INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Next-Generation Drug Delivery Systems (2020–2025): Translating Personalization into Practice

Tekumatla Gowthami, K. S. Vaishnavi, Nazneen Kausar, Oruganti Manaswi, Madishetty Raghavi, Usha Rani Peddaboina*

Department of pharmacy, University College of Technology, Osmania University, Hyderabad, India.

ARTICLE INFO

Published: 14 Sept. 2025
Keywords:
Drug delivery, Nanomedicine, Personalized medicine, Artificial intelligence, Microrobotics, Translational barriers
DOI:
10.5281/zenodo.17115597

ABSTRACT

Next-generation drug delivery systems (DDS) have advanced rapidly between 2020–2025 through innovations in nanotechnology, biopolymers, artificial intelligence (AI), and advanced manufacturing. These platforms aim not only to improve precision and reduce toxicity but also to translate personalized therapies into real-world practice. This review highlights progress in stimuli-responsive carriers, biopolymer- and protein-based systems, nanogels, microrobots, AI-integrated models, and 3D/4D printing, alongside emerging patient-specific approaches such as mRNA vaccines and gene editing. Special emphasis is placed on translational aspects—regulation, safety, scalability, and access—as fewer than 15% of innovations advance beyond early trials. Looking ahead to 2025–2030, harmonized regulation, organ-on-chip predictive testing, and patient-centered design will be essential to ensure these technologies move from bench to bedside. Together, these developments signal a paradigm shift where personalization is not only engineered but effectively translated into clinical practice.

INTRODUCTION

Drug delivery has evolved beyond conventional formulations to embrace intelligent platforms that combine engineering precision with clinical applicability. In the past five years, major strides in nanotechnology, biomaterials, and AI have enabled therapies that are not only more effective but also increasingly personalized. Personalization in drug delivery refers to tailoring treatment according to patient-specific factors such as genetic background, disease phenotype, and metabolic profile. At the same time, translational perspectives—including regulatory readiness, scalable production, and safety validation—determine whether laboratory innovations can reach real-world practice. Next-generation drug delivery systems (DDS) have rapidly progressed in

***Corresponding Author:** Usha Rani Peddaboina
Address: *Department of pharmacy, University College of Technology, Osmania University, Hyderabad, India.*
Email ✉: usharanipharma123@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

the past five years, moving beyond conventional formulations toward intelligent, patient-tailored platforms. Advances in nanotechnology, biomaterials, artificial intelligence (AI), and 3D/4D fabrication are reshaping the therapeutic landscape by enabling precision dosing, site-specific targeting, and adaptive release profiles. Personalization in DDS integrates molecular diagnostics, genetic profiling, and digital health data to optimize treatment for individual patients, while translational perspectives focus on regulatory readiness, scalable manufacturing, safety validation, and equitable access.

