerations

Regulatory Guidelines for Nanomedicine

It has seen regulatory regulations of nanomedicine change to meet the peculiar physicochemical qualities, biodistribution, and intricate processes of nanoscale drug delivery systems. Agency use These agencies (which include the U.S. FDA, EMA and ICH) put focus on strict characterization of particle size and shape, surface charge, stability and drug release kinetics. Moreover, nanomedicines have to be thoroughly assessed in preclinical testing, that is, toxicity, immunogenicity, pharmacokinetics, and long-term safety experimentations. The absence of generally standardized regulatory frameworks is a problem because the actions of nanocarriers are not always similar to conventional drugs. Consequently, regulatory authorities are promoting more and more case-by-case assessment and sophisticated analytical tools as the means of quality, safety, and efficacy assurance. Coordination of international standards and creation of international testing regimes are still essential in facilitating easier clinical translation and authorization of nanomedicine products.

Ethical Implications of Targeted Therapies

Targeted therapies provoke significant ethical concerns connected with equity of patients, access to treatment, and inappropriate application of hi-tech biomedical technologies. Since these treatments are frequently highly specialized and costly, access disparities could potentially increase the disparity between the resource rich and resource constrained populations. There are also some ethical issues when it comes to the capability of targeted systems to modify biological pathways or gene expression that concern unintended biological effects and long-term effects. Moreover, the problem of privacy might occur when the treatment is based on the work with genomic or biomarker profiling. The ethical implementation must be ensured through transparency, equitable treatment, and a well-developed system of oversight that could balance the innovation and the rights of patients and the welfare of society.

Patient Safety and Informed Consent

The safety of patients is a principal factor in the design and therapeutic use of nanocarrier-mediated targeted therapies. Because of their complex morphology and distinct biological activities, nanomedicines must be subject to comprehensive risk studies in terms of toxicity, immunogenicity, off target, and long-term exposure. Informed consent can only be achieved through clear communication of these risks so that the patients can make informed decisions on their choices of treatment. The informed consent procedures should cover the understanding of the mechanisms of action of the nanocarriers, the possible advantages, uncertainty and other treatments. Since the emerging technologies usually imply incomplete long-term data, clinicians and researchers should make sure that the patients are aware of the opportunities and constraints of targeted nanomedicine. Enhanced safety surveillance and disclosure is essential in ensuring patient trust and ethical practice.

Future Perspectives

Personalized and Precision Nanomedicinessss

The future of targeted therapy is in personalized and precision nanomedicine that focuses on personalized treatment plans, which are delivered in accordance with

genetic, proteomic, metabolic, and clinical profile. Precision nanomedicine increases the efficiency and clinical outcomes of drug targeting by customizing nanocarrier systems to the disease biomarkers, physiological conditions and clinical needs of a specific patient. It is possible to design nanocarriers that can be responsive to customized tumor microenvironment, inflammatory, or genetic mutation, and thus provide optimum drug loading, release, and biodistribution. The method enhances selectivity of therapy besides reducing toxicity and possible variability on the treatment. With the development of multi-omics technologies and clinical bioinformatics, personalized nanomedicine will become an important transformative agent in cancer, neurology and chronic disease treatment.

AI-Driven Nanocarrier Design

The design, optimization, and predictive performance of nanocarrier-based drug delivery systems are being altered by artificial intelligence (AI). Computational simulations and machine learning that allow to quickly screen thousands of nanoparticle compositions, surface capabilities, and drug-loading parameters make it possible to find optimal formulations with a high level of precision. The AI-based algorithms may forecast nanocarrier behaviour, stability, cellular uptake, biodistribution, and toxicity, without use of trial-and-error experimentation. Moreover, AI enhances the process of new targeting ligand identification, load blend optimization, or personalized nanomedicine through incorporation of patient-specific biological models. This methodology is based on data to significantly reduce the time frames of the development processes and increase the stability and scalability of the specific delivery systems.

