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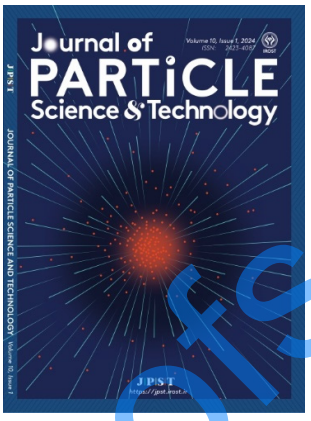

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Review of advanced materials technology for targeted and sustained drug delivery with the aim of developing a roadmap

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Abstract

The growing complexity of modern medicine necessitates advanced drug delivery systems (DDS) that surpass the limitations of conventional methods in safety, efficacy, and personalization. This review explores innovative materials—such as lipid nanoparticles, hydrogels, dendrimers, metal–organic frameworks, exosomes, silica nanoparticles, and stimuli-responsive polymers—and their potential to achieve targeted, controlled, and responsive drug release. Their biocompatibility, drug-loading efficiency, targeting specificity, and translational readiness have been assessed based on recent literature and clinical data. Furthermore, a five-phase roadmap (2025–2045) has been proposed, charting the anticipated evolution of drug delivery systems (DDS)—from material optimization and hybrid nanosystems to AI-driven design, clinical translation, and sustainable bio-integrated platforms. Emerging technologies—like CRISPR-gated hydrogels, magnetothermal brain tumor delivery, and exosome-based RNA therapies—are highlighted as key drivers of future innovation. Despite significant promise, challenges remain in regulatory alignment, scalability, and long-term safety. This review underscores the need for interdisciplinary collaboration and strategic investment to translate laboratory breakthroughs into real-world solutions—paving the way for precision medicine, equitable access, and sustainable therapeutic delivery.

Keywords: Drug delivery systems; Nanoparticles; Advanced material; Sustained drug delivery; Targeted drug delivery

1. Introduction

In the modern healthcare landscape, drug delivery systems (DDSs) serve as essential tools for administering therapeutic agents to patients with precision and efficiency. The successful delivery of therapeutic compounds depends not only on the pharmacological properties of the drugs themselves, but also on their design and delivery route, whether they can navigate the complexities of the human body while maximizing therapeutic benefits and minimizing side effects. Despite significant advances in medical science, traditional drug delivery methods continue to face major challenges that hinder their ability to achieve optimal therapeutic outcomes. These challenges underscore the urgent need for innovative approaches that leverage the unique properties of advanced materials to overcome existing limitations and usher in a new era of personalized medicine.[1, 2] Traditional drug delivery methods, including oral, injectable, and topical formulations, are fraught with inherent limitations that compromise their effectiveness in delivering therapeutic agents to target sites in the body. Oral dosage forms, such as tablets and capsules, often face obstacles such as enzymatic degradation, poor solubility, and limited permeability across biological membranes, leading to suboptimal bioavailability and variable pharmacokinetics. Similarly, parenteral routes, while bypassing gastrointestinal barriers, face challenges related to rapid drug clearance, systemic distribution, and nonspecific targeting, requiring repeated dosing and potentially leading to dose-dependent toxicities or reduced therapeutic efficacy [3]. Furthermore, traditional dosage forms often lack the ability to provide sustained release profiles or modulate drug release rates in response to physiological cues, leading to fluctuating drug concentrations and suboptimal therapeutic outcomes [4]. The emergence of modern medicine has emphasized the importance of targeted drug delivery strategies that can precisely deliver therapeutic agents to specific tissues, cells, or subcellular compartments. However, traditional drug delivery methods often lack the specificity required to selectively deliver drugs to diseased tissues while sparing healthy organs and tissues, leading to off-target effects and systemic toxicity [5, 6]. Furthermore, many therapies have narrow therapeutic windows that require precise

control over drug concentrations to achieve the desired therapeutic effect while minimizing side effects. The inability of traditional dosage forms to provide targeted delivery and controlled release of drugs is a significant obstacle to achieving optimal therapeutic outcomes and patient compliance [1]. In recent years, there has been a growing interest in the development and use of advanced materials for drug delivery applications. Advanced materials, characterized by unique physical and chemical properties and tailored functionalities, offer unprecedented opportunities to overcome the limitations of traditional drug delivery methods and design innovative delivery platforms with therapeutic efficacy and safety profiles. Nanostructured materials in particular have attracted much attention due to their nanoscale dimensions, high surface-to-volume ratios, and tunable properties, which allow for precise control over drug encapsulation, release kinetics, and target specificity. Using the principles of nanotechnology and materials science, researchers can engineer advanced drug delivery systems that are capable of crossing biological barriers, responding to environmental stimuli, and delivering therapies with unparalleled precision and efficiency [7].

Despite the great promise of advanced materials, several challenges and opportunities need to be addressed to realize their full potential in clinical practice. Biocompatibility and safety of materials remain key considerations and require thorough clinical evaluation to assess the immunogenicity, toxicity, and long-term effects of advanced drug delivery systems. In addition, scalability, reproducibility, and cost-effectiveness pose significant barriers to converting laboratory-based innovations into viable commercial products suitable for mass production and widespread clinical use. Regulatory approval and market acceptance also represent major hurdles for the acceptance of advanced drug delivery technologies, requiring close collaboration between researchers, regulatory agencies, and industry stakeholders to navigate the complex landscape of drug development and commercialization [8].