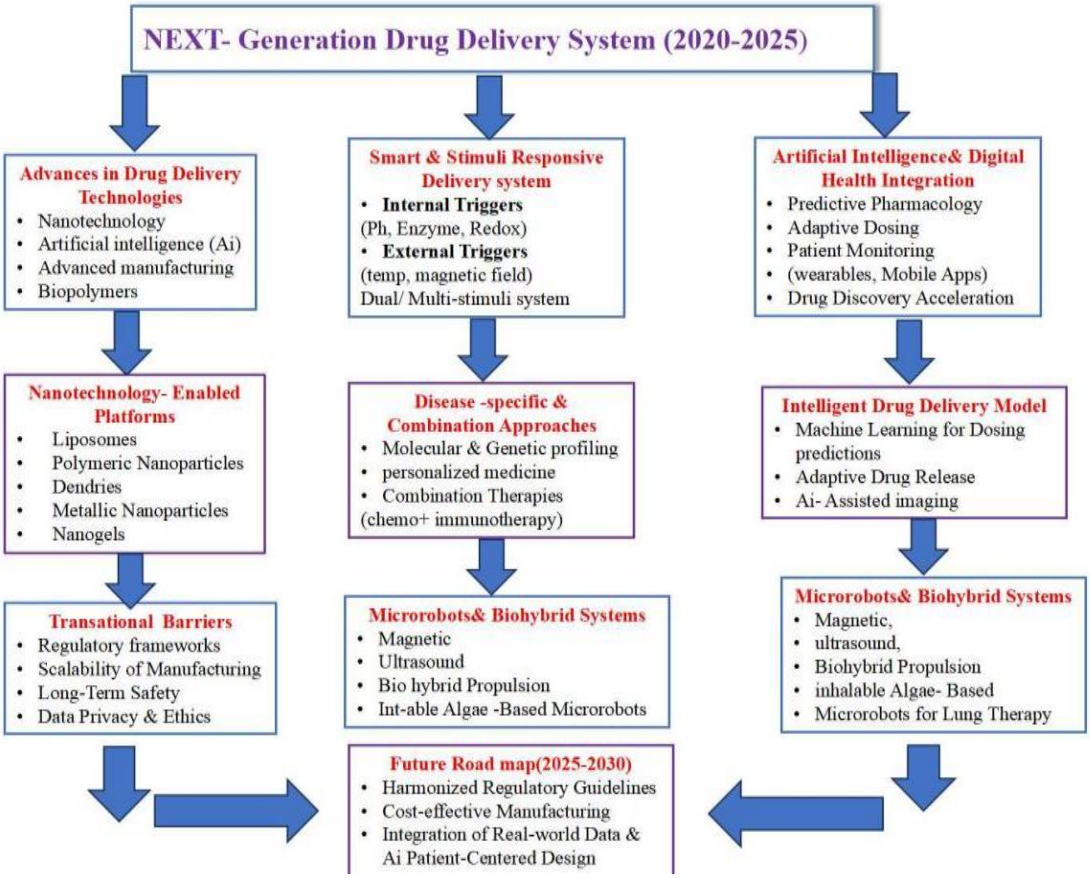

Figure-1: Next generation drug delivery systems

As illustrated in flowchart (Figure 1), emerging DDS platforms—including stimuli-responsive carriers, biopolymer systems, nanotechnology-enabled approaches, AI-integrated models, microrobotics, and nanogels—highlight both the therapeutic potential and the translational hurdles. Together, these innovations signal a paradigm shift from passive formulations toward dynamic, intelligent therapeutic ecosystems, redefining precision medicine for 2020–2025.

1. Smart and Stimuli-Responsive Delivery Systems

Stimuli-responsive drug delivery systems (DDS) have emerged as an advanced class of nanomedicine engineered to release therapeutic cargo in response to endogenous or external stimuli as shown in figure 2. These platforms overcome the limitations of conventional formulations by enabling spatiotemporal control, improved bioavailability, and reduced systemic

toxicity [1]. Internal triggers such as acidic pH, redox gradients, hypoxia, and disease-associated enzymes are frequently exploited in tumor and inflammatory microenvironments. For example, pH-sensitive micelles and hydrogels undergo structural disassembly in acidic sites, facilitating selective drug release [2]. Enzyme-activated carriers employ proteases or glycosidases as switches for targeted therapy, particularly in cancer and inflammatory disorders [3]. Redox-responsive nanocarriers utilize intracellular glutathione gradients to achieve selective activation in tumor and inflamed tissues [4]. External stimuli—including ultrasound, temperature, magnetic fields, and light—have also been integrated into carrier designs, offering non-invasive on-demand activation [5]. Recent innovations emphasize dual- or multi-stimuli-responsive platforms, where combined triggers enhance selectivity, minimize off-target effects, and enable multifunctional roles such as drug delivery coupled with imaging or theranostics [6,7]. These approaches are now central to the development of precision therapeutics for oncology, inflammation, and chronic diseases.

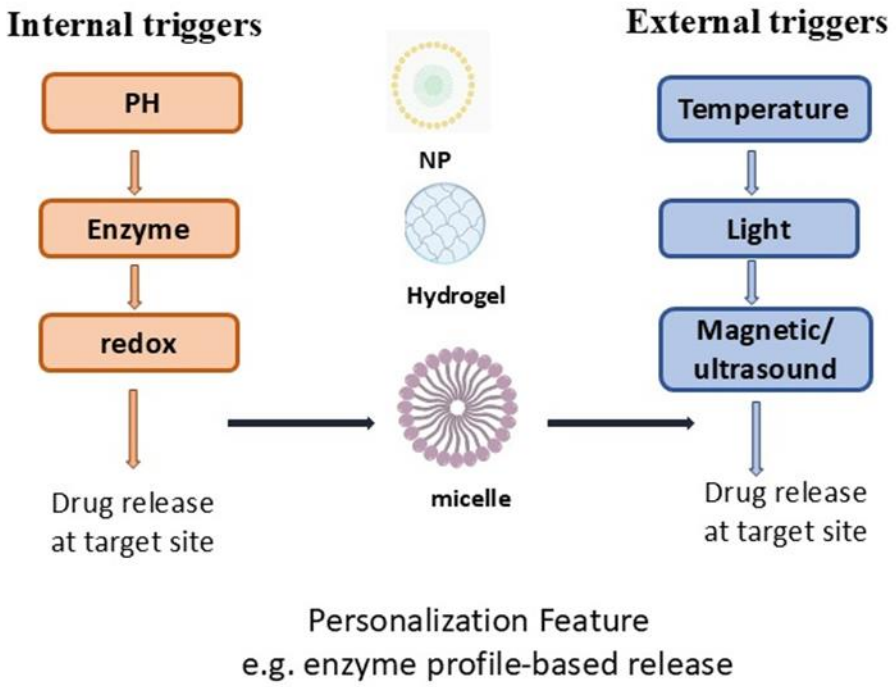

Figure 2: Mechanism of Smart and Stimuli-Responsive Delivery Systems

A comparative overview of key delivery platforms, including their advantages, limitations, and applications, is presented in **Table 1**.

