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Advancements in nano-based drug delivery systems for therapeutics: a comprehensive review

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In contemporary medicine, nano-based drug delivery systems (NDDS) have become a ground-breaking strategy, offering notable improvements in the regulated and targeted release of medicinal drugs. These systems use nanotechnology to reduce adverse effects, increase therapeutic efficacy, and improve medication absorption. In order to achieve certain drug release patterns and improve patient outcomes, recent developments have focused on the creation and optimization of nanoparticles, liposomes, dendrimers, and micelles, among other materials. With an emphasis on advancements in materials, formulation techniques, and targeting mechanisms, this paper reviews current developments in NDDS. In addition to their challenges, such as toxicity, scaling issues, and regulatory barriers, the potential applications of NDDS in the future, such as gene therapy, customized medicine, and several drug delivery systems, are also reviewed. The development of nanotechnology for drug delivery has enormous potential to transform treatment paradigms in a number of therapeutic domains, such as infectious diseases, cancer, and chronic illnesses.

1 Introduction

Natural ingredients have been used in healing since ancient times. However, many of them are still failing clinical trial stages. Among the causes are significant difficulties associated with the use of large materials in the delivery of medications, such as *in* vivo instability, lack of target-specific delivery, poor absorption, low solubility and bioavailability, and likely harmful consequences of drugs. Thus, the use of novel drug delivery methods that target certain medications may be a solution to these pressing problems.[1] Drug delivery methods have seen a revolution thanks to nanoparticles (NPs), which provide previously unheard of chances to enhance the potency, targeting, and controlled release of therapeutic agents. The pharmaceutical and medical sciences have seen a dramatic change with the discovery of nanoparticles as drug delivery vehicles. These particles, which are usually between 1 and 1000 nanometers in size, provide unmatched benefits in drug delivery systems, such as improved stability, targeted distribution, and controlled release.[2] Nanoparticles have several advantages over conventional drug delivery techniques because of their distinct size, large surface area, and capacity to alter their chemical and physical characteristics. With their diameters ranging from 1 to 100 nanometers, NPs can be designed to encapsulate a broad range of medications, from biologics to small compounds, allowing precise control over drug release kinetics, increased bioavailability, and better therapeutic results.[3] The precision provided by nanoparticle-based technologies makes it easier to create treatments that are suitable for particular diseases, reducing adverse effects and improving therapeutic results. Therefore, the constraints of conventional drug administration techniques may be addressed by nanoparticle drug delivery systems, particularly for complicated diseases such as cancer, viral infections, and genetic disorders.

In the field of medication delivery, nanoparticles may be engineered to target certain tissues or cells, minimizing adverse effects and improving treatment selectivity.

This is especially true for targeted antibacterial medicines, gene delivery, and cancer therapy. Moreover, the incorporation of multifunctional nanoparticles presents the possibility of concurrent diagnosis and treatment, an approach called theranostics, making them indispensable instruments in customized medicine.[4] Novel nano-based drug delivery systems (NDDS) seek to maximize medication absorption, reduce side effects, and improve therapeutic efficacy by using the special qualities of nanoscale materials. In order to improve patient outcomes, this review explores the latest advancements in the production and optimization of materials including nanoparticles, liposomes, dendrimers, and micelles. The problems that still exist in this area, such as toxicity, scalability, and regulatory barriers, are also discussed. The fascinating prospective applications of NDDS, such as gene therapy, tailored medication, and multidrug delivery systems, are also exam-

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ined. The ongoing development of nanotechnology has the potential to completely alter therapeutic approaches in a number of therapeutic domains, such as cancer, infectious diseases, and chronic diseases. By incorporating a new dimension, such as a synthesis of recent clinical trials and regulatory approvals that highlight translational progress, this work offers an updated and thorough overview of nano-based drug delivery systems. This review provides a more current and forward-looking picture of the changing NDDS landscape by fusing developments in materials science with clinical validation.

2 Types of nano-based drug delivery systems

The term "NDDS" refers to a broad range of nanomaterials that have been created to enable the controlled and targeted release of medications. Due to their variations in composition, structure, and mode of action, these materials can be used in a variety of therapeutic contexts. Table 1 lists different types of nano-based drug delivery systems, along with their descriptions, advantages, challenges, and applications. Fig. 1 illustrates drug delivery systems for the diagnosis of various diseases.

2.1 Nanoparticles

Nanoparticles are among the most widely studied types of NDDS. They can be composed of various materials, including lipids, polymers, metals, and ceramics, and can range in size from 1 to 1000 nanometers. Due to their small size, nanoparticles can easily penetrate biological barriers, such as the blood–brain barrier or tumor vasculature, and deliver drugs to targeted areas with high specificity.[5] Moreover, nanoparticles can be engineered to release their payload in response to external stimuli, such as pH, temperature, or enzyme activity, enabling controlled release over time.

Table 1 Different types of nano-based drug delivery systems: description, advantages, challenges and applications