In this article, a detailed overview of recent developments in drug delivery using advanced materials is provided. This project stems from the recognition of the urgent need for innovative

solutions to overcome the limitations of traditional drug delivery methods and address the challenges inherent in current healthcare practices. In today's rapidly evolving medical and biotechnology landscape, the development of advanced drug delivery systems is a major frontier in improving the efficacy, safety, and precision of therapeutic interventions. By utilizing the unique properties and capabilities of advanced materials such as nanoparticles, liposomes, polymers, and hydrogels, this project seeks to revolutionize the science of drug delivery and pave the way for a new era of medical science.

2. Current Advances in Drug Delivery Systems

To provide a comprehensive analysis of advanced drug delivery systems (DDS), an extensive literature search was conducted across global and regional databases, including PubMed, Web of Science, ScienceDirect, Google Scholar, and IranDoc. Sources reviewed encompassed peer-reviewed articles, clinical trial data, regulatory documents, and industry reports. No restrictions were applied regarding publication date or study location, ensuring broad coverage of both established and emerging technologies. Materials were classified into nine categories based on their structural and functional characteristics: lipid nanoparticles, polymer micelles, hydrogels, dendrimers, metal–organic frameworks, exosomes, silica nanoparticles, biodegradable polymers, and stimuli-responsive systems. Each category was evaluated in terms of physicochemical properties, therapeutic applications, biocompatibility, drug-loading capacity, targeting efficiency, side-effect profiles, and scalability. Emphasis was placed on materials with clinical or industrial relevance, and a forward-looking roadmap was constructed for each group to highlight future directions and translational potential.

As previously explained, various materials are currently being used in the field of drug delivery for the smart release of therapeutic agents within the body. Each material possesses specific

characteristics that can be leveraged to achieve targeted therapeutic outcomes. Table 1 lists these materials and their properties.

Table 1. Advanced materials used in drug delivery systems, highlighting their key features and corresponding applications

Materials	Key Features	Applications
Lipid Nanoparticles	Biocompatibility, controlled release	Antigen delivery, Cancer Treatment
Polymeric Micelles	Amphiphilic structure, efficient encapsulation	Chemotherapy, Imaging
Hydrogels	High water content, tunable degradation	Controlled release of proteins, Cell encapsulation
Dendrimers	Uniform particles with defined sizes, functionalized surface	Gene delivery, Targeted therapy
Metal-Organic Frameworks	High surface area, tunable pore size	Gas storage, Imaging, Drug storage
Exosomes	Natural origin, low immunogenicity	Antigen delivery, Regenerative medicine
Silica Nanoparticles	Large surface area, ease of functionalization	Biosensors, Gene delivery
Biodegradable Polymers	Biocompatibility, tunable degradation rate	Sustained release formulations, Tissue engineering
Stimuli-Responsive Systems	Triggered release mechanisms (pH, temperature)	Cancer therapy, On-demand drug release

2.1. Lipid nanoparticles

Lipid nanoparticles (LNPs), a versatile class of nanocarriers primarily composed of lipids, have emerged as a promising platform in the fields of pharmaceutics and biotechnology, particularly for the delivery of nucleic acid-based therapeutics such as mRNA and siRNA. Typically, spherical in morphology and ranging in size from 10 to 1000 nm, LNPs possess physicochemical properties that make them highly adaptable for encapsulating both hydrophilic and hydrophobic drugs. This structural flexibility, coupled with their biocompatibility and ability to enhance drug stability and bioavailability, has positioned LNPs at the forefront of nanomedicine. Subtypes of LNPs, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), offer tailored drug delivery options [9,10]. Clinically, LNPs have played a pivotal role in the development of mRNA-based

COVID-19 vaccines, such as those produced by Pfizer-BioNTech and Moderna, where they serve to encapsulate and protect the fragile mRNA strands, enabling efficient intracellular delivery and subsequent antigen expression [11]. Another landmark application is Onpattro (patisiran), the first FDA-approved LNP-based therapeutic, which utilizes siRNA encapsulation to silence mutant transthyretin gene expression in the treatment of hereditary amyloidosis (Fig 1) [12]. SLNs, composed of a solid lipid matrix, are particularly effective in solubilizing lipophilic drugs and have been explored in oncology for their potential in targeted anticancer therapy [13]. In contrast, NLCs incorporate both solid and liquid lipids, resulting in enhanced drug loading capacity and physical stability, and are under investigation for the delivery of poorly water-soluble compounds [14]. Collectively, these examples underscore the critical role of LNPs in advancing the delivery of next-generation therapeutics by combining precise targeting capabilities with enhanced pharmacokinetic profiles.

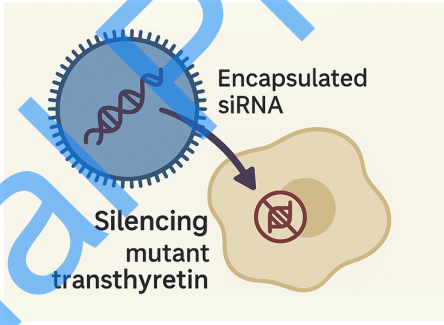

Fig 1. Onpattro utilizes siRNA encapsulation in the treatment of hereditary amyloidosis.