Integration with Wearable and Diagnostic Technologies

The combination of nanocarrier-delivered targeted therapies with wearable and real-time diagnostic technologies is creating new opportunities in the area of dynamic and continuous treatment monitoring along with the patient-centered approach. Biosensors Wearable biosensors have the potential to monitor physiological parameters, biomarkers and drug responses, so that nanocarriers can be activated or modified depending on real-time information. An example of closed-loop therapeutic systems is smart systems, including glucose-responsive nanoparticles in combination with wearable glucose monitors, or tumor marker sensors in combination with controlled-release platforms. This combination improves the treatment personalization and maximizes dosing and reduces adverse effects. In addition, the integration of diagnostic imaging agents with nanocarriers promotes the early detection of the disease, treatment follow-ups, predictive outcomes, resulting in entirely interconnected and adaptive health care plans.

CONCLUSION

Nano-carrier-based systems of therapeutic delivery and targeted drug delivery represent a revolutionary step in the contemporary pharmaceutical sphere allowing the previously unseen possibilities of enhancing the accuracy, safety and effectiveness of therapy application in an immense range of maladies. This review identifies the scientific background, technological breakthrough, clinical uses and regulatory issues that define the future of targeted nanomedicine. The myriad of collective insights conveyed is that nanocarriers, be it liposomes, polymeric nanoparticles, SLNs, dendrimers, micelles, metallic nanoparticles or hybrid constructs have transformed the manner in which drugs are delivered so that they can be delivered with improved biodistribution, controlled release and site-specific activity that are not achievable using conventional formulations. Their responsiveness to disease microenvironment, ligand-based recognition and carrying more than one agent at a time highlight the importance of their role in enhancing precision therapy. In essence, the use of drug targeting has progressed over time into complex ligand-based systems that can identify an immensely specific cellular marker as compared to basic passive accumulation. The increase in cellular uptake and intracellular delivery of active targeting with anti-bodies, aptamers, peptides, folate, transferrin, and organ specific ligands has decreased systemic toxicity and increased pharmacological response. Likewise, nanocarrier design, be it the surface to improve circulation time or targeting efficiency through PEGylation, biomimetic, or stimuli-responsive, has also been enhanced to improve the circulation time and targeting efficiency. Such developments have allowed clinicians and researchers to overcome the complex biological barriers which include bloodbrain barrier, tumor heterogeneity, biofilm structure and inflammatory microenvironment. Consequently, targeted nanomedicine has shown a significant potential in cancer, brain diseases, infectious diseases, autoimmune diseases, and cardiovascular therapy, which contributes to a stronger and personalized treatment effect. Notwithstanding these successes, there are no challenges associated with targeted nanocarrier systems. The stability and distribution of nanomedicines still are influenced by immunogenicity, hypersensitivity reactions and RES clearance. The accumulation and degradation of nanoparticles, as well as the off-target effect are some of the long-term biocompatibility questions that need strict safety tests. Complexity of manufacturing, scale-up challenges and cost overheads are other obstacles to large-scale clinical translation especially when resources are constrained. Moreover, there is still a patchwork