Types of nano-based drug delivery systems	Description	Advantages	Challenges	Applications	Ref.
Nanoparticles	Solid, submicron-sized particles (1–1000 nm) used for drug encapsulation	High drug loading capacity, controlled release	Potential cytotoxicity and long-term safety concerns	Cancer therapy, gene therapy, protein delivery	34 and 35
Liposomes	Spherical vesicles composed of lipid bilayers that encapsulate drugs	Biocompatible, reduced drug toxicity, improved bioavailability	Drug leakage during storage or *in vivo* stability issues (fusion, oxidation of lipids)	Anticancer drugs, vaccines, antifungal drugs	36 and 37
Polymeric micelles	Amphiphilic copolymers that form nanometer-scale spherical structures in aqueous environments	Enhanced solubility of hydrophobic drugs, controlled release	Low drug loading for some hydrophobic drugs, instability upon dilution in blood	Chemotherapy, protein/peptide delivery	38 and 39
Dendrimers	Branched, tree-like macromolecules with functional surface groups for drug loading	High surface area, well-defined structure, controlled release	Cytotoxicity due to high surface charge (especially cationic), high cost of synthesis and purification	Gene delivery, drug targeting, imaging	40 and 41
Solid lipid nanoparticles (SLNs)	Lipid-based nanoparticles that are solid at room temperature and encapsulate drugs	Biodegradable, improved stability, controlled release	Low drug loading capacity (compared to polymers), aggregation tendency	Drug delivery, cosmetics, controlled release formulations	42 and 43
Nanoemulsions	Nano-sized emulsions (typically 20–200 nm) consisting of oil, water, and surfactants	High drug solubilization, enhanced bioavailability	Sensitivity to temperature and pH changes, limited drug loading capacity for hydrophilic drugs	Hydrophobic drug delivery, vaccines	44 and 45
Polymeric nanoparticles	Nanoparticles made of biocompatible polymers, which can load drugs and deliver them in a controlled manner	Versatile, biodegradability, tunable release profiles	Drug leakage or burst release, reduced circulation time due to clearance by the RES	Controlled release of chemotherapeutic agents, antibiotics	46 and 47
Nanocapsules	Nanoparticles with a core–shell structure where the drug is encapsulated inside a polymer shell	Protection of drugs from degradation, targeted delivery	Limited drug loading capacity for certain drugs, regulatory hurdles due to the lack of standardization	Targeted delivery	48 and 49
Gold nanoparticles	Metal nanoparticles (typically 1–100 nm) that are used to carry drugs or for targeted therapies	Easy functionalization, high surface area, targeting ability	Long-term accumulation and poor biodegradability, regulatory and safety concerns for clinical use	Cancer treatment, imaging, gene delivery	50 and 51
Carbon nanotubes	Cylindrical nanostructures made of carbon atoms, which can load drugs and penetrate cell membranes	High drug loading, stability, targeted drug delivery	Biocompatibility and toxicity concerns (especially pulmonary and hepatic toxicity), risk of accumulation in organs	Drug delivery, gene delivery, cancer therapy	52 and 53

Fig. 1 Drug delivery systems for the diagnosis of various diseases.

2.2 Liposomes

A potential class of drug delivery methods, liposomes improve the safety and therapeutic effectiveness of a variety of pharmacological drugs. The Greek words "lipos", which means fat, and "soma", which means body, are the roots of the word "liposome". This term refers to the body's structural elements, particularly phospholipid molecules.[6] A mesomorphic structure composed of lipid, phospholipid, and water molecules is referred to as a liposome. To increase the effectiveness of medications, nutraceuticals, and other bioactive substances, liposomes primarily include phospholipid molecules that entrap and release lipid soluble, amphiphilic materials as well as water-soluble components in a regulated way.[7] A liposome is a spherical vesicle that closely mimics cell membranes in structure and is made up of one or more phospholipid bilayers.[8] Liposomes have become effective drug delivery vehicles due to their capacity to encapsulate hydrophilic or lipophilic medications.[9] They are very helpful in the delivery of nucleic acids, antibiotics, and chemotherapeutic drugs. By halting premature medication release, liposomes can increase bioavailability, decrease toxicity, and improve drug solubility.[10] Using the increased permeability and retention effect, liposome based methods efficiently deliver therapeutic molecules to the locations of the disease, improving treatment efficacy.[11] By precisely directing molecules to affected cells or tissues, this particular administration reduces side effects and improves the effectiveness of treatment.[12] PEGylation, or the addition of polyethylene glycol (PEG) chains to liposomes, was introduced in the 1990s and greatly enhanced the pharmacokinetics and biocompatibility of these liposomes. PEGylation and other surface changes can help lengthen the period of circulation of liposomes in the bloodstream, facilitating more effective drug delivery to the intended location. In liposomal formulations, polyethylene glycol, chitosan, and polydopamine are the most often utilized polymers.[13] Liposomes' efficacy in treating cancer has prompted much research, and their unique properties such as their high entrapment efficiency of active ingredients, accessibility, and scalability in production make them intriguing drug delivery systems (DDS). The quick release of the active ingredient and the capacity to alter its surface, however, restrict their use. Research into liposomal formulations for mRNA vaccines, such the Pfizer-BioNTech and Moderna vaccines, which use lipid nanoparticles (like liposomes) to transport mRNA, was pushed in 2020 by the COVID-19 pandemic. Lipid-based vesicles known as "fusogenic liposomes" are made to fuse with biological membranes in order to transport their contents straight into a target cell or organelle. Under specific circumstances (such as pH changes, the presence of particular ions, or temperature shifts), these liposomes can fuse with cell membranes because they usually contain particular lipid compositions or alterations. Fusogenic liposomes are extensively studied and used in gene therapy, vaccine development, and medication delivery systems. Fusogenic liposomes are useful instruments in pharmaceutical and medical research because they provide a regulated and focused way to distribute medicinal compounds.