2.2. Polymeric micelles

Polymeric micelles (PMs) represent a class of nanosized drug delivery vehicles particularly well-suited for the encapsulation and transport of hydrophobic therapeutic agents. Formed through the self-assembly of amphiphilic copolymers in aqueous environments above their critical micelle concentration (CMC), these colloidal structures typically range from 10 to 100 nm in diameter. The architectural design of PMs features a hydrophobic core capable of solubilizing poorly water-soluble

drugs, surrounded by a hydrophilic shell that imparts colloidal stability and extends circulation time by reducing recognition and clearance by the reticuloendothelial system. This core-shell configuration not only improves the aqueous solubility and bioavailability of hydrophobic drugs but also facilitates targeted delivery to pathological tissues through passive accumulation via the enhanced permeability and retention (EPR) effect. Several polymeric micelle-based formulations have advanced into clinical development and therapeutic use [15,16]. For instance, Genexol-PM, a paclitaxel-loaded micelle composed of methoxypoly(ethylene glycol)-block-poly (D, L-lactide) (mPEG-PDLLA), has been approved for the treatment of breast cancer and non-small cell lung cancer in multiple countries [17]. Similarly, NK105, incorporating paclitaxel within a micellar matrix of modified polyethylene glycol and polyaspartate, has shown encouraging outcomes in clinical trials targeting advanced gastric adenocarcinoma [18]. Another notable formulation, SP1049C, utilizes Pluronic block copolymers (L61 and F127) to deliver doxorubicin, and has demonstrated enhanced efficacy over conventional doxorubicin in clinical evaluations for esophageal adenocarcinoma [19]. These examples underscore the potential of PMs as versatile and effective nanocarriers, particularly for chemotherapeutic agents requiring improved solubility, stability, and site-specific delivery.

2.3. Hydrogels

Hydrogels, defined as three-dimensional, hydrophilic polymer networks capable of absorbing and retaining substantial amounts of water without dissolving, have garnered significant attention in the field of drug delivery due to their structural versatility and responsiveness to environmental stimuli. These networks, formed through physical or chemical cross-linking of natural, synthetic, or semi-synthetic polymers, can adapt to variations in pH, temperature, or ionic strength—features that are particularly valuable for targeted and controlled drug release [20,21]. Among the various hydrogel systems, chitosan-based hydrogels, derived from the natural polysaccharide chitin, have demonstrated effective pH-sensitive drug delivery, particularly in acidic microenvironments such as

tumor tissues, due to their intrinsic biocompatibility and biodegradability. Similarly, polyethylene glycol (PEG)-based hydrogels offer tunable physicochemical properties and excellent biocompatibility, allowing for precise control over drug release through modifications in crosslinking density and polymer molecular weight [22]. Semi-synthetic systems like gelatin methacryloyl (GelMA) hydrogels combine natural gelatin with methacrylate groups, facilitating crosslinking that mimics the extracellular matrix—an advantageous feature for localized drug release and tissue engineering applications [23]. Furthermore, thermoresponsive hydrogels such as those based on poly(N-isopropylacrylamide) (PNIPAAm) exhibit phase transitions around physiological temperatures, enabling temperature-regulated drug release. Expanding on this responsiveness, multifunctional stimuli-sensitive hydrogels have been developed to react to triggers such as pH, light, or enzymatic activity, thereby achieving spatiotemporal control over drug delivery in complex biological environments [23,24]. Collectively, these diverse hydrogel systems underscore the potential of smart polymeric platforms in enhancing the specificity, efficacy, and safety of modern drug delivery strategies.

2.4. Dendrimers

Dendrimers are a novel and highly sophisticated class of synthetic macromolecules characterized by a well-defined, tree-like architecture composed of a central core, repeated branching units, and terminal functional groups. This precisely controlled structure results in monodisperse nanocarriers with a high degree of molecular uniformity, tunable surface chemistry, and extensive internal cavities, all of which contribute to their exceptional potential in drug delivery applications. The dense arrangement of functional groups on the periphery allows for the conjugation of therapeutic agents, targeting ligands, and imaging moieties, making dendrimers versatile platforms for both diagnostic and therapeutic purposes [25,26]. Among the various dendrimer systems, poly(amidoamine) (PAMAM) dendrimers are the most extensively studied, particularly for their ability to enhance the

solubility, bioavailability, and targeted delivery of hydrophobic anticancer drugs such as paclitaxel and doxorubicin [27]. Functionalized dendrimers, such as folic acid-conjugated dendrimers, have been engineered to selectively deliver methotrexate to cancer cells that overexpress folate receptors, thereby improving therapeutic efficacy while minimizing systemic toxicity [28]. Additionally, dendrimer-drug conjugates employing pH-sensitive linkages enable site-specific drug release within the acidic tumor microenvironment, optimizing pharmacological outcomes and reducing off-target effects [29]. Dendrimers have also shown great promise in gene therapy; for example, cationic PAMAM dendrimers can effectively bind and deliver nucleic acids such as siRNA or plasmid DNA, facilitating gene transfection with favorable biocompatibility. Recent advancements have led to the creation of dendrimer-based hybrid nanoparticles, which combine dendritic polymers with inorganic or organic nanoparticles to form multifunctional systems capable of co-delivering drugs and diagnostic agents [30]. These diverse applications highlight dendrimers as highly customizable and multifunctional nanocarriers with significant implications for targeted and precision drug delivery.

