Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/w7rcwd63

ADVANCING DRUG INNOVATION: THE ROLE OF NOVEL DRUG DELIVERY SYSTEMS IN RESEARCH AND DEVELOPMENT

Muslim Bin Aqeel[1*], Nimrah Farooq[2], Muhammad Adnan[3], Talat Iqbal[4], Muneer Ahmad[5], Shimal Asher[6], Areeba Ghaffar[7], Mohammad Ahsan Iqbal[8], Abdullah Rasool Butt[9]

[1*] Department of Microbiology - Faculty of Science and Technology, University of Central Punjab, 54590, Lahore, Pakistan: mbadps@gmail.coms
[2] Department of Pharmacology, University of Karachi: nimrahfarooq89@gmail.com
[3] Department of Microbiology, Sarhad University of Science and Information Technology, Peshawar, Pakistan: adnankhanmuhammad017@gmail.com
[4] Department of Chemistry, Sarhad University of Science and Information Technology, Peshawar, Pakistan: talatkhattak909@gmail.com
[5] Department of Chemistry, Comsats University Islamabad, Lahore Campus:muneerahmad100b@gmail.com
[6] University Institute of Medical Lab Technology, Faculty of Allied Health Sciences, The University of Lahore: Shimalasher@gmail.com
[7] University Institute of Medical Lab Technology, Faculty of Allied Health Sciences, The University of Lahore. areebagafdar18@gmail.com
[8] University Institute of Medical Lab Technology, Faculty of Allied Health Sciences, The University of Lahore: mahsaniqbal445@gmail.com
[9] University Institute of Medical Lab Technology, Faculty of Allied Health Sciences, The University of Lahore: ababdullahrb333@gmail.com

***Corresponding Author:** Muslim Bin Aqeel
*Email:- (mbadps@gmail.com)

Abstract:
The rising demand for improved therapeutic outcomes and minimized side effects in the pharmaceutical sector has spurred a new wave of innovation and research in novel drug delivery systems. These systems aim to overcome the limitations of traditional drug administration methods, such as short half-life, poor targeting, low solubility, and bioavailability. As the fields of pharmacy, materials science, and biomedicine advance and intersect, the focus on developing efficient and safe drug delivery systems, including biopharmaceutical formulations, has grown significantly both nationally and internationally. This article provides an overview of the latest advancements in drug delivery systems, categorized into four key areas: carrier-based and coupling-based targeted drug delivery systems, intelligent drug delivery systems, and drug delivery devices, according to their primary objectives and methodologies. Furthermore, it critically examines the technological barriers, current research challenges, and future trends in the application of novel drug delivery systems.

Keywords: novel drug delivery system; targeting technology; carrier; nanotechnology; three-dimensional printing (3DP) technology

1. INTRODUCTION

Drug Delivery Systems (DDS) represent a promising technological advancement with extensive applications, engineered to release drugs in a controlled manner at predetermined rates and deliver them to specific tissues or cell types. Recent developments in drug delivery systems, such as nanoparticles, molecularly imprinted polymers, and 3D printing technology, have emerged as cutting-edge research topics. DDS is a pivotal strategy for achieving targeted and precise drug delivery. Table 1 succinctly introduces the challenges and solutions associated with drug molecular delivery.

Table 1: The challenges and solutions to drug molecular delivery.

Drug Molecular Challenges	Solutions
Protac (Proteolysis Targeting Chimeras)	High molecular weight, poor bioavailability, poor stability
Peptides and Proteins	Immunogenicity, short half-life
Antibody	Toxicity, Immunogenicity
Nucleic acid	Extrahepatic delivery, Immunogenicity, Enzyme degradation
Cell	Unstable drug characteristics, Poor tissue permeability

By leveraging multidisciplinary approaches, DDS is dedicated to developing drug delivery systems and devices that can modulate the metabolism, potency, toxicity, immunogenicity, and biorecognition of drugs, thereby enhancing the microenvironment in which the drug operates and facilitating its uptake by the body. Compared to conventional formulations, DDS offers several key advantages: (1) enhanced drug stability and minimized degradation; (2) optimized drug distribution, leading to increased target concentration and reduced adverse reactions; (3) precise drug localization, timing, and targeted release, such as breaking through the blood–brain barrier for drug delivery; and (4) decreased therapeutic dosage, reduced toxicity, and elevated therapeutic index. DDS not only delivers drugs to the affected area but also encompasses four core functions: drug targeting, controlled release, enhanced drug absorption, and improved drug stability. These functions align with the most critical demands in clinical drug applications.

The research on DDS spans multiple disciplines, intersecting and collaborating with each other. This review presents the latest research advancements in DDS from four perspectives: carrier-based and coupling-based targeted drug delivery systems, intelligent drug delivery systems, and drug delivery devices, aligning with the primary objectives and methods of drug delivery systems. Additionally, the review analyzes and discusses the technological bottlenecks in the application of novel drug delivery systems, as well as the challenges and future development trends of current research.

Figure 1 provides a visual representation of the main categories of drug delivery systems discussed in this review. It highlights the innovative strategies and methodologies employed to overcome the limitations of traditional drug delivery methods, demonstrating the integrated and comprehensive nature of modern DDS research.

The integration of cutting-edge technologies, such as nanotechnology, biotechnology, and advanced materials science, has significantly propelled the field of DDS. These advancements have led to the creation of sophisticated delivery mechanisms that can precisely control the release of therapeutic agents, enhancing their efficacy and minimizing side effects. This multidisciplinary approach ensures that DDS research remains at the forefront of pharmaceutical innovation, continually evolving to meet the complex demands of modern medicine. In conclusion, the development of novel drug delivery systems represents a significant leap forward in pharmaceutical science, offering promising solutions to longstanding challenges in drug administration. As DDS research progresses, it will undoubtedly continue to revolutionize the way we approach drug therapy, improving patient outcomes and paving the way for more effective and personalized treatments.

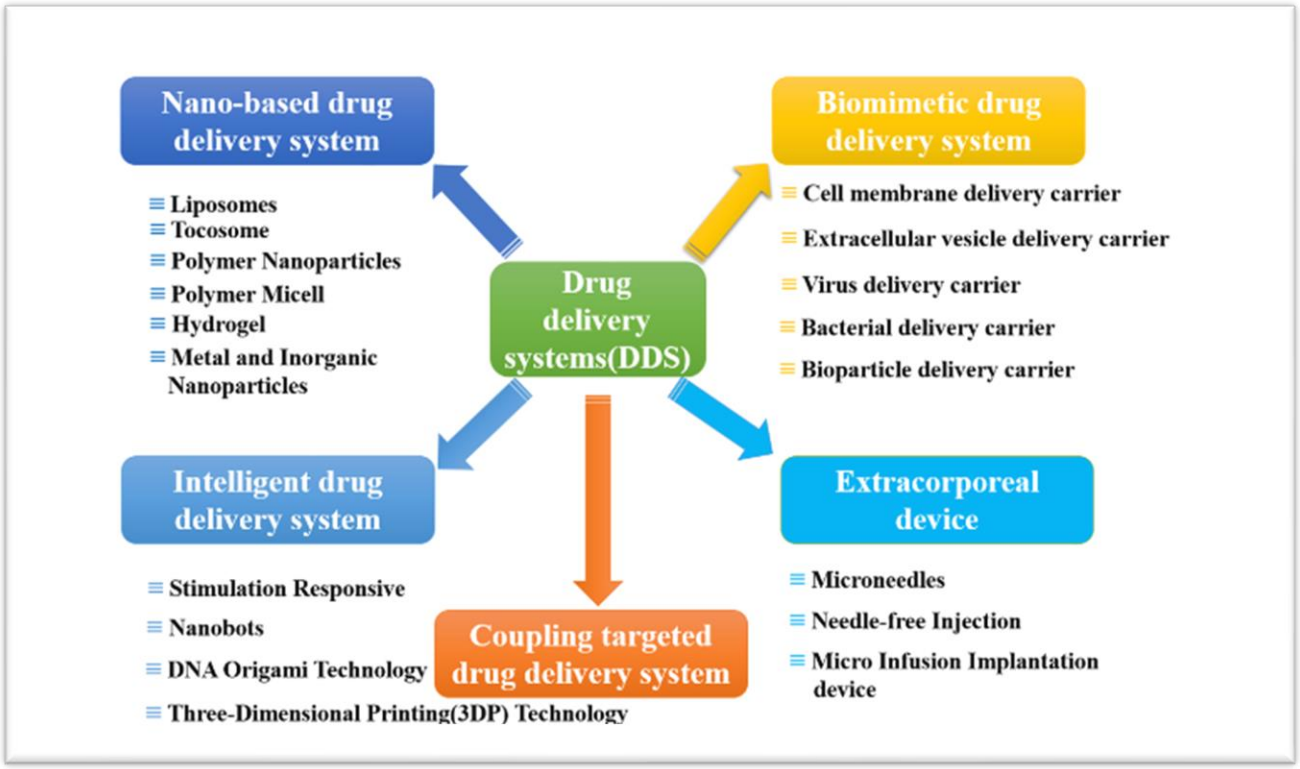

Figure 1. Main types of drug delivery systems

2. Carrier-Based Drug Delivery Systems

2.1. Nano-Based Drug Delivery Systems (NDDSs)

First proposed in 1959, the concept of "nanotechnology" has seen rapid scientific and industrial growth. Its integration with biotechnology, information technology, and cognitive science has ushered life sciences into a new era. Nanotechnology boasts unique physical, chemical, and biological properties, making nano formulations highly suitable for biomedical applications. Utilizing nanotechnology in drug delivery systems can significantly enhance drug solubility, stability, and tumor targeting while reducing toxic side effects. A diverse array of materials is employed in constructing NDDSs, including liposomes, nanodrugs, polymer micelles, hydrogels, and inorganic nanodrug delivery systems.

2.1.1. Liposomes

Liposomes are characterized by their ordered bilayers of lipids that form enclosed vesicles, featuring a hydrophobic shell and a hydrophilic core, with particle sizes ranging from 20 to 1000 nm. Their distinctive composition and structure afford them excellent biocompatibility and normal metabolic processes. Consequently, liposomes can enhance drug solubility and reduce drug toxicity. They are capable of encapsulating both hydrophilic and hydrophobic drugs, thus protecting them from degradation and preventing drug accumulation in other tissues and organs.

The development of liposome drug delivery systems grounded in nanotechnology has taken nearly half a century to be integrated into clinical practice. This advancement has catalyzed a significant leap in developing anti-tumor, anti-bacterial infection drugs, and vaccines. For instance, in the case of the anticancer agent resveratrol, using solid lipid nanoparticles for its delivery significantly increased brain concentration in Wistar rats compared to free resveratrol, indicating high penetration into brain tumors and minimal systemic toxicity.

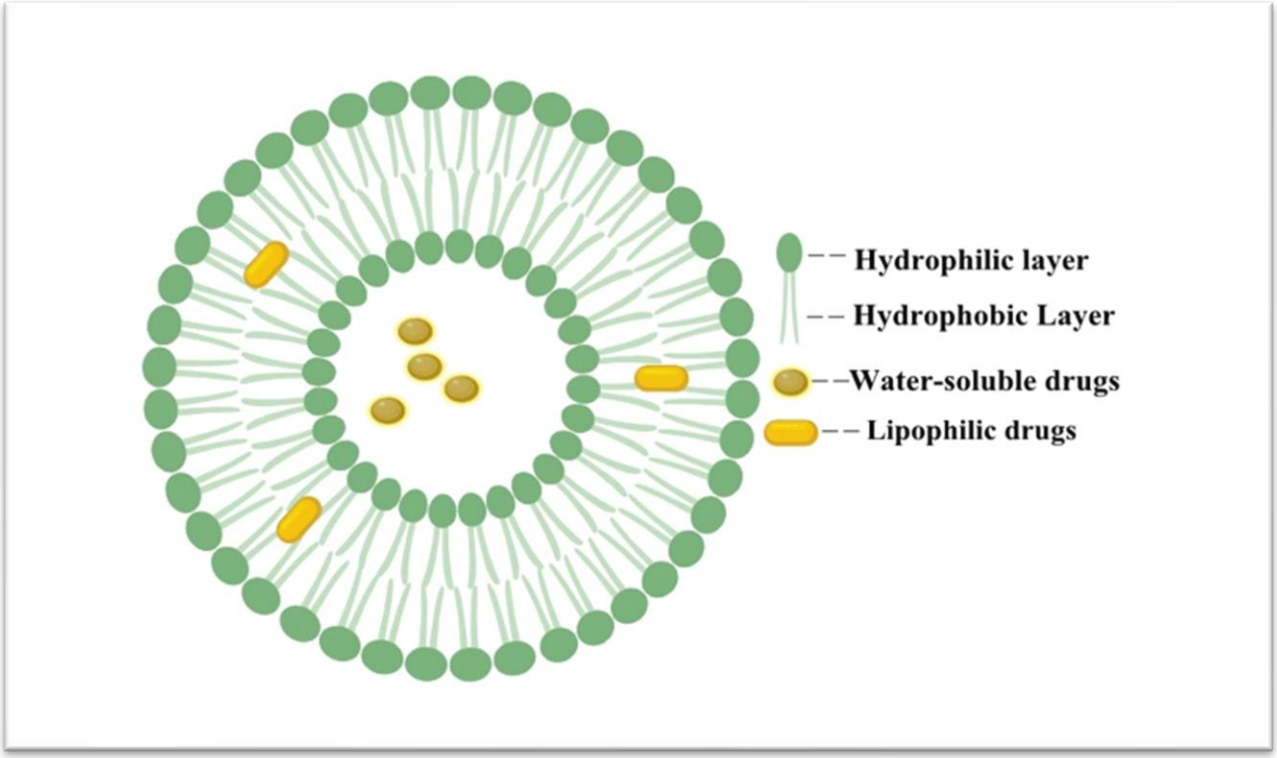

Figure 2. The hydrophilic and hydrophobic structure of liposome drug delivery system

In tumor therapy, liposome-encapsulated radiosensitizers can enhance the effects of X-ray radiation on tumor sites. For instance, Zhao et al. [14] designed an antigen-capturing stapled liposome (ACSL) with a robust structure and bioactive surface. This liposome can capture and transport tumor-associated antigens (TAAs) from lysosomes to the cytoplasm of dendritic cells (DCs), enhancing TAA cross-presentation and inducing a strong T cell-dependent antitumor response and immune memory following local irradiation. Additionally, liposomes encapsulating the anticancer agent doxorubicin have significantly reduced the cardiotoxicity associated with doxorubicin and minimized adverse reactions such as myelosuppression, alopecia, nausea, and vomiting [15]. Studies have also shown that the anticoccidial activity of decoquinate nanoliposomes (DQNLs), fabricated through thin-film dispersion-ultrasonic methods, is substantially enhanced [16].