2.3 Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are lipid nanoparticles made with a solid matrix. These are created by using solid lipids to create oil-in-water nanoemulsions. Early in the 1990s, the first SLN generations were established.[14] Cheap raw ingredients, the use of physiological lipids, the avoidance of organic solvents, the simplicity of scale-up, good biocompatibility, increased bioavailability, protection of susceptible molds from environmental threats, and controlled drug release are some of the advantages of SLNs.[15] Recently, SLNs loaded with ciprofloxacin (CIP) with potent antibacterial activity were created by ultrasonic melt emulsification.[16] SLNs, which are made of solid lipids at body temperature, are more stable than liposomes, while still retaining their drug release and biocompatibility properties. Although their manufacturing scalability and surface modification for targeted delivery are still being studied, they offer great promise for controlled drug release over long periods of time. In comparison with a bromocriptine (BCR) solution, pharmacokinetic research showed that improved bromocriptine-loaded solid lipid nanoparticle (BCR-SLN) and bromocriptine-loaded nanostructured lipid carrier (BCR-NLC) formulations increase the drug's bioavailability in the plasma and brain. M. *et al.* reported that BCR-loaded lipid nanoparticles may be potential carriers as they can improve the drug's blood–brain barrier (BBB) penetration and contribute to the enhancement of BCR's bioavailability and therapeutic efficacy in the treatment of Parkinson's disease.[17]

2.4 Dendrimers

Dendrimers are highly branched tree-shaped macromolecules that have several benefits for drug delivery. By adhering to the ligands on their surface by straightforward ionic contact or chemical conjugation to the delivery system, dendrimers demon-

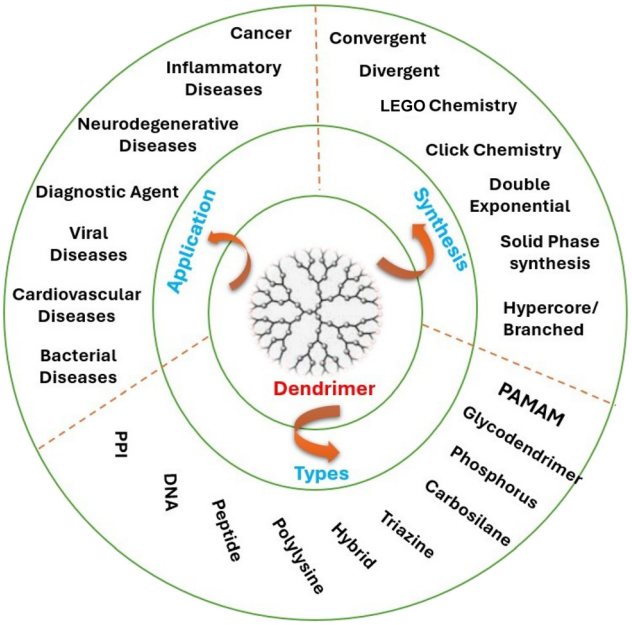

Fig. 2 Dendrimer applications, synthesis methods and types.

strate the potential to transport pharmaceuticals to the target region *via* a passive mechanism by improving penetration retention and active targeting.[18]Their exact drug loading is made possible by their well-defined structure, and adding functional groups or targeting ligands to their surface is simple. Dendrimers are unique globular, hyper-branched, three-dimensional nano-polymeric structures. These are distinguished from other nanosystems by appealing characteristics such water solubility, nanoscaled size, narrow polydispersity indices, changeable molecular structure, internal cavity, and several peripheral functional groups. Drug conjugation and targeting are made possible by terminal functionality. Additionally, these peripheral functional groups provide them customized qualities that increase their adaptability.[19] Polyamidoamine is the dendrimer that is most frequently studied for medication delivery.[20] The amine group initiates its synthesis by interacting with methyl acrylate and helping to generate two new dendrimer branches that are terminated by esters.[21] It is possible to create a "full-generation", amine-terminated dendrimer by amidating the methyl ester with ethylene diamine later on. Small compounds, proteins, and nucleic acids are among the medicinal substances that have been delivered by dendrimers.[22] They are perfect candidates for combination therapy because of their special design, which also enables controlled release and multiple-drug encapsulation. For transfection and bioimaging applications, CDs@PAMAM nanohybrids were created by self-assembling carbon dots (CDs) and G4–G6 PAMAM-NH2 dendrimers.[23] Fig. 2 shows various applications, synthesis methods and types of dendrimers.

2.5 Micelles

Micelles are self-assembled nanoparticles that are created when amphiphilic molecules group together in aqueous fluids. Poorly water-soluble medications can be encapsulated within the hydrophobic core of micelles, increasing their stability and solubility.

Micelles have been investigated for both passive and active targeting techniques and are especially helpful for the administration of hydrophobic medications, such as anticancer medicines. Ghezzi *et al*. reported that micelles are perfect for controlled release in certain conditions because of their capacity to react to variations in pH, temperature, or the presence of specific enzymes.[24] By adding ligands on their surface, micelles may be made to target certain cells or tissues, increasing drug delivery accuracy and minimizing adverse effects. Micelles are most commonly administered *via* intravenous (i.v.) injection/infusion (mostly used for chemotherapy),[25] although oral[26] and topical (ocular, nasal, buccal)[27] administration have also been shown to have highly intriguing outcomes in terms of enhanced drug bioavailability. Micelles reduce the systemic toxicity of medications by directing drug distribution to certain tissues or cells. This can lower the frequency of dosing and result in a longer-lasting therapeutic impact. Sun *et al.* reported that for the effective administration of topical ocular medications, PBA-CS-VE nanomicelles are a mucoadhesive option with improved transcorneal permeability and extended preocular retention.[28] In order to support gene therapy, micelles can also be employed to transport nucleic acids, such as DNA or RNA. Micelles are useful for treating chronic illnesses with extended pharmacological activity because of their controlled release characteristics. It can be difficult to produce micelle-based medication delivery devices on a large scale. One important area of research is ensuring that micelles stay intact in the body until they arrive at their destination. Micelle-based formulations need to be thoroughly tested for safety and effectiveness, just like any other novel drug delivery method. Micelles are often used and recognized colloidal particles in drug administration, and bCN micelles constitute a flexible, biocompatible oral drug delivery platform. Use of micelles is a promising drug delivery method, and research is being done to improve their stability, functioning, and targeting abilities. Fig. 3 illustrates the efficiency of future multifunctional nanocarriers.