2.5. Metal-Organic Frameworks (MOFs)

Metal-organic frameworks (MOFs) are a class of crystalline porous materials composed of metal ions or clusters coordinated with organic ligands, resulting in a three-dimensional network with well-defined structural characteristics. Their high surface area, tunable pore size, and chemical versatility render them particularly promising for drug delivery applications. MOFs are typically constructed from transition metals or lanthanides linked with various organic moieties such as carboxylates, phosphonates, or imidazolates, producing frameworks with exceptional porosity and guest molecule encapsulation capabilities. These materials can be synthesized via multiple techniques, including thermal solvent-based methods and microwave-assisted approaches, which allow for precise control over their physicochemical properties [31-33]. Among the earliest MOFs explored for biomedical applications, MIL-100 and MIL-101, both chromium-based frameworks, demonstrated high drug

loading capacities for compounds such as ibuprofen and doxorubicin and enabled sustained release over extended durations [33]. ZIF-8, a zinc-based MOF, has been extensively studied for its biocompatibility and stability under physiological conditions, showing enhanced delivery and reduced cytotoxicity when used to encapsulate anticancer agents like camptothecin (Fig 2).

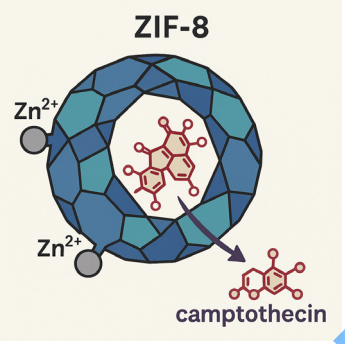

Fig 2. Role of MOFs in delivering anticancer drugs.

Another notable system, UiO-66, based on zirconium, is recognized for its structural robustness and modifiable pore environment; when functionalized with targeting ligands, UiO-66 can selectively direct drugs such as doxorubicin to tumor cells [34]. Similarly, iron-based MOFs (Fe-MOFs) have been investigated for cancer therapy due to their intrinsic biodegradability and minimal toxicity, offering an effective balance between therapeutic efficacy and safety. In recent years, nanoscale MOFs (NMOFs) have gained attention for their multifunctionality in delivering chemotherapeutics, imaging agents, and photodynamic or photothermal therapy components. Their reduced particle size significantly enhances cellular uptake, providing a strategic advantage in precision nanomedicine [35]. Overall, MOFs represent a highly modular and adaptable platform for advanced drug delivery systems, combining structural tunability with biomedical functionality.

2.6. Exosomes

Exosomes are nanoscale, membrane-bound extracellular vesicles typically ranging from 30 to 150 nm in diameter, naturally secreted by a wide variety of cell types into the extracellular

environment. These vesicles are generated within multivesicular bodies (MVBs) of the endosomal system and are released upon fusion of MVBs with the plasma membrane. Functionally, exosomes play a pivotal role in intercellular communication by transferring a broad spectrum of bioactive molecules—including proteins, lipids, mRNA, and microRNA—to recipient cells, thereby modulating their behavior and gene expression. Their endogenous origin endows them with the ability to evade immune surveillance, traverse biological barriers, and exhibit low immunogenicity and toxicity, making them particularly attractive for therapeutic delivery [36,37]. One of the most studied applications is Exo-Dox, an exosome-encapsulated doxorubicin formulation that demonstrates superior intracellular uptake and enhanced cytotoxic efficacy compared to free or liposomal doxorubicin. In the field of gene therapy, exosome-mediated siRNA delivery has shown promise, notably with engineered exosomes derived from dendritic cells effectively delivering siRNA to suppress oncogene expression in tumor models [38]. Mesenchymal stem cell (MSC)-derived exosomes, enriched with regenerative growth factors, have been applied to tissue repair scenarios, demonstrating anti-inflammatory and pro-healing effects in damaged tissues. To enhance specificity, folic acid-modified exosomes have been developed to target folate receptor-expressing tumor cells, thereby increasing the selective delivery of chemotherapeutic agents to cancerous tissues [39]. Furthermore, exosome-based vaccines are being explored as novel platforms for antigen presentation in cancer immunotherapy and infectious disease prevention, leveraging their innate ability to stimulate immune responses [40]. Collectively, the multifunctional properties and biological compatibility of exosomes position them as a highly promising class of natural nanocarriers for next-generation drug delivery strategies.

2.7. Silica Nanoparticles

Silica nanoparticles (SiNPs), particularly mesoporous silica nanoparticles (MSNs), have garnered significant interest as nanocarriers in drug delivery systems due to their distinctive