Table-1: Stimuli-Responsive Drug Delivery Systems (DDS)

Stimuli	Example Carrier	Major Applications	Personalization Potential	Reference
Internal (Redox)	Redox-sensitive nanocarriers	Oncology, chronic inflammation	Tailored release based on intracellular glutathione levels	[1]
Internal (pH)	pH-sensitive micelles/hydrogels	Tumor therapy, inflammation	Release triggered by patient-specific tumor	[2]

			acidic microenvironment	
Internal (Enzyme)	Protease-activated nanoparticles	Cancer, inflammatory diseases	Carrier activation based on patient-specific enzyme profile	**[3]**
External (Temperature)	Thermo-responsive hydrogels	Localized drug delivery	Triggered by patient-specific site heating or wearable device	**[4]**
External (Magnetic/Ultrasound/Light)	Magnetic nanoparticles, ultrasound-responsive liposomes	Targeted delivery, imaging-guided therapy	Non-invasive, patient-specific spatiotemporal control	**[4,5]**
Dual-/Multi-Stimuli	pH + Enzyme responsive nanogels	Cancer therapy	Enhanced selectivity based on patient microenvironment	**[5,6]**

2. Biopolymer and Protein-Based Carriers

Biopolymer- and protein-based carriers are gaining prominence due to their intrinsic biocompatibility, biodegradability, and tunable physicochemical properties. Natural polysaccharides such as chitosan, alginate, and cellulose derivatives provide mucoadhesive properties and pH-responsiveness, making them particularly valuable for oral, nasal, and ocular delivery [8]. Proteins such as human serum albumin and gelatin have been extensively engineered into nanoparticles and hydrogels, improving solubility of hydrophobic drugs, prolonging systemic circulation, and enabling targeted accumulation in tumors [9]. Gelatin and silk fibroin matrices, responsive to both temperature and pH, further enable localized and sustained release of therapeutic agents [10]. Recent work has integrated nanotechnology with biopolymers to generate hybrid platforms capable of stimuli-responsiveness, imaging, and gene delivery. Such carriers are being investigated as safer alternatives to synthetic polymers in precision medicine [11]. Nevertheless, large-scale reproducibility, batch-to-batch variability, and regulatory standardization remain unresolved challenges that hinder clinical translation [12].While biopolymers offer biocompatibility, advances in artificial intelligence now provide the computational backbone for personalization. As shown in Table 2, biopolymer and protein-based carriers offer biocompatible, tunable, and patient-specific delivery solutions.

Table 2: Biopolymer & Protein-Based Carriers

	Source	**Delivery Route**	**Advantages**	**Limitations**	**Personalization Potential**	**Reference**
Polysaccharides	Chitosan, Alginate, Cellulose	Oral, Nasal, Ocular	Biocompatible, mucoadhesive, pH-responsive	Stability, limited loading	Patient-specific release kinetics, targeted organ delivery	[8]
Proteins	Human Serum Albumin,	IV, Local	Biodegradable, improves hydrophob	Batch variability, immunogenicity	Tumor-targeted accumulation, patient-specific dose	[9,10]

	Gelatin, Silk Fibroin		ic drug solubility			
Hybrid Biopolymer-Nano	Biopolymer + nanoparticles	IV, Local	Stimuli-responsive, imaging-capable	Scale-up challenges	Personalized theranostic applications	[11]

3. Artificial Intelligence (AI) and Digital Health Integration

Artificial intelligence (AI) and digital health technologies are reshaping modern drug delivery by enabling predictive, personalized, and adaptive therapeutic strategies. Advanced machine learning (ML) and deep learning (DL) models now support biomarker identification, pharmacokinetic predictions, and patient stratification, thereby enhancing therapeutic precision and minimizing toxicity [12].

3.1 AI in Oncology

One of the most impactful applications of AI is in oncology, where AI-assisted imaging has improved both early tumor detection and individualized treatment planning [13]. For example, deep learning algorithms have been successfully trained to analyze MRI and CT scans, enabling the detection of subtle tumor features that guide the design of patient-specific drug delivery regimens. Predictive algorithms are also being employed to optimize chemotherapy dosing schedules, reducing adverse effects while maintaining efficacy [13].

3.2 Wearables and Real-Time Monitoring

Wearable biosensors integrated with AI platforms provide continuous, non-invasive disease monitoring, offering real-time feedback for chronic disease management [14]. For instance, AI-enhanced glucose monitoring systems have been used to optimize insulin delivery in diabetic patients, while mobile health platforms track cardiovascular biomarkers to inform personalized dosing adjustments. Such integration ensures timely interventions and supports long-term patient adherence.

3.3 AI and Electronic Health Records (EHRs)

The incorporation of AI into EHR systems strengthens predictive modeling by screening for drug–drug interactions and detecting early signals of adverse events [15]. In practice, this approach has been applied in large hospital networks, where ML models flag high-risk patients and adjust therapeutic regimens proactively, minimizing hospital readmissions and improving outcomes.

3.4 Generative AI in Drug Discovery and Delivery

Generative AI models are now accelerating drug discovery pipelines by enabling virtual screening, compound optimization, and in silico prediction of therapeutic responses [16]. For example, AI platforms have been deployed to design nanoparticle carriers with optimized size and surface properties, reducing the experimental trial-and-error burden in drug delivery research. This not only saves time but also lowers development costs.As shown in Table 4, AI and digital health approaches are increasingly integrated into DDS to enable predictive, adaptive, and patient-specific therapies.