2.6 Polymeric nanoparticles

Usually, manmade or natural polymers make up polymeric nanoparticles. Poly(lactic acid) (PLA), poly(lactic-*co*-glycolic acid) (PLGA), chitosan, and polyethylene glycol (PEG) are typical examples.[29] Their usual diameters range from 10 nm to 1000 nm, which enable them to be both large enough to encapsulate a sizable quantity of medicine and tiny enough to pass through blood arteries and infiltrate tissues. While hydrophilic medications can be attached to the surface or integrated into the shell, hydrophobic pharmaceuticals can be enclosed within the core of the nanoparticle. It is possible to design polymers to regulate the encapsulated drug's release. This may occur as a result of drug diffusion over time or deterioration of the polymer matrix. These biodegradable polymer-based nanoparticles are becoming more and more popular due to their

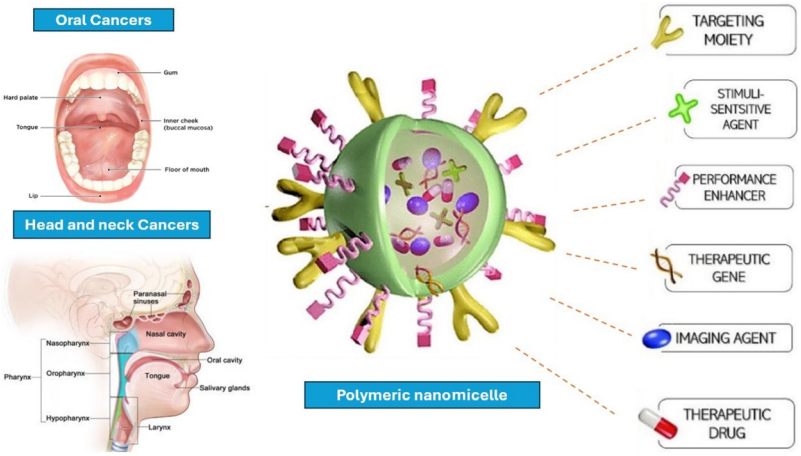

Fig. 3 Schematic illustration of future multi-functional nano-carriers.

biocompatibility and adjustable drug release patterns. Selvam *et al.* reported that when paired with polyethylene glycol (PEG), hydroxyapatite (HAp) provides increased osteoblastic potential, fracture toughness, mechanical characteristics, biocompatibility, and Young's modulus.[30] Because of their adaptability, polymeric nanoparticles may be customized for certain therapeutic uses, such gene therapy or cancer treatment. By shielding the antigens and guaranteeing their gradual release, polymeric nanoparticles can be used to deliver antigens in vaccinations, enhancing the immune response. Proteins or peptides that the body's enzymes could ordinarily break down can be delivered *via* polymers. Even while polymers like PLGA are biocompatible, some of their breakdown products might be harmful at larger doses or if they build up in particular organs. Polyethylene glycol (PLGA) NPs were used by Park *et al.*[31] to encapsulate adriamycin. In order to generate multifunctional carriers with improved capabilities, researchers are investigating hybrid systems that mix polymeric nanoparticles with other drug delivery methods (such as liposomes or micelles). The extremely hydrophobic curcumin was encapsulated in PLGA NPs by Szymusiak *et al.*,[32] which enhanced oral absorption and reduced the dosage of the medication required to produce similar amounts in mice's plasma and nervous system tissue following oral treatment by around twice as compared to unencapsulated curcumin. Bhattacharya assessed and reported docetaxel's and docetaxel-loaded polymeric nanoparticles' cellular uptake efficiency percentages and IC50 values in a variety of human cancer cell lines, including U-87 MG, HeLa, C2BBe1, HCT-116, NCI-N87, and NCI-H929-Luc-mCh-Puro.[33] However, difficulties in improving medication release and encapsulation continue to be major obstacles.

3 Formulation strategies and drug release mechanisms

The qualities of the medication, the intended therapeutic target, and the appropriate release profile must all be carefully taken into account while formulating novel nano-based drug delivery systems (NDDS). To maximize the release of medications from NDDS and guarantee their timely and effective delivery, a number of strategies have been used.

3.1 Controlled release systems

One of the most significant advantages of novel nano-based drug delivery systems (NDDS) is the ability to control the release of drugs over an extended period. Controlled release systems help maintain therapeutic drug levels within the body, minimizing fluctuations and reducing the risk of side effects. These systems can be designed to release drugs in a sustained or pulsatile manner, depending on the therapeutic needs. Polymeric nanoparticles can be engineered to distribute medications in a controlled and gradual manner. By lowering the frequency of dosing and minimizing peak plasma concentrations, this controlled release improves patient compliance. Table 2 shows a comparison between conventional and controlled drug delivery systems.

Table 2 Comparison between conventional and controlled drug delivery systems

Parameters	Conventional systems	Controlled release systems	Ref.
Blood level	Fluctuating	Constant for a period of time	54
Bioavailability	Poor	Better	55
Dosing	Frequent	Less	56
Absorption	Poor absorption	Controlled drug release	57
Premature metabolism	Frequent	Protected	58
Rate limiting step	Absorption	Drug release from dosage form	59
Release	Immediate release	Slow release after a time duration	60
Patient compliance	Poor	High	61