Liposomes are a prevalent strategy for facilitating drug permeation across the blood–brain barrier. Transferrin-modified liposomes have demonstrated efficient drug transport capabilities. In a glioma-bearing mouse model, these liposomes exhibited minimal systemic toxicity and significant regression of gliomas following non-invasive systemic administration [17]. The combination of lichenin liposomes and rifampicin has been employed in treating multidrug-resistant tuberculosis, markedly enhancing rifampicin's antibacterial activity [18,19]. The carbohydrate recognition domain (CRD) of the C-type lectin pathogen recognition receptor, DC-SIGN, can be specifically targeted by antifungal liposomes, thereby enhancing the antifungal efficacy of liposomal Amphotericin B (AmB) both in vitro and in vivo [20].

Lipid nanoparticles (LNPs) represent a pivotal technology within liposome delivery systems and have significantly advanced oligonucleotide-based therapeutic agents. LNPs are a specialized subset of liposomes without hydrophilic cavities, composed of cationic phospholipids and negatively charged nucleic acid components that are electrostatically complexed, forming multilayer cores interspersed between lipid layers. Oligonucleotides encapsulated within LNPs are protected during delivery, remain intact and undegraded by enzymes, and are effectively delivered to cells, where the carrier particles release their contents and translate them into therapeutic proteins.

The Southwest Medical Center of the University of Texas has introduced a groundbreaking strategy called Selective Organ Targeting (SORT). This approach involves incorporating SORT molecules into various LNPs, enabling precise targeting of extrahepatic tissues [21,22]. The synergy of SORT with

different gene editing techniques has significantly advanced gene therapies targeting specific tissues. Shuai et al. [23] have pioneered a novel LNP delivery system (iPLNPs), incorporating novel phospholipids (iPhos) with enhanced endocytic escape capabilities. By manipulating the chemical structure and proportion of iPhos, organ-selective delivery can be achieved with remarkable precision. Min et al. [24] identified a novel LNP variant with an amide bond in its tail, which can be fine-tuned to target various lung cell types by adjusting its head structure.

In 2022, researchers at the University of Pennsylvania administered mRNAs encapsulated within LNPs to mice with heart failure, effectively modifying T cells and restoring their cardiac function. Building upon this success, in 2023, they developed and synthesized ionizable LNPs capable of delivering mRNA to the placenta without crossing into the fetal compartment, potentially offering a new treatment avenue for pregnancy complications such as preeclampsia [25]. Researchers at the Fred Hutchinson Cancer Research Center in Seattle have harnessed gene editing to create chimeric antigen receptor (CAR) T cells from patient-derived T cells [26]. This cutting-edge technology, facilitated by the LNP delivery system, ensures that the encapsulated CAR gene can access the nucleus via nuclear localization, positioning it as an emerging and promising cancer therapy.

The modified mRNA-targeted LNPs have demonstrated remarkable potential in reducing fibrosis and restoring cardiac function post-injury, while also generating transient, yet effective CAR T cells in vivo. These CAR T cells hold immense promise as a versatile therapeutic platform for treating a wide array of diseases [27]. Addressing the challenge of exogenous mRNA penetrating the cytoplasm without undergoing degradation by nucleases, COVID-19 mRNA vaccines have universally employed LNPs as their delivery vectors. This innovation has significantly enhanced the vaccines' efficacy, stability, and safety profiles [28]. The Nanoprimer technology has been shown to reduce the uptake of LNPs by the reticuloendothelial system (RES), thereby enhancing the bioavailability of LNPs encapsulating human erythropoietin (hEPO) mRNA or factor VII (FVII) siRNA. This results in a substantial increase in hEPO production (by 32%) or FVII silencing (by 49%) [29].

Additionally, Swingle and colleagues have developed an ionizable lipid specifically for the formulation of LNPs intended for mRNA delivery to placental cells. The leading LNP formulation, encapsulating VEGF-A mRNA, induced placental vasodilation, highlighting the potential of mRNA LNPs as a protein replacement therapy for treating placental disorders during pregnancy [25]. Moreover, microbiota transplantation is a pivotal strategy for preventing and treating diseases. However, developing oral bacterial therapies is constrained by low bioavailability and inadequate gastrointestinal retention. Lipid membrane-coated bacteria (LCB) represent a straightforward yet highly effective method for encapsulating gut microbes through biointerfacial supramolecular self-assembly. Bacteria encapsulated with additional self-assembled lipid membranes have demonstrated significantly enhanced survival against environmental challenges, with minimal alterations in viability and bioactivity. They have also improved the therapeutic efficacy of oral administration in two murine models of colitis [30].

Liposomes, as the most extensively studied and successful nanocarriers in clinical applications to date, offer the benefits of low toxicity, excellent biodegradability, non-immunogenicity, and the capacity to safeguard the encapsulated drug from degradation [31]. However, liposomes still have shortcomings, such as low drug loading capacity, poor stability, high production costs, potential toxic side effects, and significant variability in accumulation at tumor sites [32]. The future research and development direction of LNP delivery systems mainly focus on upgrading targeting and responsiveness to internal and external stimuli (e.g., temperature, ultrasound, enzymes, etc.), to achieve precise treatment [33].

2.1.2. Tocosome

Tocosome, a sophisticated colloidal and vesicular bioactive carrier system, predominantly comprises alpha-tocopherol phosphate (TP), a derivative of vitamin E. Vitamin E naturally exists in eight distinct forms, with alpha-tocopherol being the most prevalent, abundant, and biologically active. TP stands out for its narrow particle size distribution, commendable encapsulation efficiency, minimal immunogenicity, exceptional biocompatibility, and augmented dissolution and penetration

capabilities, all of which contribute to its prolonged stability . The multifaceted attributes of tocophersolan render it an adaptable constituent in the engineering of drug delivery systems. Tocosomes, akin to liposomes, are composed of amphiphilic molecules that form bilayer colloidal structures, displaying analogous behaviors in drug delivery mechanisms and release patterns, despite their unique chemical compositions .

Clinical research has underscored the myriad health advantages of TP, including its role in atherosclerosis prevention, cardioprotection, anti-inflammatory effects, and inhibition of tumor metastasis . Alongside TP, tocopherol formulations incorporate various phospholipid and cholesterol combinations, which have been effectively utilized in the encapsulation and controlled release of the anticancer agent 5-fluorouracil .

Sunitinib malate and sorafenib tosylate are both targeted therapies for metastatic kidney cancer, functioning through distinct pathways to impede angiogenesis and tumor proliferation. Fariba and colleagues have pioneered the development of a coated tocosome by blending chitosan (CS) with poly(N-isopropylacrylamide) (PNIPAAm), employing the Mozafari method . This temperature-sensitive tocosomal nanocarrier boasts enhanced stability, ideal particle size, and the potential for industrial-scale production, positioning it as a promising and robust drug delivery system for the anticancer drugs sunitinib malate and sorafenib tosylate.

Tocophersolan (TPGS) is a distinctive multidirectional polymer, a polymerized synthetic derivative of vitamin E. TPGS has been sanctioned by the FDA as a secure pharmaceutical excipient. Taxol and docetaxel (DTX) epitomize a category of highly potent, low-toxicity, spectroscopic natural anticancer agents, predominantly utilized in the treatment of ovarian, breast, and bronchial cancers, among others. Their mode of action involves inhibiting cancer cell growth by facilitating microtubule assembly and preventing microtubule disassembly . Qi et al. modified TPGS with cholesterol to create a novel carrier material, TPGS-CHMC, which possesses a lower critical micelle concentration (CMC). TPGS-CHMC diminished mitochondrial membrane potential and cell membrane fluidity in paclitaxel-resistant ovarian cancer cells (A2780/T). In A2780/T tumor-bearing nude mice, TPGS-CHMC/DTX micelles exhibited significantly enhanced antitumor efficacy and reduced toxicity compared to the free DTX solution.

2.1.3. Polymer Nanoparticles

Polymer nanoparticles (PNPs) are colloidal particles with diameters spanning from 10 to 1000 nm . Liposomes with larger particle sizes are less prone to traverse the endothelial layer or blood–brain barrier, whereas PNPs with smaller particle sizes can readily permeate these barriers to reach the target site. Common PNPs include synthetic polymers such as polylactic acid, poly (lactide-co-glycolide) (PLGA), polyamino acids, and natural polymers like chitosan, alginate, gelatin, and albumin . Research has demonstrated that the PNP drug delivery system is biodegradable, capable of reducing systemic toxicity and irritation, delaying drug degradation, improving drug release kinetics, and enhancing biocompatibility, drug safety, and efficacy . Manipulating the degradation/bond scission of polymers can also modulate the in vivo release kinetics and facilitate the clearance of delivery carriers in vivo.

Surface PEGylation of nanomedicines significantly extends their circulation time in the bloodstream and enhances their permeability and retention (EPR) effect. Therefore, a Near Infrared (NIR) light-triggered dePEGylation/ligand-presenting strategy has been developed, relying on the thermal decomposition of azo bonds. This approach involves the self-assembly of Dox/Pz-IR nanoparticles from long PEG chain polymers (Pz-IR) connected by thermo-labile azo molecules, cRGD conjugated IR783 (rP-IR) with short PEG chains and doxorubicin. The Dox/Pz-IR nanoparticles achieve an optimal synergistic effect of photothermal chemotherapy at mild temperatures through progressive tumor accumulation, a precisely regulated photothermal effect and NIR-photothermal therapy (PTT) induced pulsated drug release . Van De Ven et al. utilized PLGA as the carrier material and amphotericin B to prepare drug-loaded nanoparticles, demonstrating no significant hemolytic toxicity in vitro and a good safety profile and antifungal effects .

Overcoming the regulatory barrier of the blood–brain barrier (BBB) to deliver drugs to the brain remains a significant research challenge. One strategy is the use of nanomedicines capable of crossing the BBB and delivering therapeutic molecules to specific sites in the brain (Figure 3). Dendrimers, macromolecules with a dendritic structure formed by repetitive and linear linkage of oligomers via branching units, have shown promise in this regard. Hydroxypolyamidoamine (PAMAM) dendrimers can traverse the BBB and blood-cerebrospinal fluid barriers, effectively delivering small molecule drugs to targeted sites, particularly in injured brain tissue . PAMAM dendrimers with a size of 6.7 nm exhibit longer blood circulation times and greater accumulation in the brain compared to those with a size of 4.3 nm . Furthermore, PAMAM dendrimers with cationic surface properties have been shown to cross the BBB and localize in neurons and glial cells following carotid artery administration .