regulation of nanomedicine. Due to the multidimensionality and multitasking of nanocarriers, the current pharmaceutical systems usually fail to offer coherent and uniform evaluation standards. Consequently, regulatory bodies have implemented case-based evaluation plans, which focus on physicochemical characterization, reproducibility, pharmacokinetics and long-term toxicity evaluation before they can be approved. The need to develop responsible innovations and patient-centered solutions is emphasized by ethical issues, in particular, fair access, privacy, and informed consent, as the technologies continue developing. The development of smart nanocarriers is an important breakthrough in solving most of these issues. By implementing stimuli-responsive systems, which can release therapeutics in response to certain pH signals or enzymes, thermal gradient or external stimuli (e.g. magnetic field, ultrasound) stimuli, high control of drug release can be achieved, permitting activation of therapeutics exclusively at the disease site. Dual and multi-targeted platforms also increase the performance of therapy through multi-ligand integration or co-delivery of therapy in a single carrier to permit synergy in intricate illness settings like cancer or neurodegenerative disease. Hybrid nanocarriers and theranostic systems have filled the space between diagnostics and therapy and was able to monitor in real time, make early interventions and make changes to the treatment based on imaging or biomarker responses. Also, the CRISPR and gene editing delivery systems based on nanocarriers are leading new frontiers in genetic medicine with high-level precision in addressing inherited diseases, cancer mutations, and regenerative medicine with reduced off-target effects. On the one hand, the perspective of targeted nanomedicine is its association with digital and personalized health technologies. Genomics, proteomics, metabolomics, and patient-specific disease signatures applied in personalized nanomedicine have the potential to precisely customize therapy as never before. Nanocarriers designed to suit specific tumor microenvironment, inflammatory or genetic mutations offer therapy that is highly selective, as well as highly effective. Simultaneously, artificial intelligence is transforming the science of formulations, as new nanocarrier designs may be discovered and optimized faster with the help of predictive modeling, high-dimensional data analysis, and simulations with the participation of machine learning. Guided AI minimizes experimentation, increases scalability and regulatory decision making with a high degree of confidence. In addition, the intersection point of nanomedicine with wearable biosensors and diagnostic systems is a paradigm shift to real-time, adaptive, and autonomous healthcare systems. Integrated platforms of wearable nanocarriers that can adapt to physiological features or biomarker variations provide an opportunity at closed-loop control therapeutic, i.e. meet optimal dosing, reduce side effects and increase patient compliance. The innovations enable the use of these techniques to aid in early detection of diseases, accurate adjustment of treatment, and prediction of outcomes, which eventually propel the healthcare system towards an exceptionally responsive and preventive model. To dedicated nanocarrier systems represent one of the most promising directions in the pharmaceutical science that combine molecular accuracy, therapy rate, and technological sophistication. Although safety, scalability, regulatory clarity, and ethical considerations are still problematic, continued research and interdisciplinary work are pushing the limits of what is possible. The future of nanomedicine, driven by the inclusion of AI, personalized medicine, the platform of theranostic and the sophisticated biomaterials, will redefine the future of healthcare in the world- delivering safer and smarter, more efficient cures to some of the hardest-to-treat diseases in modern civilization.

REFERENCES

1. Parvin, N., Joo, S. W., & Mandal, T. K. Biodegradable and stimuli-responsive nanomaterials for targeted drug delivery in autoimmune diseases. *JFB, 16*, 2025, 24.
2. Prencipe, F., Ronga, L., Diaferia, C., Tesauro, D., & Rossi, F. Forward precision medicine: Micelles for active targeting driven by peptides. *Molecules, 26*, 2021, 4049.
3. Peng, Y., Mahato, R. I., Bariwal, J., Kumar, V., & Tan, C. Organic nanocarriers for delivery and targeting of therapeutic agents for cancer treatment. *Advanced Therapeutics, 3*, 2020, 1900136.
4. Musielak, E., & Krajka-Kuźniak, V. Lipidic and inorganic nanoparticles for targeted glioblastoma multiforme therapy: Advances and strategies. *Micro, 5*, 2025, 2.
5. Anwar, D. M., Hedeya, H. Y., Ghozlan, S. H., Ewas, B. M., & Khattab, S. N. Surface-modified lipid-based nanocarriers as a pivotal delivery approach for cancer therapy: Application and recent advances in targeted cancer treatment. *Beni-Suef University Journal of Basic and Applied Sciences, 13*, 2024.
6. Simhadri, A., Sana, J., & Dommeti, M. A comprehensive review on the nanotechnology-based intranasal drug delivery systems for brain targeting. *JOPIR, 2*, 2024, 015–023.
7. Hami, Z. A brief review on advantages of nano-based drug delivery systems. *Annals of Military Health Sciences Research, 19*, 2021.