3.1.1 Stimuli-responsive systems. Drug delivery systems that are stimuli-responsive are made to release their payload in response to particular environmental signals, including variations in pH, temperature, or the presence of enzymes. Because tumors frequently have a lower pH than normal tissues, certain NDDS, for instance, are made to release medications only at the acidic pH of tumor tissues. This method lessens harm to healthy tissues while improving the treatment's specificity and efficacy. Improved cellular binding and internalization, more efficient drug perfusion throughout the tumor volume, and accelerated/triggered drug release at the target location can all result from drug delivery systems that use stimuli-responsive carriers, lipids, and/or prodrugs in the tumor milieu.[62] Known as "stimuli responsive materials" or "environmentally responsive materials", stimuli-based drug delivery systems incorporate the phenomenon that affects an activity at a specific place or target tissue to bring about beneficial actions for drug release *via* various processes.[63]

3.1.2 Targeting strategies. In order to reduce off-target effects and increase therapeutic efficacy, targeted medication delivery seeks to deliver therapeutic molecules precisely to sick tissues or cells. Therefore, the most popular tactic is to coat a particular targeted ligand or ligands on the surface of nanoparticles. Table 3 provides examples of NDDS designed for

Table 3 Targeted drug delivery systems (NDDS) with examples

Targeted drug delivery system	Targeting principle	Examples of NDDS developed	Ref.
Nanoparticles	The increased permeability and retention (EPR) effect is used; active targeting is possible by surface modification.	PLGA nanoparticles, chitosan nanoparticles, gold nanoparticles	67 and 68
Liposomes	Hydrophilic or hydrophobic medications are encapsulated in phospholipid vesicles, which can be PEGylated for extended circulation.	Doxil® (PEGylated liposomal doxorubicin), AmBisome® (liposomal amphotericin B)	69 and 70
Polymeric micelles	Hydrophobic medications can be dissolved using amphiphilic block copolymers, which self-assemble.	Genexol-PM® (paclitaxel loaded micelles)	71 and 72
Dendrimers	For drug conjugation, branching polymeric nanocarriers with many functional groups	PAMAM dendrimers loaded with methotrexate	73 and 74
Solid lipid nanoparticles (SLNs)	Poorly soluble medications are stabilized by a solid lipid core, allowing for regulated release.	SLN-based doxorubicin and curcumin carriers	75 and 76
Nanoemulsions	Nanosized emulsions of water in oil or oil in water improve solubility and bioavailability.	Cyclosporine nanoemulsion (Sandimmune®)	77 and 78
Nanocapsules	Drug reservoirs encapsulated in polymer shells are designed for continuous release	Poly(ε-caprolactone) nanocapsules	48 and 79
Gold nanoparticles (AuNPs)	Drug administration by photothermal and imaging guidance is made possible by surface plasmon resonance.	AuNPs loaded with doxorubicin, siRNA conjugates	80 and 81
Carbon nanotubes (CNTs)	Functionalized CNTs have a large surface area and can transport genes or medications into cells.	CNT–doxorubicin conjugates	82 and 83

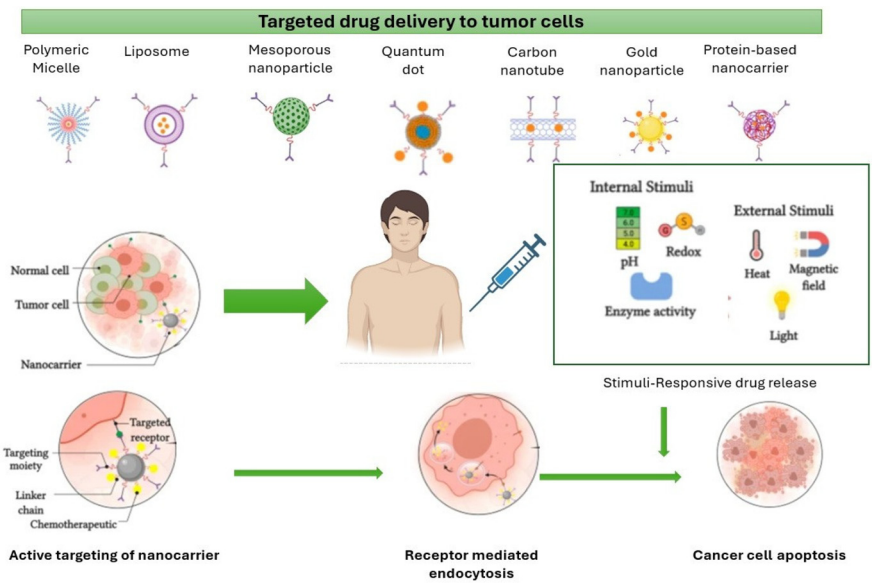

Fig. 4 Targeted drug delivery to tumor cells.

different targeted drug delivery methods. Targeted delivery has been accomplished using a variety of techniques, such as active targeting with surface modifications using ligands like peptides, antibodies, or small molecules that identify certain receptors on target cells and passive targeting with the increased permeability and retention (EPR) effect. It's possible that these targeted ligands lack the appropriate affinity and specificity.[64] For a variety of malignancies, such as EGFR-mutant non-small cell lung cancer and HER2-positive breast cancer, new targeted medicines are being developed.[65] Patients with mutations in genes like EGFR and ALK are benefiting from next generation tyrosine kinase inhibitors (TKIs), which provide more potent therapies with fewer adverse effects.[66] Fig. 4 presents a schematic diagram for targeted drug delivery to tumor cells.

4 Challenges in nano-based drug delivery systems

Although medication delivery methods using nanoparticles show promise, a number of obstacles prevent their broad clinical use.

4.1 Toxicity and biocompatibility

The possible toxicity of NDDS is one of the main issues. There are worries over the buildup of breakdown products over time, despite the fact that many of the polymers and components utilized in NDDS are biodegradable and biocompatible. These could be harmful or trigger allergic reactions. Certain nanoparticles have the ability to activate the immune system, which can result in allergic responses, inflammation, and other negative effects. When nanoparticles are employed often or in long-term therapy, this becomes particularly troublesome. There are worries about nanoparticles building up in organs like the liver, spleen, or kidneys, and long-term buildup might cause organ damage or poisoning. Therefore, in order to guarantee the safety of NDDS for human use, comprehensive biocompatibility studies and toxicity evaluations are necessary. Fig. 5 illustrates biomaterials' toxicity and biocompatibility.