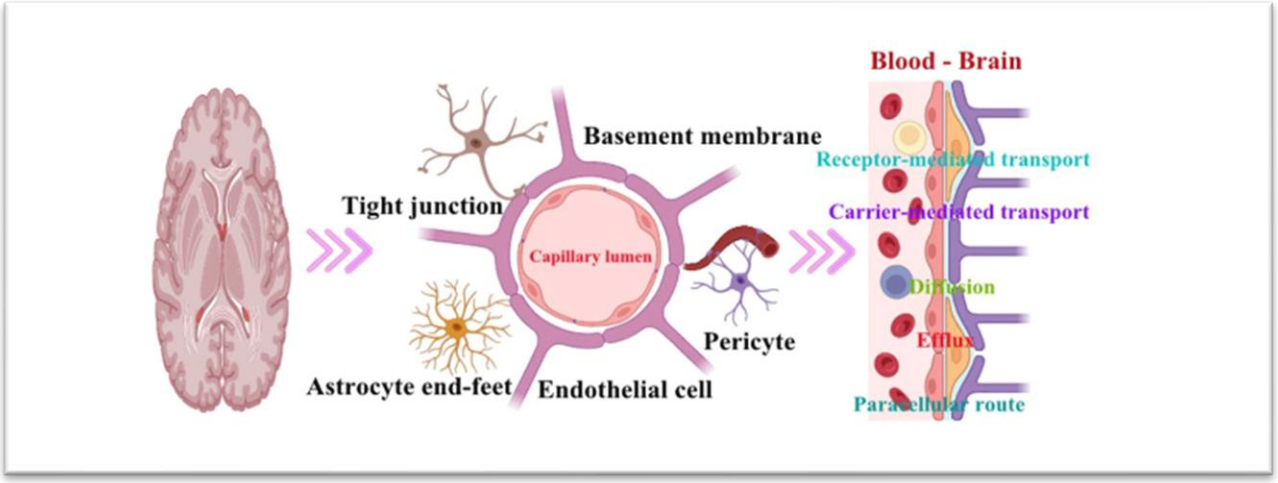

Figure 3. Nanomedicine crossing BBB and delivering therapeutic molecules to target sites in the brain

3. Chitosan and Molecularly Imprinted Polymers (MIPs) in Drug Delivery

Chitosan, functioning as a distinct receptor on the fungal membrane, has been utilized by Tang et al. to develop chitosan-binding peptide-modified PLGA nanoparticles encapsulating itraconazole. These nanoparticles possess the unique ability to recognize chitosan on fungal surfaces, thereby exerting a pronounced targeting effect on Cryptococcus neoformans . Additionally, Chitosan nanoparticles adorned with rhamnolipids (RL) have been loaded with the antimicrobial phytochemical isoliquiritigenin (ISL) (isl@rl-cs). This formulation is capable of concurrently eliminating the biofilm of methicillin-resistant Staphylococcus aureus (MRSA) throughout all stages and mitigating the associated inflammation .

Researchers at Sloan Kettering Cancer Center have recently unveiled a fucoidan-based nanocarrier that targets endothelial P-selectin, enabling penetration of the blood–brain barrier. Nanoparticles encapsulating the small molecule anti-tumor agent vismodegib were effectively delivered to brain tumor tissues via P-selectin-mediated transport, significantly enhancing the drug's therapeutic efficacy .

Molecularly imprinted polymers (MIP), also termed "synthetic antibodies", are produced through molecular imprinting technology (MIT). The fundamental concept of MIP involves the formation of a template molecule-functional monomer complex through covalent or non-covalent interactions, followed by polymerization in the presence of a cross-linking agent, and ultimately the removal of the template molecule to create a binding site or cavity that matches the template in terms of size, shape, and chemical affinity . Owing to the precise selectivity and affinity of MIP for the template molecule, sustained drug release can be achieved.

Quercetin (3,3,4,5,7-pentahydroxyflavone, QC) is a potent anticancer agent that exerts its antioxidant effects by upregulating endogenous free radical defenses and inhibiting tumorigenesis and tumor progression signaling pathways. However, the clinical application of quercetin for chemoprotection

is limited by its hydrophobicity, poor gastrointestinal absorption, and extensive heterologous metabolism in the intestine and liver. A highly selective magnetic molecularly imprinted polymer (MMIP) with a core-shell structure was synthesized by a sol-gel process in the presence of template QC using Tragacanth Gum (TG) crosslinker, Fe_3O_4/SiO_2 nanoparticles, and N-vinyl imidazole (VI) functionalized monomers. The synthesized MMIP nanogel is biocompatible due to the presence of TG, possesses a strong adsorption capacity, is easily separable, and specifically recognizes the template QC . Therefore, MIP and MMIP materials are anticipated to serve as polymeric devices for applications in rapid drug separation and drug delivery.

Polysaccharide nanoparticles (PNPs) have demonstrated significant advancements in the field of drug delivery, with notable achievements in the understanding of their mechanisms of action, environmental interactions, activity profiling, and composite material development . However, the exploration into their potential toxicity, polymer stability, and drug delivery mechanisms remains incomplete . To bridge this gap, future research must delve into a comprehensive and meticulous analysis of the pharmacokinetics, safety profiles, immunogenicity, and other critical aspects of polymer nanodrug delivery systems. This will enable the effective modulation of the physicochemical properties of these systems

4. Polymer Micelles in Drug Delivery

Polymer micelles are assembled colloidal aggregates formed by amphiphilic block copolymers in an aqueous environment . They are distinguished by their structural integrity, hydrophobic drug solubilization capabilities, and minimal toxicity. With a particle size ranging from 10 to 100 nm, these micelles can evade phagocytosis by the reticuloendothelial system, thereby extending their systemic circulation time . Moreover, the hydrophilic shell of the micelles not only prevents drug loss in the serum but also resists complement system activation, which can prematurely quickly clear drugs before they can take effect .

In the past three decades, polymer micelles have been extensively employed as carriers for highly potent, highly toxic, and poorly soluble small molecule drugs . Notably, in the realm of antifungal therapy, Albayaty et al. developed an acid-base responsive micellar system for the encapsulation of itraconazole, which boasts a high drug loading capacity and a strong affinity for Candida albicans biofilms, significantly inhibiting their activity . Poly micelles also hold the potential to be loaded with combinations of multiple chemotherapeutic agents for targeted tumor delivery, thereby reducing chemotherapy-related adverse reactions and enhancing the survival rate and quality of life for patients with pancreatic cancer. This innovation addresses key challenges in chemotherapy . The micelles developed by Zhang et al., known as Cela/GCTR, possess remarkable characteristics that make them promising candidates for the delivery of hydrophobic anti-tumor agents in the treatment of hepatocellular carcinoma. These micelles exhibit sustained release in the bloodstream and rapid release within tumor microenvironments . The hydrophobic segments are strategically positioned at the core of the nanoparticles to encapsulate hydrophobic drugs, while the hydrophilic segments form the outer corona, maintaining the micelle's structure in aqueous environments. By attaching specific ligands to the hydrophilic corona, these micelles can traverse the blood–brain barrier via transcytosis and subsequently release their therapeutic cargo upon intracellular disruption.

Various block copolymer micelles, including PAA-PEG , PLA-PEG, DGL-PEG, PTMC-PEG, and PDSGM-PEG, have been documented to facilitate the transport of therapeutic agents across this barrier. Notably, PLA-PEG micelles loaded with paclitaxel (PTX) and modified with the t-Lyp1 ligand demonstrated enhanced accumulation and internalization in glioma cells, effectively inhibiting tumor progression in animal models . Furthermore, advanced wormlike polymer micelles composed of PEG-grafted poly (2-diisopropyl methacrylate) (PDPA) copolymers (mPEG-b-PDPA) have been engineered to degrade in response to changes in the brain tumor microenvironment, thereby releasing drugs directly into the target tumor .

Micelles are also extensively utilized in traditional Chinese medicine preparations, enabling precise control over particle size, encapsulation efficiency, and drug loading for ingredients such as emodin, curcumin, baicalin, and paclitaxel ensuring slow and sustained release. However, due to the minute

size of the monomer molecules derived from the extraction and separation processes of traditional Chinese medicine, their current application is largely confined to the synthesis of monomers, with limited research on the direct conversion of traditional Chinese medicine extracts into micelles . Internationally, pharmaceuticals based on polymer micelles have been granted marketing authorization, while domestically, such polymer micelle drugs are still undergoing clinical trials . Despite the existing limitations in clinical application duration and the long-term safety assessment of formulation development, the numerous advantages of polymer micelles are poised to propel their ongoing enhancement and broad application in the delivery of hydrophobic drugs.

4.1. Hydrogel in Drug Delivery

Hydrogels are polymer networks, either physically or chemically crosslinked, that possess the unique ability to swell in the presence of water and interact with certain organic solvents . The hydrogel nanodrug delivery system exhibits remarkable biocompatibility, biodegradability, and low toxicity, facilitating the sustained release of targeted drugs.

In the context of tumor therapy, the anti-tumor immune response following radiation therapy is often insufficient, necessitating the use of immune adjuvants to augment the efficacy of antigen-presenting cells . Wang et al. engineered a hydrogel nanomotor activated by near-infrared light, capable of penetrating tumor tissue and releasing drugs intracellularly, thereby enhancing the immune activation capabilities of the body and achieving a synergistic effect through the integration of phototherapy, chemotherapy, and immunotherapy . Soft hydrogel presents an excellent material option for the repair of various tissue defects. Li et al. developed an anti-swelling nanofiber hydrogel that boasts high biocompatibility and biodegradability, effectively facilitating fibroblast migration and accelerating angiogenesis during the wound healing process . Sun et al. have developed an innovative hydrogel nanodrug delivery system designed to carry ligands that bind competitively to ATP released from tumor cells upon treatment with oxaliplatin or X-ray irradiation. This system promotes the release of immune adjuvants, thereby enhancing the synergistic therapeutic effect of the treatment .

In the realm of veterinary medicine, Gao et al. engineered a thermosensitive gel vaccine delivery system that exhibits excellent biocompatibility, degradability, and sustained release capabilities . The Newcastle disease temperature-sensitive gel nucleic acid vaccine, formulated with a recombinant plasmid, has been shown to elicit a robust humoral and cellular immune response, thereby enhancing the body’s antiviral defenses and prolonging the duration of immune protection . Recently, the Shanghai Veterinary Research Institute of the Chinese Academy of Agricultural Sciences has created an innovative supramolecular nanofiber hydrogel (Hydrogel RL) that incorporates antimicrobial peptides. In vitro studies have demonstrated that Hydrogel RL maintains sustained release, is biocompatible, and exhibits potent antibacterial activity against methicillin-resistant Staphylococcus aureus (MRSA). This development holds promise for combating multidrug-resistant bacteria and addressing healing stagnation resulting from chronic wound infections .

The hydrogel system’s resistance to degradation in the gastrointestinal tract allows for sustained drug release . Azad et al. observed that calcium alginate beads with hydrogel properties remain undegraded in the stomach and are released in the intestinal tract. Moreover, their strong adhesive properties contribute to improved drug retention in the intestinal mucosa . However, the oral hydrogel system has not demonstrated significant progress in clinical trials to date, primarily due to the rapid disintegration of the hydrogel upon contact with substantial intestinal fluids during oral administration. This issue demands focused attention in future research and development endeavors .

The hydrogel nanodrug delivery system has demonstrated notable advantages in modulating drug release kinetics, enabling the remote and controlled release of drugs, and facilitating the site-specific targeting of drugs . Nevertheless, challenges persist in the clinical application of this technology. Current studies on drug release within hydrogels are largely confined to in vitro experiments or heavily reliant on the internal microenvironment of tumors. Assessing whether hydrogels maintain their response characteristics following in vivo implantation will be a pivotal research focus for hydrogel nanodrug delivery systems moving forward . Moreover, the development of hydrogels necessitates more precise control over the properties of the hydrogel drug delivery carriers and the

release kinetics under various trigger conditions. It is evident that highly controllable and precisely adjustable hydrogels possess expansive application potential in the future .

5. Metal and Inorganic Nanoparticles in Drug Delivery

In the realm of nanomedicine delivery systems, metal and inorganic nanoparticles synthesized through physical or chemical methods from metallic or inorganic materials represent a diverse and promising category. These nanomaterials are distinguished by their exceptional physical and chemical properties, including a high specific surface area, enhanced bioavailability, low toxicity, and compatibility with most organic solvents. Consequently, they have found extensive application in the combined treatment of tumors .

Zhao et al. integrated copper ions and other substances into oxidative stress amplifiers, thereby sensitizing immunotherapy through chemotherapy. This approach has reversed the immunosuppressive tumor microenvironment, augmented immunotherapy efficacy, and significantly curtailed the growth of primary distal tumors. Their work offers novel insights into the development of combined therapy strategies for inhibiting tumor growth and metastasis .

Gong et al. developed a phosphorus and nitrogen-doped hollow carbon quantum dot DOX carrier, which has been shown to enhance the intranuclear delivery and tumor accumulation of DOX, thereby effectively inhibiting tumor growth. The multifunctional CuS nanocomposite designed for the combined administration of oligonucleotides and docetaxel promotes the infiltration of Tc cells and enhances the therapeutic efficacy of breast cancer when used in conjunction with photothermal and photodynamic therapies .