physicochemical attributes, including high surface area, tunable pore size, excellent thermal and mechanical stability, and favorable biocompatibility. These nanoscale structures, composed predominantly of silicon dioxide (SiO_2), can be engineered into either nonporous (solid) or mesoporous forms, with MSNs being especially notable for their internal pore networks ranging from 2 to 50 nm, which facilitate efficient drug loading and controlled release. The versatility of SiNPs extends to their surface functionalization, allowing for the conjugation of targeting ligands, such as folic acid or antibodies, to enhance selectivity toward pathological tissues and minimize off-target effects. Among the most extensively studied applications are MSNs loaded with chemotherapeutic agents like doxorubicin and paclitaxel, which have demonstrated sustained drug release profiles and improved therapeutic indices [41-43]. Hybrid systems, such as silica-lipid hybrid nanoparticles, have been developed to augment the solubility and bioavailability of poorly water-soluble drugs including ibuprofen and celecoxib, particularly for oral delivery [44]. Additionally, targeted silica nanoparticles have shown promise in enhancing cellular uptake and therapeutic outcomes in tumor models through receptor-mediated endocytosis [45]. Beyond chemotherapy, cationic silica nanoparticles have been explored for gene delivery, effectively encapsulating and delivering nucleic acids such as siRNA and plasmid DNA into various cell types with minimal toxicity. Moreover, silica-based systems have been investigated for mucosal drug delivery, with their robust structural integrity enabling them to protect therapeutic agents from degradation in mucosal membranes (e.g., gastrointestinal tract or nose), thereby improving absorption and systemic bioavailability [46]. Collectively, the multifunctional nature and adaptable architecture of silica nanoparticles position them as a valuable platform for a wide range of therapeutic applications in nanomedicine.

2.8. Biodegradable polymers

Biodegradable polymers have emerged as pivotal materials in the advancement of drug delivery systems due to their inherent ability to degrade into non-toxic by-products under physiological

conditions, thereby minimizing long-term toxicity and eliminating the need for surgical removal. These polymers, which can be either naturally derived or synthetically engineered, are designed to offer controlled and sustained drug release, enhancing therapeutic efficacy while reducing side effects and dosing frequency. Biodegradable polymers are defined as macromolecules that undergo degradation via enzymatic or hydrolytic pathways, resulting in metabolizable end-products that are safely absorbed or excreted by the body. They can be broadly categorized into natural polymers—such as chitosan, alginate, and gelatin—and synthetic polymers—including polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), and polylactic-co-glycolic acid (PLGA) [15,47,48]. One of the most widely studied examples, PLGA, has been employed in numerous formulations to encapsulate chemotherapeutic agents such as paclitaxel and doxorubicin, owing to its tunable degradation rate and excellent biocompatibility [49]. Similarly, PCL, known for its slower degradation profile, is utilized in long-acting implants and microspheres for extended drug release [50]. Among the natural polymers, chitosan, derived from chitin, is a natural polymer with excellent biocompatibility and biodegradability. It has been investigated for drug delivery due to its ability to form nanoparticles that effectively encapsulate drugs. Chitosan-based formulations have been used for the delivery of anticancer drugs and anti-inflammatory agents [51]. Gelatin, a natural polymer derived from collagen that has been widely studied for drug delivery applications. Its biocompatibility and ability to form hydrogels make it suitable for encapsulating various therapeutic agents, including proteins and peptides [52]. Alginate, a polysaccharide obtained from brown algae, is particularly valued for its mild gelation conditions and is used in the encapsulation and controlled release of macromolecules such as insulin and vaccines [53]. Additionally, polyorthoesters, a class of synthetic biodegradable polymers, have been engineered for applications requiring precise drug release kinetics, especially in the sustained delivery of antibiotics and anticancer drugs [54]. The versatility of biodegradable polymers in terms of chemical structure, mechanical properties, and degradation

behavior positions them as essential platforms for the development of next-generation drug delivery systems tailored to diverse therapeutic needs.

2.9. Stimuli-responsive systems

Stimuli-responsive drug delivery systems (SRDDS) represent a cutting-edge advancement in pharmaceutical technology, engineered to release therapeutic agents in response to specific internal or external stimuli. By enabling spatial and temporal control over drug release, these systems enhance treatment efficacy while minimizing systemic side effects—an especially vital feature in oncological applications. SRDDS can be broadly categorized based on the type of stimuli they respond to endogenous triggers such as pH shifts, temperature changes, and the presence of specific biomolecules (e.g., enzymes or reactive oxygen species), and exogenous triggers including light, ultrasound, and magnetic fields. A range of smart materials has been developed to harness these stimuli for controlled drug release [55,56]. For instance, pH-responsive hydrogels, such as those based on polyacrylic acid, swell or contract according to environmental pH, allowing preferential drug release in acidic tumor microenvironments [57]. Thermoresponsive polymers like poly(N-isopropylacrylamide) (PNIPAAm) exhibit a lower critical solution temperature (LCST), switching between hydrophilic and hydrophobic states to enable heat-triggered drug release, which is particularly beneficial in hyperthermia-assisted cancer therapy [58]. Similarly, light-responsive nanoparticles, including those utilizing gold nanostructures, can be activated by near-infrared (NIR) light to induce localized heating and drug release with high spatial precision [59,60]. Enzyme-responsive systems offer another level of specificity, where peptide-based carriers degrade in the presence of tumor-associated proteases, ensuring site-specific release [61]. Furthermore, magnetic field-responsive platforms utilize magnetic nanoparticles that can be directed to target sites and heated under an alternating magnetic field, promoting drug release from thermosensitive matrices [62].

Collectively, these innovative materials underscore the potential of SRDDS to revolutionize targeted drug delivery through precisely controlled and stimulus-specific mechanisms.

Table 2 presents a comparative summary of key nanomaterials used in drug delivery, highlighting their structural features, clinical applications, and therapeutic advantages to facilitate cross-platform evaluation according to the literature review.