4.2 Scalability and manufacturing

Ensuring consistency in the size, shape, and medication loading of nanoparticles is one of the primary challenges. Maintaining consistent quality on a wide scale can be challenging for nano-based systems, which need exact control during manufacturing. It can be costly to scale up the manufacturing of medicine delivery systems based on nanotechnology. In particular, when transferring lab-scale technologies to commercial production, high manufacturing costs might be a deterrent. The effectiveness, safety, and repeatability of the drug delivery system can all be significantly impacted by minor changes in the formulation or manufacturing process. To avoid negative immunological reactions, it is essential to ensure that nanoparticles are biocompatible. Toxicity requires thorough assessment and mitigation techniques, such as surface modification to lower clearance rates or promote excretion, especially when it results from the buildup of nanoparticles in organs.

4.3 Overcoming biological barriers

The blood–brain barrier, cellular membranes, and the extracellular matrix are just a few of the biological barriers that nanoparticles must be able to get through. The blood–brain barrier (BBB) is a highly selective permeability barrier that separates the brain's tissue from its blood arteries. It keeps big molecules out of the brain, including the majority of medications. The lipid bilayer membrane that envelops each cell in the body serves as a selective barrier to keep undesirable things out. To overcome this obstacle, nanoparticles must be engineered with certain properties, such as proper size, charge, and surface changes. Some tactics include employing "smart" nanoparticles that can react to changes in the brain's microenvironment, such as pH shifts, or targeting ligands, such as transferrin or antibodies, that can attach to receptors on the BBB's endothelial cells. Mucus layers serve as a physical barrier to keep infections and external objects out of the body and are found on numerous epithelial surfaces, including the lungs, gastrointestinal system, and eyes. Cellular absorption

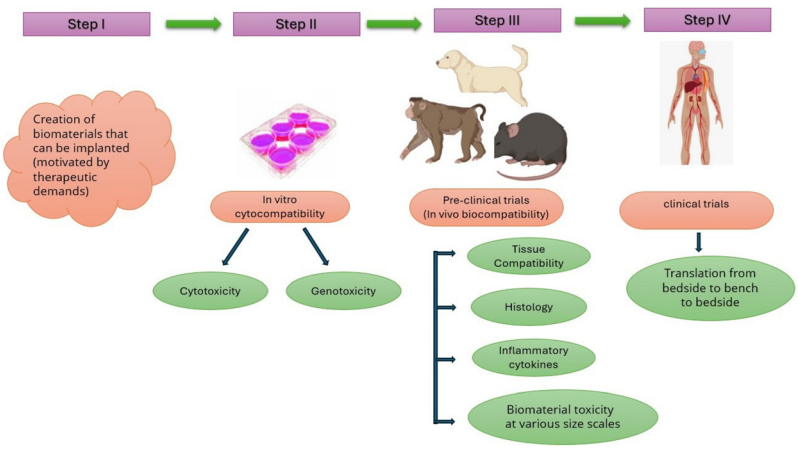

Fig. 5 Analyzing biomaterials' toxicity and biocompatibility.

can be improved by employing cationic particles or by covering the nanoparticles with lipids or proteins that resemble the cell membrane. Techniques such as receptor-mediated transcytosis, in which endothelial cells internalize nanoparticles and translocate them across the blood–brain barrier, and the application of nanoparticle coatings that can improve permeability are being investigated by researchers. One of the main challenges in clinical applications is creating nanoparticles that may successfully get through these barriers without eliciting immunological reactions.

5 Recent developments and applications

Recent developments in medication delivery using nanoparticles have shown their therapeutic promise in a number of domains.

5.1 Cancer treatment

In order to minimize harm to healthy organs, chemotherapeutic medicines have been delivered directly to tumor cells using nanoparticles. Furthermore, the creation of theranostic nanoparticles, which combine therapy and diagnosis, has been made easier by their capacity to transport imaging agents. Currently, a lot of clinical and preclinical research is being conducted on the topic of targeting macrophages in the development of cancer therapies.[84] Fig. 6 gives an idea about worldwide estimation of age-standardized incidence and mortality rates in cancer in 2024. The immune system can more successfully target cancers when medications like nivolumab (Opdivo) and pembrolizumab (Keytruda) disrupt checkpoint proteins that stop immune cells from attacking cancer cells.[85] To attract monocytes to the tumor side, cancer cells release a range of cytokines and chemokines, such as CCL2, CCL3, CCL5, CCL20, CSF-1, CSF-2, IL-6, IL-8, IL-34, and C–X–C motif chemokine 12 (CXCL12).[86] To attract monocytes, other tumor microenvironment (TME) cells may also release cytokines or chemokines. For instance, mesenchymal stem cells (MSCs) release CCL2, Th17 cells express IL-17, and cancer-associated fibroblasts (CAFs) secrete IL-8. The CSF-1–CSF-1R, CCL2–CCR2, CXCL12–CXCR4, and CCL5–CCR5 signaling axes are the main targets of current methods to stop monocyte recruitment and polarization towards the immunosuppressive M2 state. Liquid biopsies, which use blood sample analysis to find tumor DNA, have become popular as less intrusive methods for tracking the development of cancer and finding mutations.[87] They are employed to inform treatment choices and identify cancer early. By altering a patient's own T-cells, chimeric antigen receptor T-cell (CAR-T) treatment enables them to identify and combat cancer cells.[88] In particular, in blood malignancies like leukemia and lymphoma, it has demonstrated impressive outcomes. Cervarix and Gardasil are two vaccines that have previously demonstrated effectiveness in preventing cancer, particularly HPV-related cervical cancer.[89] The development of novel medications like Selpercatinib (for RET-altered cancers) and Lenvatinib (for liver cancer) has brought renewed hope to patients with previously difficult to treat tumors.[90]