In the field of veterinary medicine, Raposo et al. prepared and tested the effects of gold nanoparticles loaded with cobalt and zinc compounds on canine cancer cells. Their findings indicate that these nanoparticles are readily surface-modified and more effective in delivering cytotoxic substances than free compounds. Silver has been shown to act on bacterial enzymes and proteins, thereby inhibiting the production of bacterial toxins . Nanosilver nanoparticles (AgNPs) prepared using nanotechnology not only exhibit the characteristics of nanomaterials but also enhance the antibacterial effect of silver . The potential antibacterial mechanisms of silver nanoparticles (AgNPs) may include disruption of normal bacterial morphology by inhibiting the synthesis of cell wall peptidoglycans and inhibition of bacterial growth by inhibiting the cell division protein FtsZ and the chromosomal replication initiation protein DnaA .

Livestock manure serves as a reservoir for a multitude of antibiotic resistance genes (ARGs), and its accumulation on land may foster the emergence of antibiotic-resistant bacteria and facilitate the dissemination of ARGs. Nanoscale zero-valent iron (nZVI), with its expansive surface area and unique physicochemical properties, can effectively reduce the concentration of antibiotics and mitigate the risk of ARG transmission during composting processes . Additionally, copper nanoparticles have demonstrated efficacy in both the prevention and treatment of mastitis .

The reactivity of inorganic nanoparticles necessitates surface modification with biocompatible materials to serve as non-invasive nanomedicines. Among these, gold nanoparticles are the most extensively utilized inorganic nanomedicines in biomedical applications due to their ease of synthesis, surface modification capabilities, and high biocompatibility. Research has shown that gold nanoparticles can exploit cleavable bonds within endosomes to facilitate transport across the blood–brain barrier while simultaneously inhibiting blood reflux .

Rodrigues et al. conjugated transferrin (Tf) and rabies virus glycoprotein (RVG) peptide to the surface of liposomes, targeting transferrin and nicotinic acetylcholine receptors. They characterized the function of these liposomes in traversing the blood–brain barrier using an in vitro triple co-culture BBB model. The liposome RVG-Tf was found to continuously transfect and effectively transport primary neuronal cells in an in vitro blood–brain barrier model, and it was observed to enhance the penetration of the blood–brain barrier in vivo . Wang et al. prepared transferrin-modified liposomes (Tf-PL) for the targeted delivery of acetylcholinesterase (AChE) therapeutic gene to liver cancer cells. These liposomes exhibited higher transfection efficiency than Lipo 2000 and demonstrated a superior targeting effect on liver cancer SMMC-7721 cells in vitro. Furthermore, the subcutaneous injection

of Tf-PL/AChE significantly inhibited the growth of liver cancer xenografts in nude mice . Lu et al. have engineered a core-shell nanosphere featuring a liquid phase eutectic gallium-indium core and a thiolated polymer shell. This innovative nanomedicine is a convertible liquid metal system capable of fusing and subsequently degrading under weakly acidic conditions. This mechanism facilitates the release of doxorubicin in acidic endosomes following cellular internalization, thereby demonstrating enhanced chemotherapeutic efficacy in xenograft tumor-bearing mice .

While inorganic nanomaterials can be precisely tailored to meet various drug delivery requirements, their toxicity, biological distribution, and clearance mechanism in vivo are yet to be fully elucidated. To expedite the clinical application of inorganic nanomedicine delivery systems, future research should prioritize the investigation of drug retention effects in vivo and the enhancement of drug clearance processes.

5.2. Biomimetic Drug Delivery Systems

Traditional drug carriers often suffer from inadequate biodistribution, short blood circulation times, and reduced delivery efficiency. Nanostructured drug carriers have the potential to alter drug pharmacokinetics and biodistribution. However, they are susceptible to recognition as foreign entities by the reticuloendothelial system, which can hinder their targeted delivery [92,93]. As nanotechnology, biocoupling, and bioengineering tools advance, researchers are gaining deeper insights into the interactions between natural substances like cells and pathogens, and the body's cellular systems. This understanding has spurred efforts to mimic these structures and functions for therapeutic purposes [94]. Therefore, investigating endogenous carriers with minimal toxicity and strong biocompatibility is crucial. In recent years, biomimetic drug delivery systems employing biological carriers such as cells, extracellular vesicles, viruses, and bacteria have become a focal point in drug delivery research [95]. These biological carriers inherit the structure and function of their original sources, acting as endogenous substances to minimize immune responses and avoid direct elimination by monocytes and macrophages. Moreover, they can mimic the structural characteristics or mechanisms of action of highly infectious agents or pathogens within the body, ensuring precise drug delivery to target sites for optimal therapeutic outcomes. Consequently, biological carriers are highly regarded as a promising approach for targeted drug delivery [96].

5.2.1. Biomimetic Cell Membrane Delivery Carriers

The biomimetic cell membrane delivery carrier represents a rapidly evolving and versatile drug delivery system. It mimics the structure of somatic cell membranes, offering superior biocompatibility and minimal toxicity, which provides distinct advantages over other drug delivery vehicles [97]. These cell-based systems can be easily fabricated while preserving membrane proteins and intact structures, thus retaining diverse biological functions and targeting specificity [98]. Their unique attributes include prolonged circulation times, adaptable morphology, low immunogenicity, and precise targeting capabilities, making them increasingly favored as ideal carriers for drug delivery [99]. Biomimetic nanosystems derived from various natural cells and hybrid cell membranes have demonstrated effectiveness in targeted drug delivery by reducing immune clearance rates, extending blood circulation times, enhancing drug loading, and improving therapeutic efficacy against tumors [100].

Currently, primary carriers utilized for cell membrane-based delivery include red blood cells, platelets, various types of white blood cells, stem cells, and cancer cells. Among these, the red blood cell-based drug delivery system stands out due to its abundant availability and strong targeting ability, leading to significant advancements in treating various diseases [101]. For instance, Cao and colleagues developed cell membrane-coated bacteria (CMCB) using red blood cell membranes, demonstrating its potential as a potent tumor imaging agent through evaluations in various mouse models [102]. Platelets play a critical role in the tumor microenvironment by accumulating at wound sites post-surgery, where they induce inflammation and aid in repair. Wang et al. engineered platelets coupled with anti-PDL1 antibodies on their surface, effectively releasing anti-PDL1 during platelet activation to reduce tumor recurrence and metastasis after surgery [103].

Cell membrane-coated nanoparticles utilizing T cell membranes carry surface antigens crucial for binding to human immunodeficiency virus (HIV), showing promise as a novel therapeutic against HIV infection [104]. Chimeric antigen receptor (CAR)-T cells have emerged as a prominent technology in drug delivery systems (DDS) by modifying patient T cells to recognize tumor antigens and activate cytotoxic immune responses locally. Ma et al. demonstrated that CAR-T cells recognizing tumor-associated antigens encapsulated in nanoparticles can achieve highly specific treatment for liver cancer [105]. Despite the success of CAR-T cell therapy in treating B-cell malignancies, challenges such as prolonged treatment duration and high costs limit its broader application. Agarwalla et al. introduced an implantable Multifunctional Alginate Scaffold (MASTER) for T cell engineering and release, aiming to streamline CAR-T cell therapy administration and enhance therapeutic outcomes [106]. Additionally, researchers at the Memorial Sloan Kettering Cancer Center developed synthetic enzyme-armed killer (SEAKER) cells, a novel CAR-T cell variant that enhances anticancer efficacy when coupled with small-molecule prodrugs in vitro and in vivo [107].

Macrophages and other phagocytic cell membranes possess pattern-recognition receptors that identify and bind to pathogens, making them natural ligands for targeted drug delivery. Li et al. coated collagen-based nanoparticles with macrophage membranes, enhancing biocompatibility, increasing nanoparticle accumulation at infection sites, and improving antibacterial efficacy [108]. Tumor cell membranes, known for their inherent tumor-targeting abilities, have been utilized by Guo et al. to develop biomimetic nanoparticles (gct@cm NPs) that encapsulate tumor cell membranes for precise tumor targeting [109]. Harris et al. demonstrated that nanoparticles coated with cancer cell membranes (CCM) achieve dual functionality by shielding and targeting tumor cells while minimizing uptake by liver cells [110].

Huang et al. explored the clinical potential of various cell membrane-coated nanocarriers for targeted siRNA delivery, highlighting their efficacy compared to exosomes and other delivery systems in cancer therapy [111]. The integration of natural cell membrane functions with nanocarrier properties in biomimetic drug delivery systems presents a promising approach for diverse applications (Figure 4). These cell-derived membrane biomimetic nanocarriers exhibit prolonged circulation times, excellent biocompatibility, and robust immune evasion capabilities. However, further research is essential to fully understand their toxicity, biodistribution, and immune responses. Despite these challenges, the inherent advantages of nanocarriers combined with the abundant availability of cell membranes offer substantial potential for advancing therapeutic strategies [112].

5.2.2. Extracellular Vesicle Delivery Carrier

In the domain of extracellular vesicle (EV) delivery systems, these small vesicles are released by cells and contain biologically active molecules such as proteins and miRNAs. EVs function as biocompatible carriers with inherent material transport properties, exhibiting low immunogenicity and lacking cytotoxic or mutagenic effects. They demonstrate favorable circulatory stability, biocompatibility, physicochemical stability, and the ability to traverse biological barriers [113]. Notably, EVs derived from macrophages can penetrate the blood-brain barrier, interact with cancer cells, and accumulate within them [114].

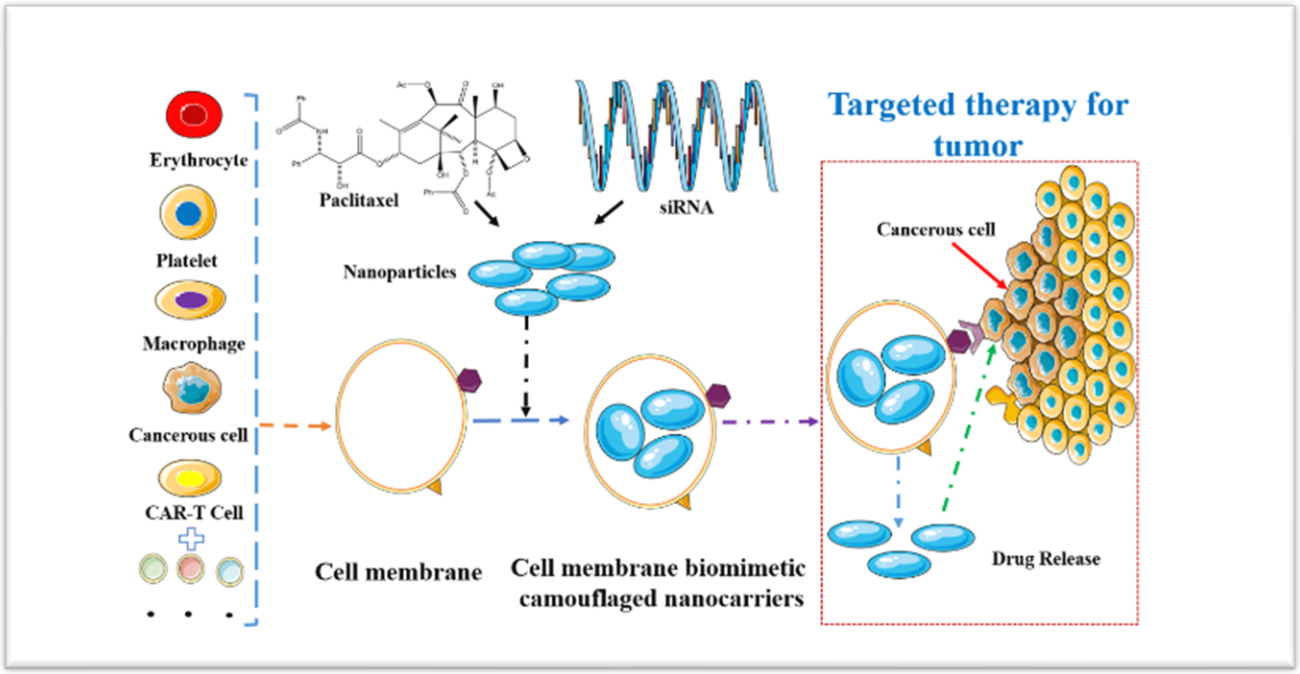

Figure 4. Cellular biomimetic drug delivery system integrating natural cell membrane functions andnanocarrier functions

Exosomes, a subtype of extracellular vesicles, have been extensively researched since 2013, particularly those ranging in diameter from 40 to 100 nanometers. These nanoscale vesicles, secreted by most cells, exhibit inherent stability, biocompatibility, minimal immunogenicity, and low toxicity. Their ability to target specific cells makes them ideal biological nanocarriers for biomedical applications [105]. Importantly, exosomes are preferentially enriched in tumor tissues compared to normal tissues. By attaching tumor-targeting ligands to exosomes, specific and targeted delivery of proteins, peptides, nucleic acids, and other compounds can be achieved through various administration routes such as intravenous, intraperitoneal, oral, and intranasal [115–117]. Tumor-derived exosomes used as carriers effectively target cancer cells, protecting therapeutic compounds from degradation in the extracellular environment, while maintaining biocompatibility and low immunogenicity [118].