8. Bandyopadhyay, A., Preetam, S., Nandy, S., Sahib, S., Gopalakrishnan, A. V., Dey, A., et al. Ligand-based active targeting strategies for cancer theranostics. *Naunyn-Schmiedeberg's Archives of Pharmacology, 396*, 2023, 3417–3441.
9. Majumder, J., & Minko, T. Multifunctional and stimuli-responsive nanocarriers for targeted therapeutic delivery. *Expert Opinion on Drug Delivery, 18*, 2020, 205–227.
10. Li, Y., Li, X.-M., Wei, L.-S., & Ye, J.-F. Advancements in mitochondrial-targeted nanotherapeutics: Overcoming biological obstacles and optimizing drug delivery. *Frontiers in Immunology, 15*, 2024.
11. Addissouky, T. A. Next generation of colorectal cancer management: Integrating omics, targeted therapies, and smart technologies. *Avicenna Journal of Medical Biochemistry, 12*, 2024, 131–143.
12. Vikal, A., Patel, P., Bhowmik, S., Maurya, R., Kurmi, B. D., & Gupta, G. D. From conventional to cutting-edge: A comprehensive review on drug delivery systems. *DDL, 14*, 2024, 226–243.
13. Li, J.-J., Hu, X.-Y., Hu, Z.-Y., Wang, K.-R., Rong, R.-X., Yang, Y., et al. Triple targeting host-guest drug delivery system based on lactose-modified azocalix[4]arene for tumor ablation. *Materials Horizons, 10*, 2023, 1689–1696.
14. Balkhi, S., Bilato, G., De Lerma Barbaro, A., Orecchia, P., Poggi, A., & Mortara, L. Efficacy of anti-cancer immune responses elicited using tumor-targeted IL-2 cytokine and its derivatives in combined preclinical therapies. *Vaccines, 13*, 2025, 69.
15. Tian, H., Zhang, T., Qin, S., Huang, Z., Zhou, L., Shi, J., et al. Enhancing the therapeutic efficacy of nanoparticles for cancer treatment using versatile targeted strategies. *Journal of Hematology & Oncology, 15*, 2022.
16. Ejigah, V., Fisusi, F. A., Owoseni, O., Adesina, S. K., Ogundipe, O. D., & Bataille-Backer, P. Approaches to improve macromolecule and nanoparticle accumulation in the tumor microenvironment by the enhanced permeability and retention effect. *Polymers, 14*, 2022, 2601.
17. Sharifi, M., Tarharoudi, R., Amin, M., Malekisarvar, H., Ansariesfahani, A., Sari, S., et al. An updated review on EPR-based solid tumor targeting nanocarriers for cancer treatment. *Cancers, 14*, 2022, 2868.
18. Wan, G., Zhang, Q., Chen, J., Chen, X., Guan, C., Wu, W., et al. Platelet membrane-based biochemotactic-targeting nanoplatform combining PDT with EGFR inhibition therapy for the treatment of breast cancer. *Biomaterials Science, 12*, 2024, 691–709.
19. Spada, A., & Gerber-Lemaire, S. Surface functionalization of nanocarriers with anti-EGFR ligands for cancer active targeting. *Nanomaterials, 15*, 2025, 158.
20. Sung, Y., Choi, Y., Kim, E. S., Ryu, J. H., & Kwon, I. C. Receptor-ligand interactions for optimized endocytosis in targeted therapies. *Journal of Controlled Release, 380*, 2025, 524–538.
21. Kim, M., Shin, M., Zhao, Y., Ghosh, M., & Son, Y.-O. Transformative impact of nanocarrier-mediated drug delivery: Overcoming biological barriers and expanding therapeutic horizons. *Small Science, 4*, 2024.
22. Dong, W., Wang, W., & Cao, C. The evolution of antibody-drug conjugates: Toward accurate DAR and multi-specificity. *ChemMedChem, 19*, 2024.
23. Ferraro, C., Dattilo, M., Patitucci, F., Prete, S., Scopelliti, G., Parisi, O. I., et al. Exploring protein-based carriers in drug delivery: A review. *Pharmaceutics, 16*, 2024, 1172.
24. Steffens, R. C., & Wagner, E. Directing the way—Receptor and chemical targeting strategies for nucleic acid delivery. *Pharmaceutical Research, 40*, 2022, 47–76.
25. Li, J., Wang, J., Li, Y., Li, H., Xu, Z., Lu, D., et al. Recent progress on the synergistic antitumor effect of a borneol-modified nanocarrier drug delivery system. *Frontiers in Medicine, 8*, 2021.
26. Meng, W., Huang, L., Guo, J., Xin, Q., Liu, J., & Hu, Y. Innovative nanomedicine delivery: Targeting tumor microenvironment to defeat drug resistance. *Pharmaceutics, 16*, 2024, 1549.
27. Hassan, A., Roy, S., Das, A., Wahed, S. A., Bairagi, A., Mondal, S., et al. Covalent organic frameworks as potential drug carriers and chemotherapeutic agents for ovarian cancers. *ACS Biomaterials Science & Engineering, 10*, 2024, 4227–4236.
28. Zhang, Z., Zhang, C., Tang, Y., Lu, Z., & Yuan, Q. ROS-responsive and active targeted drug delivery based on conjugated polymer nanoparticles for synergistic chemo-/photodynamic therapy. *Journal of Materials Chemistry B, 9*, 2021, 2240–2248.
29. Mi, P. Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy, and theranostics. *Theranostics, 10*, 2020, 4557–4588.
30. Farooq, M. A., & Trevaskis, N. L. TPGS decorated liposomes as multifunctional nano-delivery systems. *Pharmaceutical Research, 40*, 2022, 245–263.
31. Chaudhary, A. A., Fareed, M., Khan, S.-U.-D., Alneghery, L. M., Aslam, M., Alex, A., et al. Exploring the therapeutic potential of lipid-based nanoparticles in the management of oral squamous cell carcinoma. *Exploration of Targeted Anti-Tumor Therapy, 5*, 2024, 1223–1246.
32. Agrawal, S. S., Baliga, V., & Londhe, V. Y. Liposomal formulations: A recent update. *Pharmaceutics, 17*, 2024, 36.