Domain	AI Method	Application	Example	Personalization Impact	Reference
Cardiology	DL	Predict arrhythmia	AI ECG analysis	Patient-specific preventive therapy	[12]
Oncology	ML	Tumor imaging & segmentation	AI-guided MRI/CT analysis	Individualized therapy planning	[13]
Oncology	ML/DL	Predictive dosing	AI-assisted chemotherapy schedule	Optimizes dose for patient-specific PK/PD	[13]
Oncology	DL	Immunotherapy response prediction	AI predicts checkpoint inhibitor response	Personalized immunotherapy schedule	[13]
Chronic Disease	Wearables + ML	Adaptive therapy	Continuous glucose monitoring + insulin dosing	Real-time personalized adjustment	[14]
Pain Management	ML + Wearables	Opioid dosing	Smart patch tracks pain signals	Tailored opioid release per patient needs	[14]
Infectious Disease	ML	Drug-resistance prediction	AI predicts resistant TB strains	Guides patient-specific regimen	[15]
Geriatric Care	ML	Polypharmacy optimization	AI monitors interactions in elderly	Minimizes adverse effects personalized to patient	[15]
Drug Discovery	Generative AI	Virtual screening	Simulation of therapeutic response	Rapid patient-specific drug candidate identification	[16]
Rare Diseases	ML	Pharmacogenomics	Personalized enzyme replacement therapy	Patient-specific treatment plan	[17]

3.5 Intelligent Drug Delivery Models

Smart drug delivery systems (SDDSs) integrate advanced biomaterials, nanotechnology, and computational modeling to enhance therapeutic precision and patient-specific outcomes. These platforms leverage dynamic design principles to optimize drug release, improve bioavailability, and minimize adverse effects, moving beyond traditional static delivery methods [18].

3.6 Machine Learning in Drug Release Optimization

Recent advances in machine learning (ML) algorithms—including XG Boost, Light GBM, and Cat Boost—have demonstrated strong predictive capability for drug release kinetics and personalized dosing regimens [18]. By analyzing multidimensional datasets, including patient demographics, pharmacokinetics, and disease biomarkers, ML models can forecast drug

absorption and circulation profiles with higher accuracy than conventional modeling approaches.

3.7 Evidence of Efficacy, Challenges, and Translational Potential

Recent studies demonstrate that ML-enhanced drug delivery systems can improve predictive accuracy, optimize therapeutic efficacy, and reduce adverse events compared with conventional approaches [19]. These intelligent platforms support individualized dosing schedules, combination therapy optimization, and integration with nanocarriers or microrobotic delivery systems. Despite this promise, translation into clinical practice faces major hurdles. Concerns include data privacy, algorithmic bias, and limited validation across diverse patient populations [17]. Furthermore, regulatory approval for AI-driven dosing and seamless integration with healthcare IT infrastructure remain underdeveloped [20]. Large-scale datasets and well-designed clinical trials are still required to establish safety and reliability. Addressing these challenges will be essential for regulatory acceptance and real-world adoption. Nonetheless, intelligent DDS represent an important step toward fully personalized therapeutic ecosystems, where drug delivery adapts dynamically to individual patient needs, bridging computational prediction with clinical application [17,19-20].

4. Advanced Manufacturing: 3D and 4D Printing

Additive manufacturing (AM) has emerged as a transformative technology in biomedical engineering, allowing the design of patient-specific and customizable drug delivery systems (DDS). Unlike conventional fabrication methods, AM enables precise spatial control over geometry, porosity, and drug distribution, resulting in improved drug stability, release kinetics, and therapeutic targeting [18]. Both 3D and 4D printing are now being explored for translational applications in drug delivery and regenerative medicine.

4.1 Three-Dimensional (3D) Printing in Drug Delivery

3D printing enables the fabrication of drug-loaded scaffolds, implants, prosthetics, and oral dosage forms with tailored drug-release profiles . By layering bioinks and polymers, drugs can be incorporated at specific regions, achieving spatially controlled delivery.