Exosomes derived from dendritic cells are rich in antigen-presenting and co-stimulatory molecules, capable of activating T cells, enhancing natural killer cell function, and promoting tumor elimination [119]. Immune cell-derived exosomes possess immunomodulatory properties and therapeutic potential, expressing a variety of surface antigens crucial for antigen presentation, immune activation, and metabolic regulation aimed at eliminating cancer cells, thereby playing a significant role in cancer therapy [120]. Recent studies have demonstrated the production of custom-engineered exosomes by engineering cells in vivo [121]. For example, engineered exosomes generated by implanting cells into live mice have shown sustained delivery of mRNA to the brain for treating Parkinson's disease, opening new avenues for in vivo production of engineered exosomes [122].

Engineered exosomes have significantly enhanced the efficacy and precision of therapeutic agent delivery, positioning them as advanced multifunctional nano-delivery systems pivotal in targeted therapeutic research across diseases including oncology, inflammatory conditions, and degenerative disorders [123]. Compared to synthetic nanocarriers, extracellular vesicle drug delivery systems offer substantial advantages in terms of targeting, safety, and pharmacokinetics. However, challenges such as extraction methods, low separation efficiency, high heterogeneity, limited targeting capabilities, and reduced intracellular drug efficacy currently limit their clinical application [124,125]. Despite being in the early stages of research, exosomes hold promise as diagnostic biomarkers and carriers for anti-tumor drugs. Moreover, artificial extracellular vesicles or extracellular vesicle mimics have

emerged as key players in extracellular vesicle drug delivery, leveraging their advantages of sterility, scalability, and regulatory ease [126,127].

5.2.3. Virus Delivery Carrier

Virus nanoparticles (VNP), derived from bacteriophages, animal, and plant viruses, constitute a novel class of nanoparticle carriers with sizes ranging from 10 to 1000 nm, including some infectious variants. Their inherent ability to infect cells underscores their potential as delivery vectors, first explored in drug delivery as early as 1977. Viral vectors are extensively used in both in vivo and in vitro settings for drug delivery research, particularly valued for their efficiency in gene delivery and expression [128].

Currently, the main categories of virus vectors are lentivirus (LV), adenovirus (ADV), and adeno-associated virus (AAV). These vectors find extensive application in gene therapy, with 70–80% of gene therapy programs utilizing them. The advent of CRISPR technology has further enhanced their utility in treating congenital diseases and cancers. For instance, Cheng et al. developed an in vivo gene editing adenovirus CRISPR/Cas9 system in 2014, achieving tissue-specific gene knockout and resulting phenotypic changes [130].

To improve the stability, cellular targeting, and therapeutic efficacy of CRISPR-based drug delivery systems, researchers combine viral and non-viral vectors. For example, Yin et al. in 2016 used AAV vectors for delivering sgRNA and liposome materials for delivering Cas9 protein to mitigate liver damage symptoms and lower CRISPR off-target effects [131].

With advancements in biological sequencing technology, researchers have identified diverse protein family sequences. Machine learning models trained on experimental data offer a means to exploit the full potential diversity of engineered proteins. Bryant et al. applied deep learning to design variants of adeno-associated virus 2 (AAV2) capsid proteins capable of efficiently loading DNA, promising significant applications in improving viral vectors and protein therapies [132].

Targeting tumor-specific delivery, sophisticated gene therapy platforms like SHREAD (Shielded, Retargeted Adenovirus) have been developed. These platforms selectively target cells based on specific surface markers, effectively converting them into biofactories capable of secreting therapeutic molecules. Human adenovirus serotype 5 (Ad5), a prevalent viral vector, has been successfully retargeted to FAP+ fibroblasts by Hartmann et al., demonstrating efficient delivery and release of therapeutic agents within the tumor microenvironment, leading to significant inhibition of tumor growth [134].

Oncolytic viruses (OVs) possess unique capabilities to target and dissolve tumors. Wu et al. developed a novel viral strategy involving OVs treated with liquid nitrogen shock to eliminate pathogenicity, achieving targeted tumor delivery and preventing viral clearance in the bloodstream [135].

Despite their high transfection efficiency, viral vectors pose safety concerns and have limited loading capacities, which can restrict large-scale production. Strategies such as removing non-essential viral genes to mitigate toxicity or constructing self-inactivating viral vectors aim to improve the safety profiles of these vectors [136].

5.2.4. Bacterial Delivery Carrier

Bacterial delivery carriers represent an innovative approach in drug delivery systems, merging chemical biotechnology with bacterial systems. Engineered bacteria are particularly valuable for targeted drug delivery due to their ability to sense and respond to changes in physiological and pathological conditions within the host, coupled with their efficient in vivo transport capabilities [137–139]. Certain bacteria are adept at targeting hypoxic microenvironments, which can be challenging for other drug delivery systems [140–142].

In addition to these capabilities, specific interactions between bacteria and fungi have been observed. For instance, Streptococcus can adhere to Candida albicans through cell surface polysaccharide receptors and peptide adhesins, highlighting potential avenues for developing targeted antifungal therapies [143]. Similarly, Lactobacillus acidophilus and Lactobacillus salivarius can recognize and

coaggregate with Candida albicans via polysaccharide receptors, suggesting strategies for combating fungal infections [144–147].

One notable advancement is the development of a delivery system by Solomon et al., which encapsulates paclitaxel within bacterial vesicles targeting overexpressed epidermal growth factor receptor (EGFR) in solid tumor cells. This approach has demonstrated potent anti-tumor effects in xenograft models [148]. An intriguing innovation involves bacterial membrane-coated nanoparticles (BM-NP), where bacterial outer membranes are integrated with nanoparticles to enhance their physicochemical properties and immune stimulatory effects. Gao et al. utilized Escherichia coli to coat nanoparticles with bacterial outer membranes, resulting in BM-NP that significantly enhanced dendritic cell activation, antibody production, and T cell responses in vivo compared to using bacterial outer membranes alone [149].

Moreover, Wang et al. engineered bacteria to secrete extracellular matrix to form natural biofilms encapsulating probiotics, which improved gastrointestinal tolerance and mucosal adhesion in animal models [150]. This approach also demonstrated enhanced decolonization effects in mice colonized with Staphylococcus aureus.

Despite significant advancements in research and clinical trials, bacterial delivery systems face challenges in practical clinical applications. These include scaling up production, ensuring bacterial survival during drug delivery, precise control of bacterial colonization, dosage determination, and addressing potential biosafety concerns. Researchers are actively exploring biological and chemical engineering strategies to broaden the application scope of bacterial-based drug delivery systems in biomedical science [139].

5.2.5. Bioparticle Delivery Carrier

Bioparticle delivery carriers encompass a diverse array of biological particles, prominently virus-like particles (VLPs), which have emerged as effective vehicles for RNA delivery. VLPs leverage viral structural proteins that naturally interact with RNA packaging signals (PS), facilitating the transfer of RNA between cells. However, their specificity for RNA molecules, particularly retroviruses like HIV-1, can be enhanced through strategies such as fusing RNA binding proteins or incorporating specific recognition sequences, though this may impact VLP assembly and secretion processes.

An innovative approach highlighted by Segel et al. involves utilizing the endogenous protein PEG10 to form VLPs from human cells. PEG10 selectively binds and promotes the vesicular secretion of its mRNA, allowing for the encapsulation and delivery of specific RNAs in a system termed selective endogenous cell delivery encapsulation (SEND). This method, derived from human viruses, minimizes immune responses compared to traditional virus vectors and lipid nanoparticles, demonstrating efficient gene editing tool delivery in both mouse and human cells [151].

Furthermore, bioparticle systems extend to endosymbiotic bacteria, which have evolved complex delivery systems such as extracellular contraction injection systems (eCISs). These syringe-like macromolecular complexes, exemplified by the Photorhabdus virulence cassette (PVC), can inject proteins into host eukaryotic cells. Kreitz et al. explored the potential of PVC systems for delivering various proteins into human and mouse cells, suggesting applications in gene therapy, nucleic acid delivery, and biological control [153].

The evolution of biomimetic drug delivery systems integrates biological carriers with functional agents, inheriting superior properties from natural carriers while enhancing permeability, carrying capacity, and specificity through modification [154]. Challenges remain in elucidating their in vivo mechanisms, refining in vitro modification techniques, and addressing issues like drug loading impact and the separation/purification of cell membranes [155]. Mixed cell membrane systems, noted for their extended circulation times and active targeting properties, represent a promising direction in this field [156].

As research progresses, biomimetic drug delivery systems are poised to offer efficient and targeted delivery solutions, advancing therapeutic applications across various biomedical disciplines.

6. Coupling Targeted Drug Delivery Systems

In recent years, targeted drug delivery technologies have seen significant advancements, with antibody-drug conjugates (ADCs) emerging as a forefront approach. ADCs combine a targeting antibody with a drug molecule via a linker chain, creating a sophisticated therapeutic agent capable of delivering drugs specifically to tumor sites. The antibodies serve as vehicles, binding with high specificity to tumor-associated antigens, thereby directing the drug payload precisely where it's needed. This targeted approach enhances therapeutic efficacy while reducing systemic side effects compared to traditional chemotherapy alone.

Currently, the U.S. Food and Drug Administration (FDA) has approved 13 ADCs for treating various blood cancers and solid organ tumors (Table 2) [157]. For instance, CD276 has been identified as a promising target for cancer treatment. Feng et al. developed a fully human CD276 monoclonal antibody-drug conjugate that significantly enhances the therapeutic index, providing an advanced platform for selective targeting of solid tumors [158]. Similarly, Xu et al. designed a novel ADC targeting trophoblast cell-surface antigen 2 (TROP2) for treating TROP2-positive pancreatic cancer [159].

The integration of ADCs into clinical practice marks a pivotal advancement in cancer therapy, demonstrating improved treatment outcomes through precise targeting and enhanced therapeutic efficacy. As research continues, ADCs hold promise for expanding the scope of targeted therapies across various types of cancers.

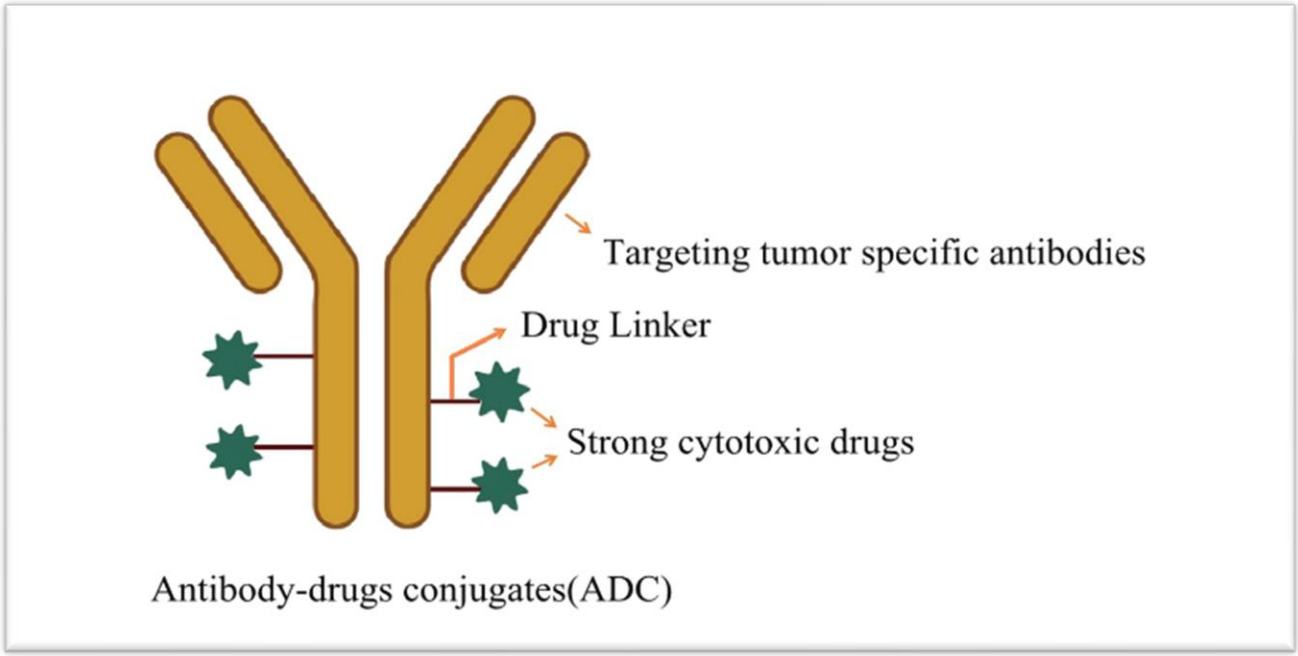

Figure 5. The coupled targeted delivery technology represented by antibody–drug conjugates (ADC)

Table 2. FDA approved ADCs (Antibody-Drug Conjugates):