33. Jan, N., Akram, F., Ashammakhi, N., Ertas, D., Contag, C. H., Bostanudin, M. F., et al. Biomimetic cell membrane-coated poly(lactic-co-glycolic acid) nanoparticles for biomedical applications. *Bioengineering & Translational Medicine, 8*, 2022.
34. Yang, F., Langert, K. A., Cabe, M., & Nowak, H. A. Chitosan/poly(lactic-co-glycolic) acid nanoparticle formulations with finely-tuned size distributions for enhanced mucoadhesion. *Pharmaceutics, 14*, 2022, 95.
35. Udaipuria, N., & Bhattacharya, S. Novel carbohydrate polymer-based systems for precise drug delivery in colon cancer: Improving treatment effectiveness with intelligent biodegradable materials. *Biopolymers, 116*, 2024.
36. Mo, K., Yoon, H., Choe, S., Shin, M., & Kim, A. Overview of solid lipid nanoparticles in breast cancer therapy. *Pharmaceutics, 15*, 2023, 2065.
37. Gandhi, S., & Shastri, D. H. Lipid-based nanoparticulate drug delivery. *PNT, 12*, 2024.
38. Haider, M., Abdin, S. M., Kamal, L., & Orive, G. Nanostructured lipid carriers for delivery of chemotherapeutics: A review. *Pharmaceutics, 12*, 2020, 288.
39. Bao, Z., Hickman, R. J., Yung, F., Bannigan, P., Allen, C., & Aspuru-Guzik, A. Data-driven development of an oral lipid-based nanoparticle formulation of a hydrophobic drug. *Drug Delivery and Translational Research, 14*, 2023, 1872–1887.
40. Dubey, S. K., Agrawal, M., Tiwari, S., Alexander, A., Singhvi, G., Saraf, S., et al. Understanding the pharmaceutical aspects of dendrimers for the delivery of anticancer drugs. *Current Drug Targets, 21*, 2020, 528–540.
41. Wang, X., Zhang, M., Li, Y., Cong, H., Yu, B., & Shen, Y. Research status of dendrimer micelles in tumor therapy for drug delivery. *Small, 19*, 2023.
42. Grześkowiak, B. F., Kozłowska, A., Coy, E., Kertmen, A., Mrówczyński, R., & Maziukiewicz, D. Polyamidoamine dendrimers decorated multifunctional polydopamine nanoparticles for targeted chemo- and photothermal therapy of liver cancer model. *International Journal of Molecular Sciences, 22*, 2021, 738.
43. Gupta, P., Paul, M. K., Handa, N., Mittal, A. K., & Mishra, K. Current expansion of silver and gold nanomaterials towards cancer theranostics: Development of therapeutics. *Current Nanoscience, 20*, 2024, 356–372.
44. Villalobos Gutiérrez, P., Viveros Paredes, J., Sandoval Salazar, C., Gutiérrez Coronado, O., & Muñoz Carrillo, J. Functionalized metal nanoparticles in cancer therapy. *Pharmaceutics, 15*, 2023, 1932.
45. Assiri, A. A., Glover, K., Mishra, D., Waite, D., Vora, L. K., & Thakur, R. R. S. Block copolymer micelles as ocular drug delivery systems. *Drug Discovery Today, 29*, 2024, 104098.