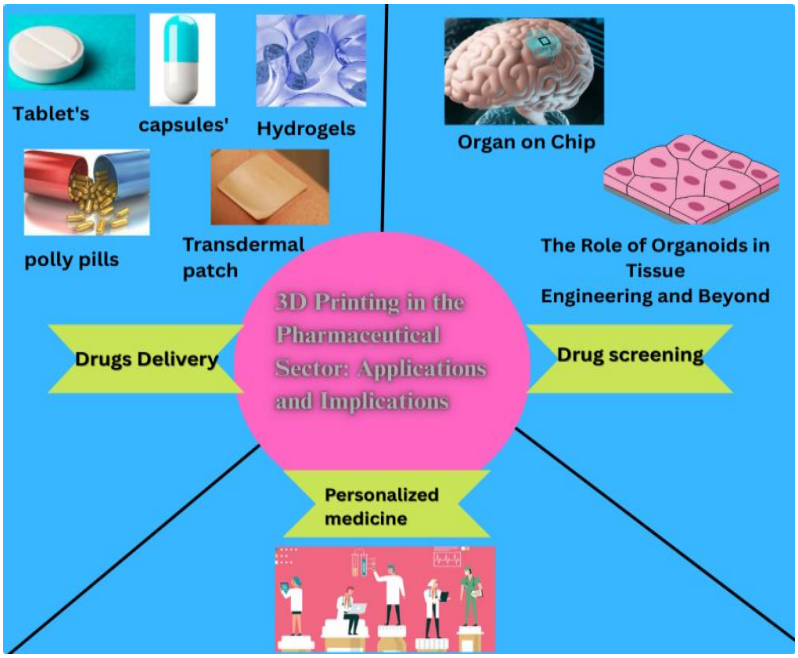

Figure 3: Three-Dimensional (3D) Printing in Drug Delivery

Example in oral drug delivery: The FDA-approved Spritam® (levetiracetam), produced using ZipDose® 3D printing technology, demonstrated the clinical feasibility of rapid-dissolving tablets for epilepsy treatment [21].

Example in tissue engineering: Drug-eluting 3D-printed scaffolds have been applied in bone regeneration, releasing antibiotics or growth factors in situ to prevent infection and accelerate healing [21].

4.2 Four-Dimensional (4D) Printing: Responsive Platforms

Building on 3D printing, 4D printing incorporates smart biomaterials that can undergo predictable transformations when exposed to physiological triggers such as pH, light, temperature, or magnetic fields [22]. This adds a dynamic element to implants and DDS.

Shape-memory polymers: Used for minimally invasive implants that expand at body temperature, ensuring site-specific functionality [22].

Hydrogels: pH-responsive hydrogels have been applied in tumor microenvironments, where they swell and release drugs in response to acidic conditions [23]. These systems allow on-demand and adaptive drug release, moving closer to real-time personalized medicine. As shown in Table 5, 3D and 4D printing enable patient-specific and adaptive drug delivery platforms, offering enhanced precision and customization.

Table 4: 3D and 4D Printing Applications in Drug Delivery

Material / Bioink	Stimuli	Example DDS	Clinical Potential	Personalization Feature	Reference
PLA, PLGA	None	3D-printed drug-loaded scaffold	Implantable device, localized therapy	Custom implant geometry based on patient anatomy	[21]

Alginate composites	Ionic	3D-printed nasal inserts	Nasal drug delivery	Adjusted drug load per patient nasal anatomy	[21]
PCL/PLA blends	None	Custom orthopedic implant	Bone regeneration	Tailored implant size and porosity for patient	[21]
Gelatin methacryl ate	Temperature + pH	Dual-responsive scaffold	Tissue engineering, localized therapy	Adaptive response to patient-specific microenvironment	[22]
Smart hydrogels	pH	4D-printed shape-memory hydrogel	Dynamic drug release	Adjusts release to patient-specific tissue pH	[22-23]
Smart hydrogels	Temperature	Thermo-responsive hydrogel implant	Cancer therapy, wound healing	Releases drugs in response to local tissue temperature	[23]
Polyurethane hydrogels	Temperature + light	4D-printed adaptive DDS	Oncology, local drug release	Patient-specific controlled therapy	[23]
PEG-based hydrogels	Light	Light-responsive implant	Controlled localized therapy	On-demand activation personalized to patient schedule	[23]
Silk fibroin-based bioink	pH + enzyme	Smart implant	Wound healing	Personalized release kinetics based on patient-specific enzymes	[25]
Biopolymer composites	Enzyme-triggered	4D hydrogel for wound healing	Regenerative medicine	Personalized enzymatic degradation-based release	[25]

Despite rapid progress, several challenges limit widespread clinical translation of AM-based DDS:

Scalability and reproducibility: High production costs and variability in mechanical strength remain barriers to large-scale use.

Biocompatibility and safety: Long-term effects of bioinks and synthetic polymers require systematic evaluation [24].

Regulatory hurdles: Few AM-based systems have reached FDA or EMA approval stages due to limited validation standards.

The development of biomimetic materials and advanced bioinks is expected to expand clinical applications of AM in drug delivery and regenerative medicine [25].

Future research is focusing on:

Hybrid constructs combining 3D-printed scaffolds with 4D smart materials for dynamic, patient-tailored therapy. Integration with AI and biosensors, enabling feedback-driven adaptive implants. Such advances will position AM technologies as key enablers of precision therapeutics in the coming decade.

5. Nanotechnology-Enabled Platforms

Nanotechnology has revolutionized modern therapeutics by enabling precise molecular-scale targeting, improved solubility of poorly water-soluble drugs, and controlled release kinetics. By

manipulating carriers at the nanoscale, researchers can achieve site-specific delivery, reduced systemic toxicity, and multifunctional therapeutic outcomes. Nanocarriers today encompass a broad spectrum, including liposomes, polymeric nanoparticles, dendrimers, metallic nanosystems, and hybrid nanostructures, each offering unique physicochemical properties tailored for specific therapeutic applications [26] as depicted in figure-4.