Generic Name	Trade Name	Target	Payload/Payload Class	Payload Action	Approval Year
Mirvetuximab soravtansine	ELAHERE	FRα	Maytansinoid DM4	Folate receptor alpha	2022
Tisotumab vedotin-tftv	Tivdak	Tissue factor	MMAE/auristatin microtubule inhibitor	2021	2021
Loncastuximab tesirine-lpyl	Zynlonta	CD19	SG3199/PBD dimer DNA cleavage	2021	2021

Belantamab mafodotin-blmf	Blenrep	BCMA	MMAF/auristatin microtubule inhibitor	2020, withdrawn in 2022	2020
Sacituzumab govitecan	Trodelvy	TROP2	SN-38/camptothecin TOP1 inhibitor	2020	2020
Trastuzumab deruxtecan	Enhertu	HER2	DXd/camptothecin TOP1 inhibitor	2019	2019
Enfortumab vedotin	Padcev	Nectin4	MMAE/auristatin microtubule inhibitor	2019	2019
Polatuzumab vedotin-piiq	Polivy	CD79	MMAE/auristatin microtubule inhibitor	2019	2019
Moxetumomab pasudotox	Lumoxiti	CD22	PE38 (Pseudotox)	2018	2018
Inotuzumab ozogamicin	Besponsa	CD22	ozogamicin/calicheamicin DNA cleavage	2017	2017
Trastuzumab emtansine	Kadcyla	HER2	DM1/maytansinoid microtubule inhibitor	2013	2013
Brentuximab vedotin	Adcetris	CD30	MMAE/auristatin microtubule inhibitor	2011	2011
Gemtuzumab ozogamicin	Mylotarg	CD33	ozogamicin/calicheamicin DNA cleavage	2017, 2000	2017, 2000

These ADCs utilize various targeting strategies and payloads to deliver therapeutic agents specifically to cancer cells, highlighting the diversity and innovation in targeted drug delivery technologies. Here's a breakdown of the key technologies mentioned:

1. **GalNAc Conjugation**: Originally pioneered by Alnylam Pharmaceuticals, GalNAc (N-acetylgalactosamine) conjugation has revolutionized small nucleic acid drug delivery systems. Modifications like O-hexadecyl (C16) have extended the reach beyond liver-targeted therapies, achieving gene knockout effects in organs like the central nervous system, eyes, and lungs for prolonged durations.
2. **ATTACK Technique**: Wang et al. developed the Active Tissue Targeting via Anchored Click Chemistry (ATTACK) technique, which leverages glycoside-containing azides (Ac4ManNAz) to selectively label and target cancer cells. This method enables precise delivery of toxins or therapeutic agents through click chemistry, enhancing specificity and efficacy in cancer treatment.
3. **CAPAC™ Platform**: Shaqi Biopharmaceuticals' Click Activated Protodrugs Against Cancer (CAPAC™) platform, represented by SQ3370, utilizes a tumor-localizing biopolymer coupled with a doxorubicin protodrug. This approach achieves controlled, tumor-specific drug release, showcasing potential for clinical applications.
4. **Peptide-Drug Conjugates (PDC)**: PDCs integrate peptide advantages such as small molecular weight, biodegradability, and low immunogenicity. Modification of the peptide chain enhances hydrophobicity, ionization, and cell permeability, overcoming challenges like poor solubility and metabolism issues. OPDC3, developed by Gong et al., exemplifies targeting cells with high peptidase activity, suggesting novel treatments for malignant tumors.
5. **Other Conjugated Drugs**: The summary also mentions various other conjugated drug technologies including Antibody-Cell Conjugates (ACC), Viral Drug Conjugates (VDC), Antibody Fragment Conjugates (FDC), Antibody Oligonucleotide Conjugates (AOC), Antibody Immunostimulatory Conjugates (ISAC), and Antibody Biopolymer Conjugates (ABC). These technologies expand the repertoire of drug delivery strategies, each tailored to specific therapeutic needs and conditions.

These advancements underscore the versatility and innovation in drug delivery systems, aiming to enhance efficacy, specificity, and safety in therapeutic interventions across various diseases and conditions.

7. Intelligent Drug Delivery System

key technologies and developments discussed:

7.1. Stimulus-Responsive Systems: These systems utilize various triggers such as pH, reactive oxygen species (ROS), enzymes, temperature, light, magnetic fields, ultrasound, electric pulse, and high-energy radiation to activate or enhance drug release. They enable on-demand drug delivery, enhancing precision and efficacy while minimizing off-target effects.

7.2. pH-Sensitive Systems: Leveraging the stomach's acidic environment, pH-sensitive drug delivery systems can remain dormant in the stomach and activate upon exposure to the less acidic environment of the intestines. This approach is particularly useful for targeted delivery to specific gastrointestinal sites.

7.3. Thermosensitive Systems: Temperature-sensitive polymers like PMEECL-b-POCTCL dissolve at specific temperatures, releasing drugs like Nile Red and doxorubicin. This technology is being explored for conditions where local heating can aid in drug release, such as in tumor environments.

7.4. Light-Responsive Systems: Chromophores such as azobenzene and indocyanine green (ICG) confer photosensitivity to drug delivery systems. These systems respond to near-infrared light, enabling controlled drug release with improved stability and targeted delivery, as demonstrated in photothermal and photodynamic therapy applications.

7.5. Magnetic-Responsive Systems: Utilizing Fe3O4 nanoparticles, magnetic-sensitive nanodelivery systems can precisely deliver drugs to targeted sites under the influence of magnetic fields. This approach shows promise for non-invasive and targeted drug delivery, particularly in cancer therapy.

7.6. Ultrasound-Responsive Systems: Ultrasound, when combined with microbubbles or nanoparticles, enhances drug delivery by transiently increasing vascular permeability and triggering drug release through thermal and mechanical effects. This method is effective in enhancing drug penetration and therapeutic efficacy in diseased tissues.

7.7. Engineered Cells: Engineered cells modulated by compounds like protocatechuic acid (PCA) demonstrate potential in regulating gene expression, controlling therapeutic systems like CRISPR-Cas9, and modulating insulin release. This approach offers a dynamic and responsive platform for therapeutic applications.

These intelligent drug delivery systems represent cutting-edge advancements in the field, aiming to improve therapeutic outcomes by overcoming traditional limitations in drug delivery such as systemic toxicity and lack of specificity. Each technology offers unique advantages tailored to specific therapeutic needs, paving the way for more effective and personalized treatment strategies in medicine.

8. Conclusions

In recent decades, drug delivery systems (DDSs) have undergone significant evolution, moving from macro- to nanoscale technologies and advancing towards intelligent, targeted delivery mechanisms. This review highlights the latest advancements in DDS technologies, particularly in nanoscale drug delivery systems utilizing a variety of materials, including organic, inorganic, and hybrid substances. These systems harness the unique properties of nanoparticles, such as size effects, volume effects, surface effects, and quantum effects, to improve drug solubility, stability, and targeting precision, thus showing great promise in biomedical applications.

Despite these advancements, several challenges remain. The complex interactions between nanocarriers and biological membranes, as well as the extracellular matrix, require further investigation. Additionally, addressing issues like cytotoxicity and immunogenicity necessitates

comprehensive nanotoxicological studies in animal models to evaluate pharmacokinetic and pharmacodynamic properties. Biological carriers derived from endogenous substances, retaining their structural and functional attributes, offer potential in minimizing immune responses. These carriers mimic the structures and actions of infectious agents or pathogens, enabling precise drug delivery to targeted sites, making them a promising avenue for DDS.

Integration of DDS with innovative technologies such as microfluidics, 3D printing, CRISPR-Cas9, and quantum sensing holds potential for future advancements. However, these approaches are largely conceptual, and current FDA-approved DDSs (Table 4) highlight the practical limitations and the need for extensive research and clinical trials to optimize efficacy for broader clinical applications. Combining multiple DDS strategies, considering factors like toxicity, adverse effects, administration mode, and dosage, could enhance therapeutic outcomes. For instance, intelligent nanocarrier-based systems capable of dynamically adjusting drug release in response to tumor microenvironment changes show promise in improving efficacy and reducing side effects. Synergistic use of multiple DDS may pave the way for innovative therapeutic strategies with broader clinical impact compared to single-system approaches.

Table 3. FDA-approved DDSs and their significant drugs:

DDS	Trade Name	Significance	Year
Spansule technology	Spansule®	First 12-hour release technology	1952
Polymer	Lupron Depot®	Long-acting injectable PLGA polymer formulation	1989
Nanoparticles	Abraxane®	Drug-polymer composite nanoparticles	2005
Liposomes	Doxil®	PEGylated liposome	1995
Lipid-based nanoparticles	Onpattro®	Delivery of siRNA	2018
Lipid-based nanoparticles	Comirnaty®	COVID-19 vaccine	2021
Nanocrystal	Rapamune®	Nanocrystal formulation	2000
Antibody-Drug Conjugate (ADC)	Mylotarg®	Antibody-drug conjugate	2009

This table highlights various DDS technologies approved by the FDA along with their notable drugs and the year of approval.

REFERENCES

1. Vargason, A.M., Anselmo, A.C., & Mitragotri, S. (2021). The evolution of commercial drug delivery technologies. *Nature Biomedical Engineering, 5*(10), 951–967. https://doi.org/10.1038/s41551-021-00763-6
2. Enrique, N., Alberto, O., Antonio, J., Bravo, I., & Alonso-Moreno, C. (2021). Polyester polymeric nanoparticles as platforms in the development of novel nanomedicines for cancer treatment. *Cancers, 13*(13), 3387. https://doi.org/10.3390/cancers13133387
3. Huang, P., Wang, X., Liang, X., Yang, J., Zhang, C.N., Kong, D.L., & Wang, W.W. (2019). Nano-, micro-, and macroscale drug delivery systems for cancer immunotherapy. *Acta Biomaterialia, 85*, 1–26. https://doi.org/10.1016/j.actbio.2018.12.027
4. Su, X., Cao, Y., Liu, Y., Ouyang, B.S., Ning, B., Wang, Y., Guo, H.S., Pang, Z.Q., & Shen, S. (2021). Localized disruption of redox homeostasis boosting ferroptosis of tumor by hydrogel delivery system. *Materials Today Bio, 12*, 100154. https://doi.org/10.1016/j.mtbio.2021.100154
5. Abolfazl, A., Rogaie, R., Soodabeh, D., Joo, S.W., Zarghami, N., Hanifehpour, Y., Samiei, M., Kouhi, M., & Nejati-Koshki, K. (2013). Liposome: Classification, preparation, and applications. *Nanoscale Research Letters, 8*, 102. https://doi.org/10.1186/1556-276X-8-102
6. Jesorka, A., & Orwar, O. (2008). Liposomes: Technologies and analytical applications. *Annual Review of Analytical Chemistry, 1*, 801–832. https://doi.org/10.1146/annurev.anchem.1.031207.112905