Table 2. Summary of key features, applications, and advantages of major drug delivery materials based on literature review

Material Type	Key Features	Representative Drugs/Applications	Advantages
Lipid Nanoparticles (LNPs)	High adaptability, biocompatibility; used in mRNA vaccines and siRNA therapy	mRNA (Pfizer, Moderna), siRNA (Onpattro)	Enhances drug stability, targeting, and cellular uptake
Polymeric Micelles (PMs)	Self-assembled; improves solubility and bioavailability of hydrophobic drugs	Paclitaxel (Genexol-PM, NK105), Doxorubicin (SP1049C)	Prolongs circulation, reduces RES clearance
Hydrogels	3D polymer networks responsive to stimuli; enable controlled release	Chitosan, PEG, GelMA-based hydrogel delivery systems	Stimuli-responsive, tunable release profiles
Dendrimers	Tree-like, monodisperse; enable multifunctional drug and gene delivery	Paclitaxel, Doxorubicin, Methotrexate, siRNA	Customizable, multivalent, and suitable for co-delivery
Metal-Organic Frameworks (MOFs)	High porosity and tunability; used for sustained and targeted delivery	Doxorubicin, Ibuprofen, Camptothecin	High loading capacity, modular synthesis
Exosomes	Natural vesicles; excellent biocompatibility and immune evasion	Doxorubicin (Exo-Dox), siRNA, regenerative medicine	Low immunogenicity, natural targeting
Silica Nanoparticles (SiNPs)	High surface area; efficient loading and targeted delivery	Doxorubicin, Paclitaxel, Ibuprofen, siRNA	Customizable pores and surfaces for controlled release
Biodegradable Polymers	Biodegradable and biocompatible; enable sustained and localized release	Paclitaxel, Doxorubicin, Insulin, Vaccines	Safe degradation, long-acting formulations
Stimuli-Responsive Systems (SRDDS)	Release triggered by pH, temperature, light, or enzymes	Polyacrylic acid, PNIPAAm, Gold NPs, Enzyme/magnetic responsive materials	Precision control of release in response to stimuli

3. Roadmap for the Future

Recent advances in drug delivery systems have revolutionized precision medicine through innovation in multifunctional materials such as lipid nanoparticles, hydrogels, and stimuli-responsive platforms. Key challenges include optimizing biocompatibility, manufacturing scalability, and overcoming regulatory pathways for next-generation therapeutics. Emerging trends are driving the integration of artificial intelligence (AI), bio-orthogonal chemistry, and sustainable synthesis methods to reduce global health disparities and advance personalized medicine. Figure 5 illustrates the proposed five-phase roadmap (2025–2045) for the evolution of advanced drug delivery systems, highlighting key milestones from material optimization to sustainable, bio-integrated therapeutic platforms.

3.1. Phase 1: Material Innovation and Optimization (2025–2027)

Lipid Nanoparticles (LNPs): Building on their success in mRNA vaccines, LNPs are being redesigned to improve targeting via surface functionalization with ligands such as antibodies or aptamers. A critical milestone is reducing immunogenicity while increasing RNA payload capacity beyond 90% encapsulation efficiency. Hybrid LNPs integrating stimuli-responsive polymers (e.g., thermosensitive shells) are under development to enable on-demand release in tumor microenvironments [63].

Silica nanoparticles: The design of MSNs with tunable pore sizes for the controlled release of insoluble drugs (ibuprofen, camptothecin) suggests a bright future for these nanoparticles in the drug delivery industry [64].

Dendrimers: PAMAM dendrimers with surface modification of lactobionic acid are being developed for targeting liver cancer cells via the asialoglycoprotein receptor [65].

Hydrogels: Current research focuses on overcoming burst release through multilayer architectures and nanocomposite integration. For instance, embedding silica nanoparticles within

alginate hydrogels reduces premature diffusion of small-molecule drugs. Bio-orthogonal crosslinking methods, such as strain-promoted azide-alkyne cycloaddition, are being prioritized to prevent side reactions with encapsulated biologics like exosomes or CRISPR-Cas9 complexes [66].

Metal–Organic Frameworks (MOFs): Innovations in green synthesis routes, such as solvent-free mechanochemical approaches, aim to reduce toxicity risks while maintaining high drug-loading capacities (>60% wt/wt). MOFs functionalized with pH-sensitive linkers are being tested for colon-specific delivery of biologics, leveraging the acidic gut environment.

3.2. Phase 2: Preclinical Validation and Hybrid Systems (2028–2030)

Hydrogels: CRISPR-gated hydrogels demonstrate:

- Sequence-specific actuation against 25+ targets including vancomycin resistance and virulence factor [67]
- Tunable release kinetics controlled by PEG-DNA crosslinking density [67]
- Living cell delivery of primary human cells through Cas12a-mediated matrix degradation [68]

Stimuli-Responsive DDS: Magneto-thermal systems combining magnetic nanoparticles (MNPs) and thermosensitive hydrogels are entering preclinical trials for glioblastoma. Under alternating magnetic fields, localized heating triggers hydrogel contraction, releasing temozolomide with spatial precision. Early data show a 40% reduction in off-target toxicity compared to conventional chemotherapy [69].