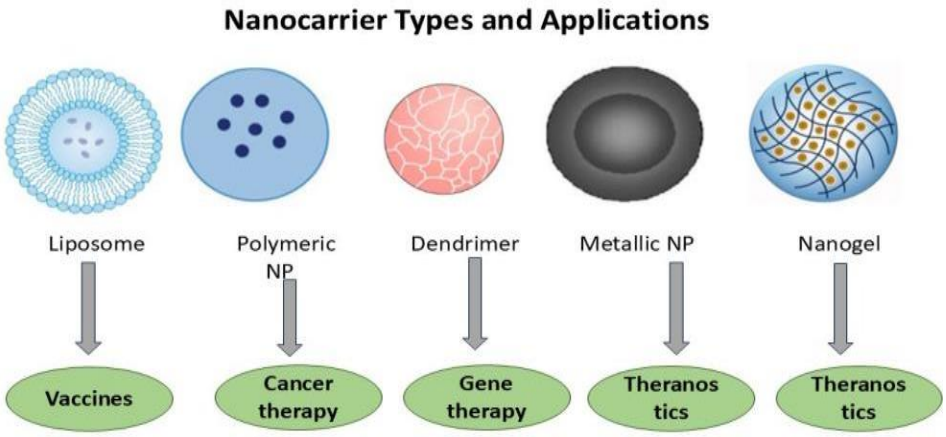

Figure-4: Nanocarrier types and applications

5.1 Lipid-Based Nanocarriers

Liposomes and lipid nanoparticles (LNPs) remain among the most clinically successful nanocarriers due to their biocompatibility, ability to encapsulate both hydrophilic and hydrophobic drugs, and modifiable surface properties. [26].

5.2 Polymeric Nanoparticles and Dendrimers

Polymeric nanocarriers such as poly (lactic-co-glycolic acid) (PLGA) nanoparticles provide controlled release and biodegradability, while dendrimers, with their highly branched architecture, enable multivalent drug conjugation and surface functionalization [27,28].

Example in oncology: Dendrimer-based platforms have been evaluated for siRNA delivery, enhancing gene silencing efficiency while minimizing off-target toxicity [28].

Example in infectious diseases: PLGA nanoparticles loaded with antimicrobial peptides are being tested to overcome antibiotic resistance, prolonging drug circulation and improving intracellular penetration [27].

5.3 Metallic and Hybrid Nanocarriers

Metallic nano systems, including gold nanoparticles, iron oxide nanoparticles, and quantum dots, offer unique optical, magnetic, and electronic properties that enable theranostic applications [28].

Imaging example: Magnetic nanoparticles are used as MRI contrast agents, allowing simultaneous imaging and drug delivery.

Photothermal therapy example: Gold nanoparticles can be externally activated by near-infrared light, producing localized hyperthermia to destroy cancer cells while co-delivering chemotherapy agents [28].

5.4 Nanogels as Drug Delivery Platforms

Nanogels are hydrophilic, crosslinked polymeric nanoparticles—have emerged as highly versatile carriers in personalized medicine. Their soft, water-rich structure and tunable size allow efficient encapsulation of small molecules, biologics, and nucleic acids, while maintaining excellent biocompatibility and controlled release profiles [33-34]. These characteristics make nanogels particularly suitable for patient-specific therapies, where drug dose, release kinetics, and targeting can be customized based on individual disease pathology [33,35]. Recent advancements have focused on stimuli-responsive nanogels, which undergo structural or conformational changes in response to pH, temperature, redox potential, or enzymatic activity. This responsiveness enables selective drug release within the disease microenvironment, such as acidic tumor tissues, inflamed sites, or intracellular compartments, thereby reducing systemic toxicity [34]. Functionalization with ligands, antibodies, or aptamers further allows active targeting of diseased cells, enhancing therapeutic efficacy [33,35]. Nanogels offer a highly adaptable platform for translational applications, including cancer therapy, infectious disease management, and autoimmune or inflammatory conditions [33-34]. Preclinical studies have demonstrated that nanogel carriers can improve bioavailability, prolong circulation, and deliver combination therapies in a site-specific manner. For instance, doxorubicin-loaded, pH-sensitive nanogels have shown enhanced tumor accumulation and reduced off-target cardiotoxicity in murine models [34]. Despite their promise, clinical translation of nanogels faces challenges such as large-scale reproducible manufacturing, regulatory approval, and long-term safety evaluation [33,35]. Advances in polymer chemistry, scalable fabrication techniques, and robust quality control are expected to facilitate the development of nanogels as clinically translatable, patient-tailored drug delivery systems. Future directions include integration with imaging-guided delivery, hybrid smart materials, and multi-drug loading strategies to achieve precision, safety, and personalized therapeutic outcomes [34,35].

Despite the transformative potential of nanotechnology, several barriers persist:

Safety and immunogenicity: Long-term effects of inorganic nanoparticles and accumulation in non-target tissues remain uncertain [30].