46. Kaur, P., Rani, R., Singh, A. P., & Singh, A. P. An overview of niosomes. *Journal of Drug Delivery and Therapeutics, 14*, 2024, 137–146.
47. Alas, M., Kaur, K., & Saghaeidehkordi, A. Peptide-drug conjugates with different linkers for cancer therapy. *Journal of Medicinal Chemistry, 64*, 2020, 216–232.
48. Zeng, H., Ning, W., Liu, X., Luo, W., & Xia, N. Unlocking the potential of bispecific ADCs for targeted cancer therapy. *Frontiers in Medicine, 18*, 2024, 597–621.
49. Giudice, V., Mensitieri, F., Izzo, V., Filippelli, A., & Selleri, C. Aptamers and antisense oligonucleotides for diagnosis and treatment of hematological diseases. *International Journal of Molecular Sciences, 21*, 2020, 3252.
50. Liu, M., Wang, C., Fang, X., & Yang, Y. Peptide-enabled targeted delivery systems for therapeutic applications. *Frontiers in Bioengineering and Biotechnology, 9*, 2021.
51. Camorani, S., Tortorella, S., Agnello, L., Spanu, C., D'Argenio, A., Nilo, R., et al. Aptamer-functionalized nanoparticles mediate PD-L1 siRNA delivery for effective gene silencing in triple-negative breast cancer cells. *Pharmaceutics, 14*, 2022, 2225.
52. Pilch, J., Kowalik, P., Kowalczyk, A., Bujak, P., Kasprzak, A., Paluszkiewicz, E., et al. Foliate-targeting quantum dots-β-cyclodextrin nanocarrier for efficient delivery of unsymmetrical bisacridines to lung and prostate cancer cells. *International Journal of Molecular Sciences, 23*, 2022, 1261.
53. Harrell, C. R., Volarevic, A., Djonov, V., & Volarevic, V. Mesenchymal stem-cell-derived exosomes as novel drug carriers in anti-cancer treatment: A myth or reality? *Cells, 14*, 2025, 202.
54. Ferro-Flores, G., Ancira-Cortez, A., Ocampo-García, B., & Meléndez-Alafort, L. Molecularly targeted lanthanide nanoparticles for cancer theranostic applications. *Nanomaterials, 14*, 2024, 296.
55. Wei, Z., Zhou, Y., Wang, R., Wang, J., & Chen, Z. Aptamers as smart ligands for targeted drug delivery in cancer therapy. *Pharmaceutics, 14*, 2022, 2561.
56. Fındık, B. K., Lognon, E., Catak, S., & Monari, A. In silico study of active delivery of a photodynamic therapy drug targeting the folate receptor. *Photochemical & Photobiological Sciences, 2025.*
57. Gong, Z., Zhou, B., Wang, J., Yuan, X., Sun, X., Tan, H., et al. Enzyme-induced transformable peptide nanocarriers with enhanced drug permeability and retention to improve tumor nanotherapy efficacy. *ACS Applied Materials & Interfaces, 13*, 2021, 55913–55927.