Hybrid dendrimers: The use of hybrid dendrimers (e.g., PAMAM-PEG-Transferrin) for the simultaneous delivery of doxorubicin and plasmid in mouse glioma has increased survival by up to 28.5 days [65].

Exosome Engineering: Exosomes derived from mesenchymal stem cells are being modified with click chemistry tags for modular loading of siRNA or mRNA. A 2029 milestone includes achieving

>80% tumor retention in metastatic breast cancer models using CD47-modified exosomes to evade phagocytosis [63,69].

AI-Driven Predictive Modeling: Machine learning (ML) algorithms trained on 10,000+ degradation profiles of PLGA nanoparticles now predict release kinetics with 92% accuracy, accelerating formulation optimization. Partnerships between computational biologists and material scientists are critical to refining these models for hybrid materials like dendrimer-MOF composites [70].

3.3. Phase 3: Clinical Translation and Regulatory Integration (2031–2035)

Conducting Polymers (CPs): Electrically responsive polypyrrole implants for Parkinson's disease are in Phase II trials. These devices release levodopa in response to aberrant neural activity detected via embedded biosensors, reducing dyskinesia risk by 55%. Challenges include minimizing fibrous encapsulation, which currently limits device longevity to 18 months [71].

Connected Inhalers: FDA-cleared smart inhalers with integrated MEMS sensors now provide real-time adherence tracking for asthma patients. Next-generation devices, such as DGIST's foldable smart patch (2033), combine biometric monitoring with intranasal delivery of anti-amyloid antibodies for Alzheimer's prophylaxis [72,73].

Metal-organic frameworks: MOFs, including UIO-66, in combination with folate have shown promise as suitable drug delivery vehicles for targeting breast cancer [74].

Dendrimers: The clinical trial of dendrimer SPL7013 (VivaGel®) for the prevention of HPV and HIV transmission in topical vaginal formulations shows the promising future of dendrimers in the treatment and prevention of viral infections [75].

Lipid Nanoparticles: Low-cost lyophilized LNP kits enable mRNA vaccine reconstitution in resource-limited settings, achieving stability at 25°C for 6 months. Partnerships with NGOs like PATH aim to distribute 500 million doses annually by 2035[76].

3.4. Phase 4: Commercial Scalability and Global Equity (2036–2040)

Green Synthesis: Plant-mediated synthesis of gold nanoparticles reduces production costs by 70% compared to chemical methods. Mycogenic synthesis using *Fusarium oxysporum* is scaling to produce 10 kg/month of cisplatin-loaded MNPs for cervical cancer therapy [77].

3D-Printed Implants: On-demand printing of biodegradable PCL scaffolds loaded with vancomycin is eliminating surgical site infections (SSI) in Low- and middle-income countries [47].

Hybrid exosomes: A 2021 study showed that engineered hybrid exosomes could be used for targeted chemotherapy to treat triple-negative breast cancer (TNBC). These exosomes deliver the drug paclitaxel to cancer cells with an EGFR-targeting peptide [78].

3.5. Phase 5: Next-Generation Systems and Sustainability (2041–2045)

CRISPR-Cas12a Hydrogels: Light-activated hydrogels delivering base editors for sickle cell anemia achieve 95% allelic correction in non-human primates. A 2043 milestone involves initiating trials for in vivo editing without viral vectors [79]. Moreover, light-activated CRISPR-Cas12a hydrogels achieve programmable cargo release through collateral ssDNA cleavage activity (Fig 3). These systems: 1) Detect nucleic acids down to 11 attomolar using microfluidic paper-based devices with Cas12a-mediated hydrogel degradation 2) Release enzymes (e.g., HRP) within 10 minutes at 10 nM DNA trigger concentrations via ssDNA anchor hydrolysis 3) Enable multiplexed detection through differential fluorophore release (Cy3/6-FAM) using blocked ssDNA linkers [67].

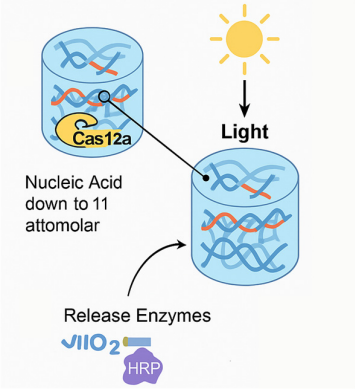

Fig 3. Expected role of light-activated CRISPR-Cas12a hydrogels in achieving programmable cargo release

Exosome detection: CRISPR/Cas12a-loaded DNA hydrogels now provide dual signal outputs (fluorescent/colorimetric) for tumor-derived exosomes, achieving ultrasensitive one-step assays [80].

Living Materials: Engineered *Bacillus subtilis* biofilms secreting anti-TNFα antibodies are being tested for Crohn's disease (Fig 4). These self-renewing systems reduce injection frequency from biweekly to annual [81].

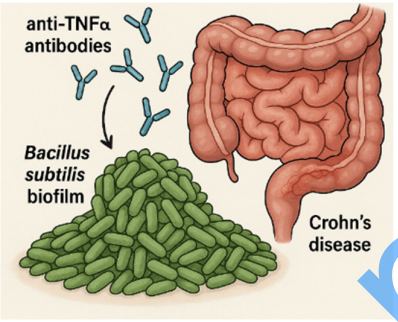

Fig 4. Expected role of Bacillus subtilis biofilms in treatment of Crohn's disease

Neural Interface DDS: Graphene-based neural dust particles (<100 nm) monitor dopamine levels and release L-DOPA in Parkinson's patients via closed-loop feedback, achieving symptom control within ±5% of baseline [82].