5.2 Vaccines for infectious diseases

In order to overcome issues such drug resistance and low absorption, nanoparticles have demonstrated potential in delivering antiviral and antibacterial medications with increased potency. Tariq *et al.* reported that the potential of protein nanoparticle-based vaccines and virus-like particle (VLP)-based vaccines as effective and viable immunization agents to produce immunity against virulent infectious agents, such as SARS-CoV-2, has been described.[91] Fig. 7 shows a comparison of the dangers of traditional vaccinations with those of VLP-based vaccines. Table 4 summarizes infectious diseases, the efficacy of NDDS, and the pace at which the diseases can be cured utilizing the nanodrug delivery technology.

5.3 Gene delivery

Because nanoparticles can transfer nucleic acids (DNA, RNA, and siRNA) directly to target cells, they are increasingly being used in gene therapy, offering promise for genetic diseases and customized treatment.

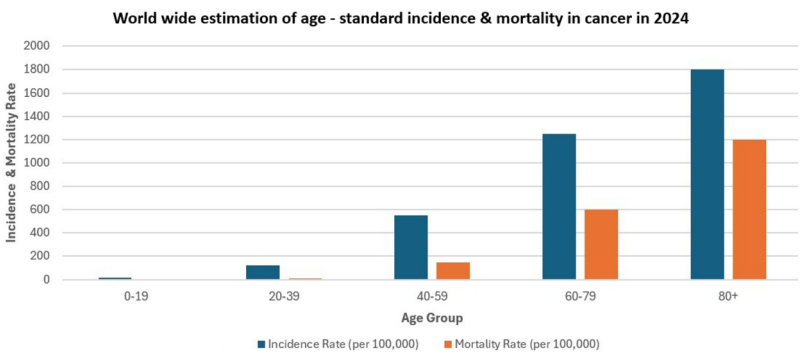

Fig. 6 Age-standardized incidence and mortality rates in cancer.

VLP vaccines V	S Conventional vaccines
Fast manufacturing process	Lengthy formulation process
No allergens	The possibility of an allergic reaction
No risk of mutation due to lack of genetic material	Mutation risks
Non-infectious	Reversion to virulent form
Safe for immune-compromised individuals	Toxicity
Unlike other subunit vaccinations, they are more stable.	Stability issues

Fig. 7 A comparison of the dangers of traditional vaccinations with those of VLP-based vaccines.

Table 4 Infectious diseases and their curable rates using nano-based drug delivery systems

Infectious disease	Curable rate using NDDS	Nano-based drug delivery technology	Effectiveness of the NDDS	Ref.
Tuberculosis (TB)	70–90% (drug-resistant cases)	Liposomes, solid lipid NPs, polymeric NPs	Improves drug bioavailability and penetration, enhances efficacy in resistant strains	92
HIV/AIDS	Moderate (not curable)	NPs, dendrimers, liposomes	Increases drug stability, improves targeted delivery, reduces side effects	93
Malaria	90%+ (if treated early)	Lipid-based NPs, nanosuspensions, micelles	Improves drug solubility, enhances targeting of infected cells	94
Hepatitis B and C	Moderate to high	Liposomes, polymeric NPs	Provides sustained release of antiviral agents, targets liver cells effectively	95
Bacterial infections	90–95% (if treated with right antibiotics)	Silver NPs, gold NPs, antimicrobial peptides	Enhances antibiotic penetration, reduces bacterial resistance, targets infected tissues.	96
Fungal infections	70–80% (depending on the type)	Polymeric NPs, liposomes, nanocomposites	Improves drug solubility, reduces toxicity, targets fungal cells.	
Leishmaniasis	70–80%	Liposomes, polymeric NPs, nanoencapsulated antimonials	Enhances drug delivery, reduces side effects, improves treatment outcomes	97
Dengue fever	No cure yet	NPs, nanoemulsions	Aids in supportive treatments, drug delivery systems still under research	98
Pneumonia	80–90% (with appropriate antibiotics)	NPs, nanoshells, antimicrobial peptides	Improves antibiotic delivery to the lungs, enhances the cure rate	99
Zika virus disease	No cure yet	Nanoemulsions, lipid-based NPs	Potential for developing antiviral therapies, still under research	100
COVID-19 (SARS-CoV-2)	Varies (mild to severe)	Nanoparticles, nanocarriers, vaccine delivery systems	Improves delivery of antivirals, enhances vaccine efficacy and immune response	101
Chagas disease	60–80% (early treatment)	Nanoparticles for controlled release of antiparasitic drugs	Overcomes poor drug absorption, enhances efficacy	102

6 Future directions in nano-based drug delivery

NDDS have a bright future thanks to continuing research aimed at solving present problems and investigating novel therapeutic uses. To increase efficacy and overcome resistance to treatment, it is being investigated to combine several treatment modalities, such as immunotherapy with chemotherapy or targeted therapy. Clinical trials of these combo treatments are yielding encouraging results. These advancements reflect a team effort to promote access to therapies, decrease side effects, improve survival rates, and customize cancer care. There is optimism that even more advancements will be made in cancer therapy in the years to come thanks to continuous research and clinical trials. Table 5 summarizes the comparison of major NDDS platforms (based on their size, composition, drug loading strategies, release triggers, and clinical status) (see also Table 6).