58. Zeng, H., Lu, H., Yang, J., & Hu, P. An update on recent drug delivery systems targeting brain diseases via the transnasal pathway. *Pharmaceutics, 41*, 2024, 2121–2141.
59. Mulvihill, J. J., Ross, A. M., Tosi, G., Duskey, J. T., Cunnane, E. M., & Grabrucker, A. M. Drug delivery across the blood-brain barrier: Recent advances in the use of nanocarriers. *Nanomedicine (London), 15*, 2020, 205–214.
60. Wang, J., Rodrigues, J., Zhang, G., Wang, Z., Shi, X., Tomás, H., et al. Blood-brain barrier-crossing dendrimers for glioma theranostics. *Biomaterials Science, 12*, 2024, 1346–1356.
61. Li, J., Fan, K., Zhang, Z., Zhang, B., & Yan, X. Transferrin receptor 1 targeted nanomedicine for brain tumor therapy. *Biomaterials Science, 11*, 2023, 3394–3413.
62. Emeihe, E., Nwankwo, E., Olaboye, J., Maha, C., & Ajegbile, M. Revolutionizing drug delivery systems: Nanotechnology-based approaches for targeted therapy. *International Journal of Life Sciences Research Archives, 7*, 2024, 040–058.
63. Campos, J. V., Pontes, J. T. C., Canales, C. S. C., Roque-Borda, C. A., & Pavan, F. R. Advancing nanotechnology: Targeting biofilm-forming bacteria with antimicrobial peptides. *BME Front, 6*, 2025.
64. Feng, X., Li, G., Ding, J., Xu, W., & Liu, J. Tackling autoimmunity with nanomedicines. *Nanomedicine (London), 15*, 2020, 1585–1597.
65. Kotla, N. G., Singh, R., Baby, B. V., Rasala, S., Rasool, J., Hynes, S. O., et al. Inflammation-specific targeted carriers for local drug delivery to inflammatory bowel disease. *Biomaterials, 281*, 2022, 121364.
66. Leung, H. M., Liu, L. S., Cai, Y., Li, X., Huang, Y., Chu, H. C., et al. Light-activated nanodiamond-based drug delivery systems for spatiotemporal release of antisense oligonucleotides. *Bioconjugate Chemistry, 35*, 2024, 623–632.
67. Nikolova, M. P., Kumar, E. M., & Chavali, M. S. Updates on responsive drug delivery based on liposome vehicles for cancer treatment. *Pharmaceutics, 14*, 2022, 2195.
68. Viegas, C., Nadhman, A., Fonte, P., Chintamaneni, P. K., Patrício, A. B., & Prata, J. M. Solid lipid nanoparticles vs. nanostructured lipid carriers: A comparative review. *Pharmaceutics, 15*, 2023, 1593.
69. Kumar, A., Kumar, A., Islam, M. M., Narang, R. K., Sharma, T., Mukherjee, D., et al. Recent trends in nanocarrier-based drug delivery system for prostate cancer. *AAPS PharmSciTech, 25*, 2024.
70. Shi, P., Cheng, Z., Zhao, K., Chen, Y., Zhang, A., Gan, W., et al. Active targeting schemes for nano-drug delivery systems in osteosarcoma therapeutics. *Journal of Nanobiotechnology, 21*, 2023.
71. Chandra, P., Ruhela, M., Kumar, P., Porwal, M., Verma, A., Sharma, H., et al. Nanotechnology-based approaches for targeted drug delivery to the small intestine: Advancements and challenges. *Current Pharmaceutical Design, 31*, 2025, 1939–1957.
72. Mukherjee, D., & Raikwar, S. Recent update on nanocarrier(s) as the targeted therapy for breast cancer. *AAPS PharmSciTech, 25*, 2024.
73. Jindal, A., Mainuddin, M., Kumar, A., Ratnesh, R. K., & Singh, J. Nanotechnology driven lipid and metalloid-based formulations targeting blood-brain barrier (3B) for brain tumor. *Indian Journal of Microbiology, 65*, 2024, 92–119.
74. Mujahid, K., Rana, I., Suliman, I. H., Li, Z., Wu, J., He, H., et al. Biomaterial-based sustained-release drug formulations for localized cancer immunotherapy. *ACS Applied Bio Materials, 7*, 2023, 4944–4961.
75. Li, D., Meng, F., Liu, F., Lee, J., Gao, L., Lan, M., et al. Nanoparticle drug delivery systems responsive to tumor microenvironment: Promising alternatives in the treatment of triple-negative breast cancer. *WIREs Nanomedicine and Nanobiotechnology, 16*, 2024.
76. Krishnan, J., Poomalai, P., Ravichandran, A., Reddy, A., Sureshkumar, R. A concise review on the effect of PEGylation on the properties of lipid-based nanoparticles. *ASSAY and Drug Development Technologies, 22*, 2024, 246–264.
77. Essa, D., Choonara, Y. E., Kondiah, P. P. D., & Pillay, V. Comparative nanofabrication of PLGA-Chitosan-PEG systems employing microfluidics and emulsification solvent evaporation techniques. *Polymers, 12*, 2020, 1882.
78. El-Tanani, M., Satyam, S. M., Rabbani, S. A., El-Tanani, Y., Aljabali, A. A. A., Al Faouri, I., et al. Revolutionizing drug delivery: The impact of advanced materials science and technology on precision medicine. *Pharmaceutics, 17*, 2025, 375.

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