4. Conclusion

This review has explored the evolving landscape of advanced drug delivery systems, with a focus on cutting-edge materials such as lipid nanoparticles, polymeric micelles, hydrogels, dendrimers, metal–organic frameworks, exosomes, silica nanoparticles, biodegradable polymers, and stimuli-responsive systems. Each material platform was examined in terms of structural characteristics, therapeutic applications, and translational potential. Comparative analysis through added tables further clarified their unique benefits and limitations.

The paper also outlined key challenges in clinical translation, regulatory integration, and scalability. A forward-looking roadmap (see Figure 5) was proposed to guide DDS development from

2025 to 2045, emphasizing innovations such as AI-assisted formulation, CRISPR-gated systems, and sustainable bio-integrated platforms.

Moving forward, interdisciplinary collaboration and strategic investment will be essential to unlock the full potential of these technologies, ultimately advancing precision medicine and global therapeutic access

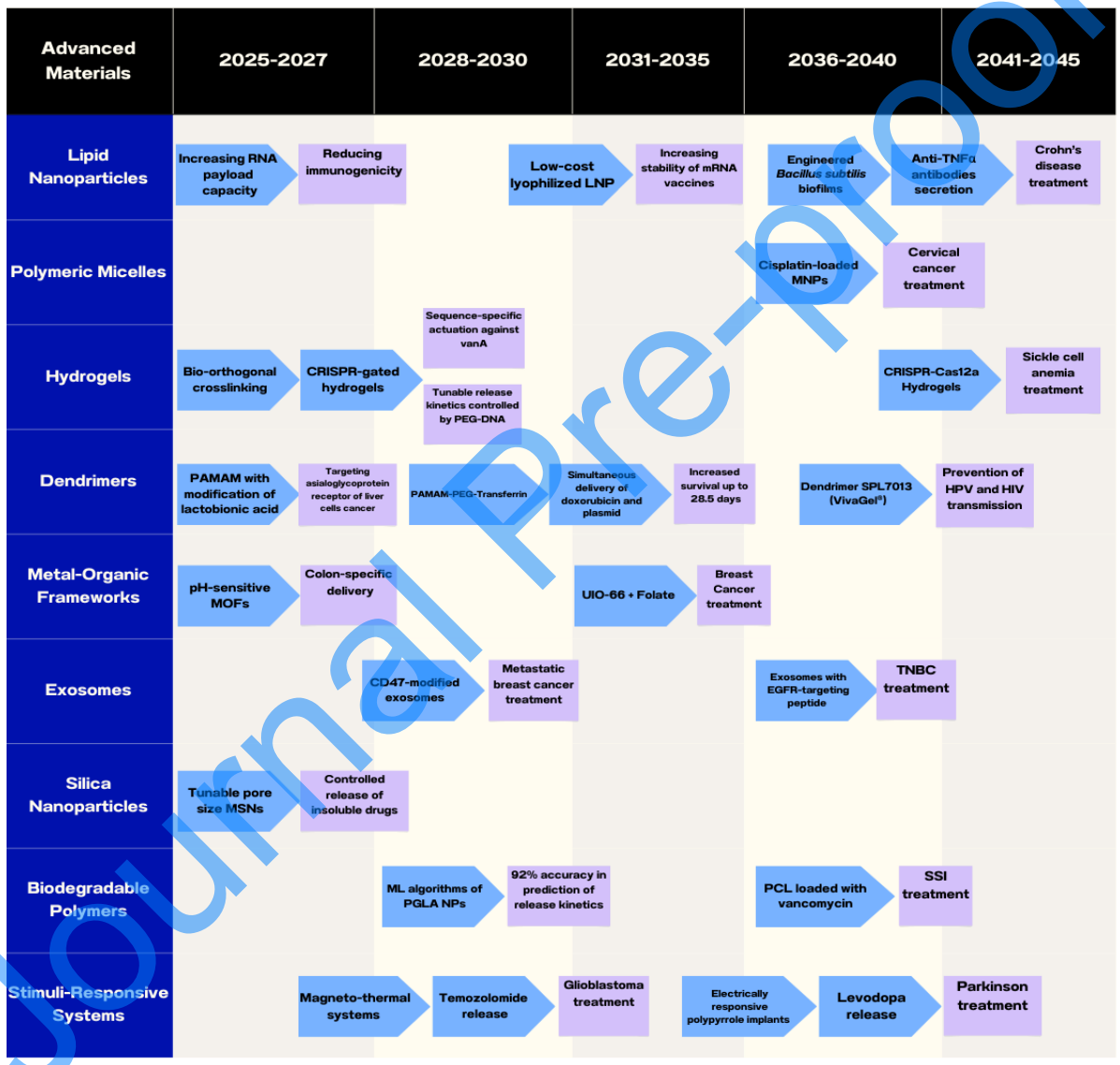

Fig 5. Projected roadmap (2025–2045) for the application of advanced materials in smart and controlled drug delivery systems. The timeline illustrates anticipated developments and therapeutic applications across various material platforms.

Conflict of Interest

The authors declare no conflicts of interest regarding this manuscript.

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