6.1 Personalized medicine

Personalized medicine is one of NDDS' most interesting future opportunities. NDDS can assist maximize treatment success and reduce adverse effects by customizing drug delivery systems to each patient's unique requirements, including their genetic profiles and illness features. Patients with some malignancies are seeing better results thanks to

Table 5 Overview of nanodrug delivery systems (NDDS) with examples

NDDS platform	Typical size range	Composition	Drug-loading strategies	Release triggers	Clinical status/ examples	Ref.
Liposomes	50–200 nm	Phospholipid bilayers with an aqueous core	Hydrophilic drugs in the core; hydrophobic drugs in the bilayers	pH, temperature, enzymatic degradation	Several FDA approved (*e.g.*, Doxil®, AmBisome®)	103–107
Polymeric nanoparticles	10–200 nm	Biodegradable polymers (*e.g.*, PLGA, PLA, PEGylated polymers)	Encapsulation, adsorption, or covalent conjugation	pH, enzymatic, hydrolysis	Some in clinical trials (BIND-014, CRLX101)	47 and 108–111
Solid lipid nanoparticles (SLNs)	50–500 nm	Solid lipids stabilized with surfactants	Drug dispersed or solubilized in a lipid matrix	Temperature, enzymatic	Some in clinical trials	75 and 112–114
Polymeric micelles	10–100 nm	Amphiphilic block copolymers (*e.g.*, PEG-PLA)	Hydrophobic drugs in the core, hydrophilic drugs at the corona	pH, redox potential, temperature	Clinical trials (*e.g.*, Genexol-PM)	29 and 115–118
Dendrimers	5–20 nm	Branched, highly ordered polymers (*e.g.*, PAMAM dendrimers)	Surface functionalization, encapsulation in interior cavities	pH, enzymatic	Preclinical and some clinical candidates	119–123
Nanoemulsions	20–200 nm	Oil-in-water or water-in-oil emulsions with surfactants	Solubilization of lipophilic drugs in the oil phase	Dilution, enzymatic digestion	Some marketed formulations (Neoral®)	124–127
Nanocapsules	50–300 nm	Polymer shell encapsulating a liquid/solid core	Drug reservoir in the core, the polymer controls release	pH, hydrolysis, enzymatic	Preclinical and experimental trials	128–132
Gold nanoparticles (AuNPs)	10–150 nm	Metallic gold core with surface modifications	Surface conjugation with drugs/ligands	Light (photothermal), pH	Preclinical and early-phase clinical trials	133–136
Carbon nanotubes (CNTs)	1–100 nm (diameter)	Cylindrical carbon allotropes (single/ multi-walled)	Adsorption, covalent functionalization, encapsulation	pH, NIR light, enzymatic	Mostly pre-clinical; under exploration for oncology	137–140

Table 6 List of the benefits and drawbacks of various drug delivery systems

Drug delivery systems	Benefits	Drawbacks	Ref.
Pulmonary	Requires less dosage	Deposition issues in the throat	141
Transdermal	Prevents deterioration of drugs	May cause enzymatic deterioration	142
Intranasal	Rapid onset of action	Intolerance in the nasal mucosa	143
Oral drug	Cost effective	Difficulty in consumption	144
Rectal	Avoids enzymatic degradation	Rectal irritation	145
Intravenous	Short latent period	Undesirable immune reaction	58
Intramuscular	Rapid and uniform absorption	May cause hematoma	54
Subcutaneous	Self-administered	Low rate of absorption	146

proton therapy, which targets tumors while causing the least amount of harm to nearby healthy tissue. This is especially true for pediatric and head/neck cancers.[147] High doses of radiation are delivered with pinpoint accuracy using stereotactic body radiotherapy (SBRT), which decreases the number of treatment sessions while increasing efficacy.[148]

6.2 Gene therapy

NDDS have demonstrated considerable potential in the field of gene therapy, which entails delivering genetic material to target cells in order to treat or prevent illnesses. Potential cures for genetic diseases and tumors may be possible with the effective delivery of DNA, RNA, or gene-editing agents like CRISPR to cells *via* nanoparticles, liposomes, and dendrimers.

6.3 Multi-drug delivery systems

To improve the treatment of complicated illnesses like HIV and cancer, multi-drug delivery systems which mix many therapeutic agents on a single platform are being intensively investigated. These systems can lower the likelihood of drug resistance, enhance patient compliance, and facilitate synergistic effects.

7 Conclusion

Nano-based drug delivery systems represent a transformative advancement in modern therapeutics, offering precise, controlled, and efficient drug delivery. These methods greatly improve drug absorption, reduce side effects, and allow for custom treatment techniques using nanotechnology. With several formulations already licensed or undergoing late-stage clinical review, liposomes and polymeric nanoparticles stand out among the developed systems as the most clinically

advanced, especially in the treatment of chronic diseases and cancer. Broader translation into clinical practice is currently limited by a number of significant issues that have not yet been addressed, such as worries about toxicity and long-term biocompatibility, challenges in achieving cost-effective large-scale production, and the lack of standardized international regulatory guidelines. Theranostic platforms that simultaneously combine therapeutic delivery and diagnostic imaging, the development of more predictive *in vivo* models to close the gap between laboratory success and patient outcomes, and the use of artificial intelligence and machine learning tools to speed up nanocarrier design and predict biological interactions are just a few of the exciting prospects for furthering NDDS research in the future. By getting beyond these obstacles and embracing new developments, NDDS can move closer to scalable, secure, and customized nanomedicine solutions that have the potential to revolutionize the way that cancer, infectious diseases, and chronic illnesses are treated.

Author contributions

The sole author conceived the study and designed the structure of the article. She was responsible for the conceptualization, methodology, investigation, original draft writing, and review and editing.

Conflicts of interest

The author declares that there are no conflicts of interest regarding the publication of this paper.

Data availability

All the data supporting the findings of this study are included in this paper.

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