Manufacturing and scale-up: Reproducibility, stability, and regulatory compliance remain major hurdles for translating lab-scale nanocarriers into clinically approved therapies. Case in point: Although liposomal formulations (e.g., Doxil® for doxorubicin delivery) and LNP-based mRNA vaccines have been clinically successful, many experimental platforms fail during scale-up due to batch variability and cost-intensive processes [31]. Continuous innovations in surface modification, hybrid nanosystems, and AI-guided nanomedicine design are expected to accelerate clinical translation in oncology, infectious diseases, and regenerative medicine.

Table 5: Nanocarrier Platforms, Applications, and Personalization Potential

Carrier Type	Drug / Biologic	Advantages	Clinical Status	Personalization Potential	Reference
Liposomes	mRNA vaccines, chemotherapeutics	Biocompatible, controlled release	FDA-approved (COVID-	Targeted mRNA delivery for	[26]

			19 vaccines)	patient-specific antigens	
Polymeric NP	siRNA, small molecules	Stimuli-responsive, modifiable	FDA-approved (Inclisiran)	Patient-specific ligand targeting, dosing	[27]
Dendrimers	Chemotherapy agents	High loading, surface functionalization	Preclinical / Early-phase trials	Customizable surface for patient tumor biomarkers	[28]
Metallic NP	Imaging & drug delivery	Theranostics	Preclinical	Patient-specific imaging-guided therapy	[29]
Nanogels	Biologics, nucleic acids	High payload, stimuli-responsive	Preclinical	Multi-stimuli design for tumor microenvironment personalization	[32]

6.Emerging Therapeutic Approaches in Disease-Specific and Combination Approaches

6.1 Integration of Omics and Precision Diagnostics

The integration of genomics, transcriptomics, proteomics, and metabolomics into clinical workflows is facilitating more precise treatment design. By combining multi-omics data with advanced bioinformatics, clinicians can identify disease subtypes, predict therapeutic response, and adjust dosing regimens on an individual basis. Despite these advances, challenges such as safety, toxicity management, and optimized dosing continue to impede widespread clinical implementation [36]. Moreover, the high cost of omics-guided therapy and the need for standardized protocols remain practical hurdles for broader adoption. The therapeutic landscape is expanding rapidly with innovations in gene editing, cell therapies, immunotherapies, personalized vaccines, and digital health interventions.

6.2. Gene Editing Therapies

In December 2023, the FDA approved Casgevy™ (exagamglogene autotemcel), a pioneering CRISPR-Cas9 cell-based therapy, for patients aged 12 and older with sickle cell disease and vaso-occlusive crises—marking the first clinical use of CRISPR in medicine [37]. Additional CRISPR-based treatments are currently under clinical investigation for conditions such as inherited retinal disorders, Duchenne muscular dystrophy, and various cancers, reflecting the precision and personalization potential of these genome-editing strategies.

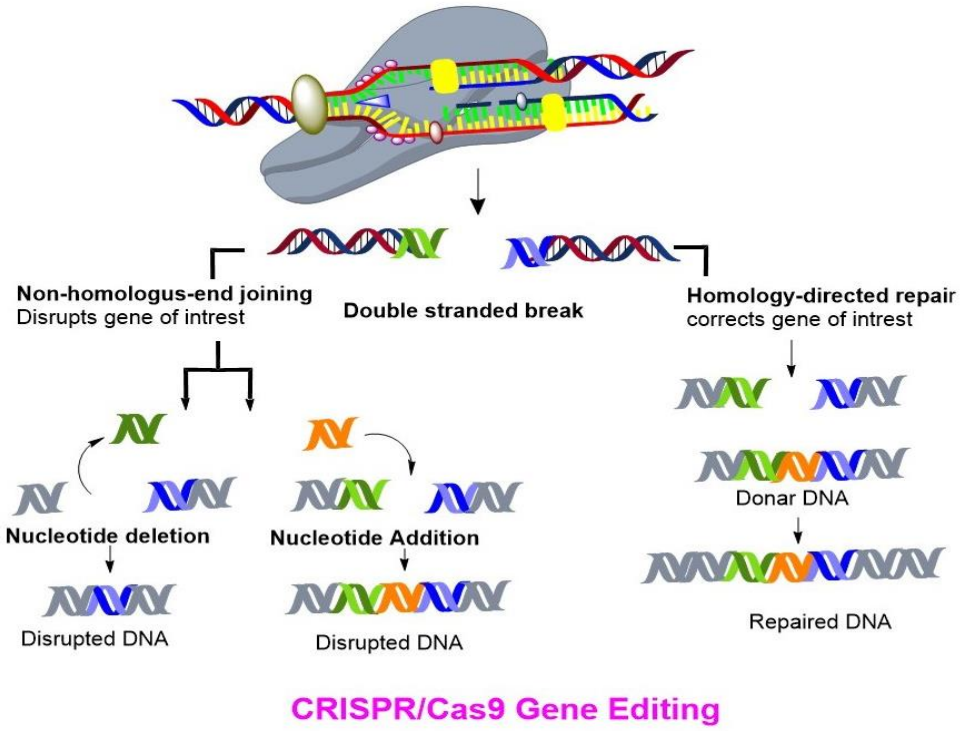

Figure-5: CRISPR/Cas Gene Editing technology

6.3 Cell-Based Immunotherapies

CAR-T and TCR-engineered therapies maintain high efficacy in hematologic cancers. Recent advances are focusing on dual-targeted CAR-T constructs capable of reducing antigen escape and expanding applicability to solid tumors. Preliminary clinical data, including dual-target CAR-T in glioblastoma, demonstrate early signs of tumor regression and improved persistence, although challenges with the tumor microenvironment and solid tumor penetration remain [38].