7. Kisak, E.T., Coldren, B., Evans, C.A., Boyer, C., & Zasadzinski, J.A. (2004). The vesosome—A multicompartment drug delivery vehicle. *Current Medicinal Chemistry, 11*(2), 199–219. https://doi.org/10.2174/0929867043364948
8. Lian, T., & Ho, J. (2001). Trends and developments in liposome drug delivery systems. *Journal of Pharmaceutical Sciences, 90*(5), 667–680. https://doi.org/10.1002/jps.10351
9. Peyman, A., Ahmad, M., Nahid, S., & Abastabar, M. (2021). Nanoliposome-loaded antifungal drugs for dermal administration: A review. *Current Medical Mycology, 7*(2), 71–78. https://doi.org/10.18502/cmm.7.2.5435
10. Francian, A., Widmer, A., Olsson, T., Ramirez, M., Heald, D., Rasic, K., Adams, L., Martinson, H., & Kullberg, M. (2021). Delivery of toll-like receptor agonists by complement C3-targeted liposomes activates immune cells and reduces tumor growth. *Journal of Drug Targeting, 29*(7), 754–760. https://doi.org/10.1080/1061186X.2021.1907355
11. Park, S.J. (2020). Protein-nanoparticle interaction: Corona formation and conformational changes in proteins on nanoparticles. *International Journal of Nanomedicine, 15*, 5783–5802. https://doi.org/10.2147/IJN.S256029
12. Yu, B., Goel, S., Ni, D.L., Ellison, P.A., Siamof, C.M., Jiang, D.W., Cheng, L., Kang, L., Yu, F.Q., Liu, Z., et al. (2018). Reassembly of 89Zr-labeled cancer cell membranes into multicompartment membrane derived liposomes for PET-trackable tumor-targeted theranostics. *Advanced Materials, 30*(10), 1704–1734. https://doi.org/10.1002/adma.201705435
13. Jose, S., Anju, S.S., Cinu, T.A., Aleykutty, N.A., Thomas, S., & Souto, E.B. (2014). In vivo pharmacokinetics and biodistribution of resveratrol-loaded solid lipid nanoparticles for brain delivery. *International Journal of Pharmaceutics, 474*(1–2), 6–13. https://doi.org/10.1016/j.ijpharm.2014.07.046
14. Zhao, Y., Hou, X.X., Chai, J.S., Zhang, Z.Z., Xue, X., Huang, F., Liu, J.F., Shi, L.Q., & Liu, Y. (2022). Stapled liposomes enhance cross-priming of radio-immunotherapy. *Advanced Materials, 34*(8), 2107–2121. https://doi.org/10.1002/adma.202104974
15. Wu, T.Y., Gong, Y.C., Li, Z.L., Li, Y.P., & Xiong, X.Y. (2020). Application of nanoparticle-based co-delivery strategies for cancer therapy. *Materials Reports, 34*, 516–522. https://doi.org/10.1016/j.matrep.2020.09.008
16. Bo, R.N., Dai, X.R., Huang, J., Wei, S.M., Liu, M.J., & Li, J.G. (2020). Evaluation of optimum conditions for decoquinate nanoliposomes and their anticoccidial efficacy against diclazuril-resistant Eimeria tenella infections in broilers. *Veterinary Parasitology, 283*, 109186. https://doi.org/10.1016/j.vetpar.2020.109186
17. Lakkadwala, S., Rodrigues, B.D., Sun, C.W., & Singh, J. (2019). Dual functionalized liposomes for efficient co-delivery of anti-cancer chemotherapeutics for the treatment of glioblastoma. *Journal of Controlled Release, 307*, 247–260. https://doi.org/10.1016/j.jconrel.2019.06.013
18. Sanjeet, B. (2023). WHO's global tuberculosis report 2022. *The Lancet Microbe, 4*(2), e20. https://doi.org/10.1016/S2666-5247(22)00013-1
19. Ferraz-Carvalho, R.S., Pereira, M.A., Linhares, L.A., Lira-Nogueira, M.C.B., Cavalcanti, I.M.F., Santos-Magalhaes, N.S., & Montenegro, L.M.L. (2016). Effects of the encapsulation of usnic acid into liposomes and interactions with antituberculous agents against multidrug-resistant tuberculosis clinical isolates. *Memórias do Instituto Oswaldo Cruz, 111*(5), 330–334. https://doi.org/10.1590/0074-02760160085
20. Ambati, S., Pham, T., Lewis, Z.A., Lin, X., & Meagher, R.B. (2021). DC-SIGN targets amphotericin B-loaded liposomes to diverse pathogenic fungi. *Fungal Biology and Biotechnology, 8*, 22. https://doi.org/10.1186/s40694-021-00136-7
21. Cheng, Q., Wei, T., Farbiak, L., Johnson, L.T., Dilliard, S.A., & Siegwart, D.J. (2020). Selective organ targeting (SORT) nanoparticles for tissue-specific mRNA delivery and CRISPR-Cas gene editing. *Nature Nanotechnology, 15*(4), 313–320. https://doi.org/10.1038/s41565-020-0676-8
22. Wang, X., Liu, S., Sun, Y.H., Yu, X.L., Lee, S.M., Cheng, Q., Wei, T., Gong, J.Y., Robinson, J., Zhang, D., et al. (2023). Preparation of selective organ-targeting (SORT) lipid nanoparticles

(LNPs) using multiple technical methods for tissue-specific mRNA delivery. *Nature Protocols, 18*(1), 265–291. https://doi.org/10.1038/s41596-022-00654-2

23. Liu, S., Cheng, Q., Wei, T., Yu, X.L., Johnson, L.T., Farbiak, L., & Siegwart, D.J. (2023). Design principles and components of organ-specific SORT LNPs for mRNA delivery to the liver, heart, kidney, and lung. *Advanced Drug Delivery Reviews, 179*, 114056. https://doi.org/10.1016/j.addr.2022.114056
24. Raza, A., Hayat, U., Rasheed, T., Bilal, M., Iqbal, H.M.N., & Asghar, M.A. (2022). pH-sensitive nanocarriers in drug delivery: From synthesis to clinical applications. *Nanomaterials, 12*(5), 961. https://doi.org/10.3390/nano12050961
25. Zhang, C., Wang, J., Deng, X., Shen, L., Zhang, J., Hou, Y., & Shi, Y. (2020). Enzyme-sensitive liposomes for anticancer drug delivery. *Asian Journal of Pharmaceutical Sciences, 15*(4), 400–414. https://doi.org/10.1016/j.ajps.2020.04.009
26. Taneja, G., Sud, S., & Bijjem, K.R.V. (2021). Liposomal drug delivery systems—A comprehensive review. *International Journal of Pharmaceutical Sciences and Research, 12*(5), 2156–2171. https://doi.org/10.13040/IJPSR.0975-8232.12(5).2156-71
27. Al-Jamal, W.T., Al-Jamal, K.T., Bomans, P.H.H., Frederik, P.M., Kostarelos, K., & Kostarelos, K. (2009). Functionalized-quantum-dot-liposome hybrids as multimodal nanoparticles for cancer. *Small, 5*(11), 1406–1415. https://doi.org/10.1002/smll.200900189
28. You, J.O., Auguste, D.T., & Kabanov, A.V. (2008). Synthesis and drug delivery. *Nature Reviews Drug Discovery, 7*(12), 1093–1094. https://doi.org/10.1038/nrd2731
29. Haque, S., & Whittaker, M.R. (2020). Nanoformulations for the treatment of neurodegenerative disorders. *Nano Today, 35*, 100946. https://doi.org/10.1016/j.nantod.2020.100946
30. Roney, C., Kulkarni, P., Arora, V., Antich, P., Bonte, F., Wu, A., & Mallikarjuana, N.N. (2005). Targeted nanoparticles for drug delivery through the blood–brain barrier for Alzheimer's disease. *Journal of Controlled Release, 108*(2–3), 193–214. https://doi.org/10.1016/j.jconrel.2005.07.034
31. Smith, R.A., & Porteous, C.M. (2008). GMP and clinical trials—What are the requirements for investigational new drug (IND) applications? *Therapeutic Innovation & Regulatory Science, 42*(5), 494–502. https://doi.org/10.1177/009286150804200506
32. Avramescu, R.G., Bedwell, D.M., Farin, F.M., Wong, E.S., Keeling, K.M., & Lopes-Pacheco, M. (2023). Combination therapies for cystic fibrosis lung disease: Improving current treatments for the future. *Frontiers in Pharmacology, 14*, 1038. https://doi.org/10.3389/fphar.2023.1038
33. Torabizadeh, S., Sajjadi, M., Alizadeh, A.M., & Shamsasenjan, K. (2018). Comprehensive review on mesenchymal stem cell growth conditions: The Good Manufacturing Practice requirements and their application in cell therapy. *Stem Cell Reviews and Reports, 14*(5), 833–848. https://doi.org/10.1007/s12015-018-9823-1
34. Bangham, A.D., Horne, R.W., & Glauert, A.M. (1962). Action of saponin on biological cell membranes. *Nature, 196*, 952–955. https://doi.org/10.1038/196952a0
35. Fenton, O.S., Olafson, K.N., Pillai, P.S., Mitchell, M.J., Langer, R., & Mitragotri, S. (2018). Immunotherapy applications of non-viral nanoparticles. *Advanced Drug Delivery Reviews, 114*, 240–255. https://doi.org/10.1016/j.addr.2017.05.008
36. Moon, J.J., Huang, B., Irvine, D.J., & Moon, J.J. (2012). Engineering nano- and microparticles to tune immunity. *Advanced Materials, 24*(28), 3724–3746. https://doi.org/10.1002/adma.201200446
37. Bobo, D., Robinson, K.J., Islam, J., Thurecht, K.J., & Corrie, S.R. (2016). Nanoparticle-based medicines: A review of FDA-approved materials and clinical trials to date. *Pharmaceutical Research, 33*(10), 2373–2387. https://doi.org/10.1007/s11095-016-1958-5
38. Anselmo, A.C., & Mitragotri, S. (2016). Nanoparticles in the clinic: An update. *Bioengineering & Translational Medicine, 1*(1), 10–29. https://doi.org/10.1002/btm2.10003
39. Hrkach, J., Von Hoff, D., Mukkaram Ali, M., Andrianova, E., Auer, J., Campbell, T., De Witt, D., Figa, M., Figueiredo, M., Horhota, A., et al. (2012). Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological

profile. *Science Translational Medicine, 4*(128), 128ra39. https://doi.org/10.1126/scitranslmed.3003651
40. Gref, R., Minamitake, Y., Peracchia, M.T., Trubetskoy, V., Torchilin, V., & Langer, R. (1994). Biodegradable long-circulating polymeric nanospheres. *Science, 263*(5153), 1600–1603. https://doi.org/10.1126/science.8128245
41. Ernsting, M.J., Murakami, M., Roy, A., Li, S.D., & Ernsting, M.J. (2013). Factors controlling the pharmacokinetics, biodistribution and intratumoral penetration of nanoparticles. *Journal of Controlled Release, 172*(3), 782–794. https://doi.org/10.1016/j.jconrel.2013.09.013
42. Jain, R.K., Stylianopoulos, T., & Munn, L.L. (2014). Lessons from physics: Understanding the biology of intratumoral transport for improved cancer drug delivery. *Nature Reviews Clinical Oncology, 12*(7), 385–390. https://doi.org/10.1038/nrclinonc.2015.83
43. Stylianopoulos, T., Martin, J.D., Chauhan, V.P., Jain, S.R., Diop-Frimpong, B., Bardeesy, N., Smith, B.L., Ferrone, C.R., Hornicek, F.J., Boucher, Y., et al. (2012). Causes, consequences, and remedies for growth-induced solid stress in murine and human tumors. *Proceedings of the National Academy of Sciences, 109*(38), 15101–15108. https://doi.org/10.1073/pnas.1213353109
44. Peer, D., Karp, J.M., Hong, S., Farokhzad, O.C., Margalit, R., & Langer, R. (2007). Nanocarriers as an emerging platform for cancer therapy. *Nature Nanotechnology, 2*(12), 751–760. https://doi.org/10.1038/nnano.2007.387
45. Davis, M.E., Chen, Z.G., & Shin, D.M. (2008). Nanoparticle therapeutics: An emerging treatment modality for cancer. *Nature Reviews Drug Discovery, 7*(9), 771–782. https://doi.org/10.1038/nrd2614
46. Parveen, S., Sahoo, S.K., & Sahoo, S.K. (2008). Nanomedicine: Clinical applications of polyethylene glycol conjugated proteins and drugs. *Clinical Pharmacokinetics, 47*(1), 3–7. https://doi.org/10.2165/00003088-200847010-00002
47. Jokerst, J.V., Lobovkina, T., Zare, R.N., & Gambhir, S.S. (2011). Nanoparticle PEGylation for imaging and therapy. *Nanomedicine (London, England), 6*(4), 715–728. https://doi.org/10.2217/nnm.11.19
48. Allen, T.M., & Cullis, P.R. (2013). Liposomal drug delivery systems: From concept to clinical applications. *Advanced Drug Delivery Reviews, 65*(1), 36–48. https://doi.org/10.1016/j.addr.2012.09.037
49. Torchilin, V.P. (2005). Recent advances with liposomes as pharmaceutical carriers. *Nature Reviews Drug Discovery, 4*(2), 145–160. https://doi.org/10.1038/nrd1632
50. Gabizon, A., Shmeeda, H., & Barenholz, Y. (2003). Pharmacokinetics of pegylated liposomal Doxorubicin: Review of animal and human studies. *Clinical Pharmacokinetics, 42*(5), 419–436. https://doi.org/10.2165/00003088-200342050-00002
51. Goren, D., Horowitz, A.T., Tzemach, D., Tarshish, M., Zalipsky, S., & Gabizon, A. (2000). Nuclear delivery of doxorubicin via folate-targeted liposomes with bypass of multidrug-resistance efflux pump. *Clinical Cancer Research, 6*(5), 1949–1957. https://clincancerres.aacrjournals.org/content/6/5/1949.long
52. Barenholz, Y. (2012). Doxil®—The first FDA-approved nano-drug: Lessons learned. *Journal of Controlled Release, 160*(2), 117–134. https://doi.org/10.1016/j.jconrel.2012.03.020
53. Park, K. (2007). Synthesis and functionalization of silica nanoparticles for targeted drug delivery. *Applications of Nanoscience in Drug Delivery, 1*(1), 57–69. https://doi.org/10.1201/9781420003443.ch4
54. Foy, S.P., Manthe, R.L., Foy, S.T., Dimitrijevic, S., & Krishnamurthy, N. (2010). Lab-on-a-chip compatibility and synchronous impedance monitoring of porous silicon photonic crystal particles during electrokinetic trapping and transport. *Electrophoresis, 31*(5), 828–835. https://doi.org/10.1002/elps.200900427
55. He, S.; Zhang, L.; Bai, S.; Yang, H.; Cui, Z.; Zhang, X.; Li, Y. Advances of molecularly imprinted polymers (MIP) and the application in drug delivery. Eur. Polym. J. 2021, 143, 110179.

56. Hemmati, K.; Masoumi, A.; Ghaemy, M. Tragacanth gum-based nanogel as a superparamagnetic molecularly imprinted polymer for quercetin recognition and controlled release. Carbohydr. Polym. 2016, 136, 630–640.
57. Kim, K.S.; Suzuki, K.; Cho, H.; Youn, Y.S.; Bae, Y.H. Oral nanoparticles exhibit specific high-efficiency intestinal uptake and lymphatic transport. ACS Nano 2018, 12, 8893–8900.
58. Kaur, J.; Mishra, V.; Singh, S.K.; Gulati, M.; Kapoor, B.; Chellappan, D.K.; Gupta, G.; Dureja, H.; Anand, K.; Dua, K.; et al. Harnessing amphiphilic polymeric micelles for diagnostic and therapeutic applications: Breakthroughs and bottlenecks. J. Control. Release 2021, 334, 64–95.
55. Ghezzi, M.; Pescina, S.; Padula, C.; Santi, P.; Del Favero, E.; Cantù, L.; Nicoli, S. Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. J. Control. Release 2021, 332, 312–336.
56. Hwang, D.; Ramsey, D.; Kabanov, V. Polymeric micelles for the delivery of poorly soluble drugs: From nano-formulation to clinical approval. Adv. Drug Deliv. Rev. 2020, 156, 80–118.
57. Owens, E.; Peppasn, A. Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles. Int. J. Pharm. 2006, 307, 93–102.
58. Albayaty, Y.N.; Thomas, N.; Ramirez-Garcia, P.D.; Davis, T.P.; Quinn, J.F.; Whittaker, M.R.; Prestidge, C.A. pH-Responsive copolymer micelles to enhance itraconazole efficacy against Candida albicans biofilms. J. Mater. Chem. 2020, 8, 1672–1681.
59. Mitchell, D.; Ronghui, Q. Polymer micelles for the protection and delivery of specialized proresolving mediators. Eur. J. Pharm. Biopharma. 2023, 184, 159–169.
60. Zhang, X.; Xu, X.Y.; Wang, X.Y.; Lin, Y.J.; Zheng, Y.L.; Xu, W.; Liu, J.; Xu, W. Hepatoma-targeting and reactive oxygen species-responsive chitosan-based polymeric micelles for delivery of celastrol. Carbohydr. Polym. 2023, 303, 120439.
61. Zhang, C.; Nance, E.A.; Mastorakos, P.; Chisholm, J.; Berry, S.; Eberhart, C.; Tyler, B.; Brem, H.; Suk, J.S.; Hanes, J. Convection enhanced delivery of cisplatin-loaded brain penetrating nanoparticles cures malignant glioma in rats. J. Control. Release 2017, 263, 112–119.
62. Hu, Q.Y.; Gao, X.L.; Gu, G.Z.; Rang, T.; Tu, Y.F.; Liu, Z.Y.; Song, Q.X.; Yao, L.; Pang, Z.Q.; Jiang, X.G.; et al. Glioma therapy using tumor homing and penetrating peptide-functionalized PEG-PLA nanoparticles loaded with paclitaxel. Biomaterials 2013, 34, 5640–5650.
63. Zeng, L.J.; Zou, L.L.; Yu, H.J.; He, X.Y.; Cao, H.Q.; Zhang, Z.W.; Yin, Q.; Zhang, P.C.; Gu, W.W.; Chen, L.L.; et al. Treatment of malignant brain tumor by tumor-triggered programmed wormlike micelles with precise targeting and deep penetration. Adv. Funct. Mater. 2016, 26, 4201–4212.
64. Yu, L.L.; Bao, H.C. Research on the application of micelles in traditional Chinese medicine preparations. Shandong Chem. Ind. 2018, 47, 58–60.
65. Gao, W.W.; Zhang, Y.; Zhang, Q.Z.; Zhang, L.F. Nanoparticle-hydrogel: A hybrid biomaterial system for localized drug delivery. Ann. Biomed. Eng. 2016, 44, 2049–2061.
66. Wang, Y.F.; Chen, W.; Wang, Z.; Zhu, Y.; Zhao, H.X.; Wu, K.; Wu, J.; Zhang, W.H.; Zhang, Q.; Guo, H.Q.; et al. NIR-II light powered asymmetric hydrogel nanomotors for enhanced immunochemotherapy. Angew. Chem. Int. Ed. Engl. 2023, 62, e202212866.
67. Li, S.S.; Li, X.Y.; Xu, Y.D.; Fan, C.R.; Li, Z.A.; Zheng, L.; Luo, B.C.; Li, Z.P.; Lin, B.F.; Zha, Z.G.; et al. Collagen fibril-like injectable hydrogels from self-assembled nanoparticles for promoting wound healing. Bioact. Mater. 2024, 32, 149–163.
68. Sun, L.L.; Shen, F.Y.; Tian, L.L.; Tao, H.Q.; Xiong, Z.J.; Xu, J.; Liu, Z. ATP-responsive smart hydrogel releasing immune adjuvants synchronized with repeated chemotherapy or radiotherapy to boost antitumor immunity. Adv. Mater. 2021, 33, e2007910.
69. Gao, Y.; Ji, H.; Peng, L.; Gao, X.; Jiang, S. Development of PLGA-PEG-PLGA hydrogel delivery system for enhanced immuno-reaction and efficacy of newcastle disease virus DNA vaccine. Molecules 2020, 25, 2505.
70. Shang, L.; Liu, J.; Wu, Y.T.; Wang, M.; Fei, C.Z.; Liu, Y.C.; Xue, F.Q.; Zhang, L.F.; Gu, F. Peptide supramolecular hydrogels with sustained Release Ability for Combating Multidrug-Resistant Bacteria. ACS Appl. Mater. Interfaces 2023, 15, 26273–26284.

71. Azad, A.; Al-Mahmood, S.M.A.; Chatterjee, B.; Sulaiman, W.M.A.W.; Elsayed, T.M.; Doolaanea, A. Encapsulation of black seed oil in alginate beads as a pH-sensitive carrier for intestine-targeted drug delivery: In vitro, in vivo and ex vivo study. Pharmaceutics 2020, 12, 219.
72. Li, J.; Liu, W.; Wang, J.; Li, J.; Liu, M.; Bo, R. Application prospect of new drug delivery system for oral administration. Prog. Vet. Med. 2023, 44, 121–126.
73. Adapun, S.; Ramakrishna, S. Controlled drug delivery systems: Current status and future directions. Molecules 2021, 26, 5905.
74. Ding, H.T.; Tan, P.; Fu, S.Q.; Tian, X.H.; Zhang, H.; Ma, X.L.; Gu, Z.W.; Luo, K. Preparation and application of pH-responsive drug delivery systems. J. Control. Release 2022, 348, 206–238.
75. Alshehri, S.; Imam, S.S.; Rizwanullah, M.; Akhter, S.; Mahdi, W.; Kazi, M.; Ahmad, J. Progress of cancer nanotechnology as diagnostics, therapeutics, and theranostics nanomedicine: Preclinical promise and translational challenges. Pharmaceutics 2020, 13, 24.
76. Zhao, L.P.; Zheng, R.R.; Liu, L.S.; Chen, X.Y.; Guan, R.; Yang, N.; Chen, A.; Yu, X.Y.; Cheng, H.; Li, S.Y. Self-delivery oxidative stress amplifier for chemotherapy sensitized immunotherapy. Biomaterials 2021, 275, 120970.
77. Gong, X.J.; Zhang, Q.Y.; Gao, Y.F.; Shuang, S.M.; Choi, M.M.F.; Dong, C. Phosphorus and nitrogen dual-doped hollow carbon dot as a nanocarrier for doxorubicin delivery and biological imaging. ACS Appl. Mater. Interfaces 2016, 8, 11288–11297.
78. Chen, L.; Zhou, L.L.; Wang, C.H.; Han, Y.; Lu, Y.L.; Liu, J.; Hu, X.C.; Yao, T.M.; Lin, Y.; Jin, Y. Tumor targeting based on the effect of enhanced permeability and retention (EPR) and the receptor-mediated mechanism on nano-drug delivery systems. Molecules 2018, 23, 2286.
79. Naskar, S.; Sharma, S.; Kuotsu, K. Stimuli-responsive hydrogels in drug delivery and tissue engineering. Drug Deliv. 2018, 25, 1791–1806.
80. Li, M.; Guo, D.; Wang, T.; Zhong, Z.; Zhang, M. Recent advances in pH-sensitive polymeric nanoparticles for drug delivery and cancer therapy. Cancer Biol. Med. 2021, 18, 1013–1032.
81. Guan, S.S.; Li, Z.; Zhang, Y.P.; Li, D.J.; Luo, Y.H.; Hu, D.D. A Review of Natural Polysaccharides for Drug Delivery Applications: Hot Spots and Progresses. Pharmaceutics 2021, 13, 1266.
82. Wu, J.L.; Duan, Y.M.; Li, Y.; Li, W.L.; Guo, C.Y.; Hu, G.H.; Li, X. A review on the effects of N-carboxyethyl chitosan (NCC) on drug delivery. Molecules 2021, 26, 5417.
83. Wu, L.L.; Wu, L.B.; Liu, Q.; Wu, F.; Yang, X.D.; Ma, X.C. Chitosan-based nanoparticles for cancer therapy. Curr. Drug Metab. 2019, 20, 804–812.
84. Rokhade, A.P.; Shelke, N.B.; Patil, S.A.; Aminabhavi, T.M. Novel interpenetrating polymer network microspheres of chitosan and methylcellulose for controlled release of theophylline. Carbohydr. Polym. 2007, 68, 218–228.
85. Farooq, M.A.; Snigdha, S.; Ranjan, S.; Akhtar, S.; Hasan, O.; Alhakamy, N.A.; Md, S.; Ahuja, A.; Panda, A.K.; Kushwah, V. Polymeric nanoparticles as a promising tool for drug delivery in the treatment of skin-related diseases. Int. J. Pharm. 2021, 610, 121178.
86. Khalid, I.; Shafiq, S.; Shah, S.A.A.; Ahmed, F.; Rehman, A.U.; Iqbal, J.; Baloch, M.K.; Muhammad, N. Chitosan-based nanocarriers for drug delivery applications. J. Pharm. Pharmacol. 2021, 73, 1049–1075.
87. Wang, S.; Zhang, X.L.; Shi, W.; Yang, S.Y.; Xing, X.; Zhao, Y.L.; Sun, Y.H.; Wang, X.Y.; Tang, L.H.; Yin, S.W. Optimization of amphiphilic cyclodextrin-based nanoparticles for effective delivery of anticancer drugs to solid tumors. Carbohydr. Polym. 2021, 274, 118580.
88. Verma, A.; Jain, A.; Tiwari, A.; Saraf, S.; Panda, P.K.; Agrawal, G.P. Approaches for assessing oral mucosal drug delivery systems: A comprehensive review. Int. J. Pharm. 2021, 596, 120207.
89. Liu, Z.F.; Jiao, Y.P.; Wang, Y.Y.; Zhou, C.L.; Zhang, Z.X. Polysaccharides-based nanoparticles as drug delivery systems. Adv. Drug Deliv. Rev. 2008, 60, 1650–1662.
90. Fathi, M.; Hajialyani, M.; Farzaei, M.H.; Echeverria, J.; Nabavi, S.M.; Bishayee, A.; Farzaei, F. Targeting cancer with phytochemicals via their fine-tuning modulation of the cell cycle. BioFactors 2019, 45, 745–763.
91. Yhee, J.Y.; Lee, S.; Kim, K.; Kwon, I.C. Progress in inorganic nanoparticles for therapeutic applications. J. Pharm. Investig. 2021, 51, 113–133.

92. Kostarelos, K.; Novoselov, K.S. Exploring the interface of graphene and biology. Science 2014, 344, 261–263.
93. Lin, L.S.; Cong, Z.X.; Cao, J.B.; Ke, K.M.; Peng, Q.L.; Gao, J.; Yang, H.H.; Liu, G.; Chen, X. Graphitic-phase C3N4 nanosheets as efficient photosensitizers and pH-responsive drug nanocarriers for cancer imaging and therapy. J. Mater. Chem. B 2014, 2, 1031–1037.
94. Gurunathan, S.; Kim, J.H. Synthesis, toxicity, biocompatibility, and biomedical applications of graphene and graphene-related materials. Int. J. Nanomedicine 2016, 11, 1927–1945.
95. Sanna, V.; Pala, N.; Dessì, G.; Manconi, P.; Mariani, A.; Dedola, S.; Rassu, G.; Crosio, C.; Iaccarino, C.; Sechi, M. Single-step green synthesis and characterization of graphene oxide-whey proteins nanocomposite for bioapplications. Colloids Surf. B Biointerfaces 2018, 167, 412–420.
96. Yang, K.; Feng, L.Z.; Shi, X.Z.; Liu, Z. Nano-graphene in biomedicine: Theranostic applications. Chem. Soc. Rev. 2013, 42, 530–547.