6.4 Personalized Vaccines and mRNA Therapeutics

Personalized neoantigen mRNA vaccines administered alongside checkpoint inhibitors have delivered promising outcomes. A Phase IIb trial combining mRNA-4157 with pembrolizumab in resected high-risk melanoma reduced recurrence risk by approximately 44% compared to immunotherapy alone, highlighting the role of individualized vaccine design in enhancing antitumor immunity [39].

6.5 Psychedelic-Assisted and Digital Therapeutics

Emerging treatments for neuropsychiatric illnesses include psilocybin-assisted psychotherapy, which has shown significant antidepressant effects in individuals with treatment-resistant depression in recent trials [40]. Concurrently, digital therapeutics—software-driven, evidence-based interventions—are increasingly being deployed to treat chronic conditions such as type 2 diabetes, chronic pain, and mental health disorders, offering scalable, personalized care options [41]. These emerging technologies—ranging from CRISPR and cell therapies to individualized vaccines and digital interventions—underscore the evolving landscape toward truly patient-centric medicine. However, challenges in scaling production, standardizing

regulatory pathways, and ensuring long-term safety continue to influence their translational trajectory. Recent breakthroughs illustrate the transformative potential of precision drug delivery in diverse disease contexts. A timeline of landmark therapies highlights how nanomedicine, gene editing, and mRNA technologies are advancing from concept to clinical practice. some are listed in table 7.

Table 6: Landmark Advances in Precision and Combination Drug Delivery Approaches

Year	Technology / Product	Therapeutic Area	Key Features	Regulatory Status / Clinical Phase	Reference
2020	mRNA-1273 (Moderna COVID-19 vaccine, LNP-based)	COVID-19	LNP-delivered mRNA vaccine	EUA 2020; Full approval 2022	[42]
2020	BNT162b2 (Pfizer BioNTech vaccine)	COVID-19	Ionizable LNP mRNA vaccine	EUA 2020; Full approval 2021	[43]
2021	Inclisiran (Leqvio®)	Hyper cholesterolemia	GalNAc-conjugated siRNA	FDA approved 2021	[44]
2022	VYXEOS® (liposomaldaunorubicin/cytarabine)	AML	Liposomal co-delivery chemotherapy	FDA/EMA approved	[45]
2023	Casgevy™ (CRISPR-Cas9 therapy)	Sickle cell, β-thalassemia	First CRISPR gene-editing drug	FDA & EMA approved Dec 2023	[46]
2023	Obecabtagene autoleucel (CAR-T)	Lymphoma	Personalized CAR-T therapy	FDA approved 2023	[47]
2024	Personalized mRNA cancer vaccines	Melanoma, Pancreatic cancer	Neoantigen-based mRNA platforms	Phase II/III trials ongoing	[48]
2025	Inhalable algae-based microrobots	MRSA pneumonia (preclinical)	Biohybrid NP microrobots	Preclinical murine proof–of–concept	[49]

7. Mobile Microrobots for Active Drug Delivery

Recent advances in micro- and nanorobotics have established mobile microrobots as a transformative approach for precision and patient-specific drug delivery. These devices actively navigate complex biological environments, overcoming obstacles such as dense extracellular matrices, vascular flow, and tissue heterogeneity. Propulsion mechanisms include magnetic fields, ultrasound, chemical gradients, or biohybrid actuation, enabling controlled transport of therapeutic payloads to specific disease sites [50-51]. By tailoring microrobot size, shape, and propulsion method to the patient's anatomy and disease microenvironment, personalized therapeutic strategies can be realized, enhancing efficacy while minimizing off-target toxicity.

7.1 Biohybrid Microrobots

Biohybrid microrobots combine living cells or microorganisms with synthetic components, integrating natural motility with engineered functionality. Bacteria-driven microrobots, for example, can selectively migrate toward hypoxic tumor regions, carrying chemotherapeutic agents or gene-editing tools. Similarly, cell-derived microrobots using red blood cells or platelets exhibit immune evasion and prolonged circulation, making them highly suitable for tumor therapy, targeted gene delivery, and regenerative applications [52]. These systems allow personalized modulation of drug load and release kinetics according to patient-specific tumor biology or regenerative requirements, supporting translational medicine approaches.

7.2. Targeting Strategies and Therapeutic Applications

Microrobots employ active and passive targeting strategies to improve drug localization. Functional coatings and stimuli-responsive materials enable cargo release in response to pH, enzymes, or local temperature, allowing site-specific and adaptive therapy. Preclinical studies have demonstrated enhanced therapeutic efficacy and reduced systemic toxicity relative to conventional delivery. For instance, tumor-targeted microrobots carrying chemotherapeutics have shown higher local drug concentrations and better tumor regression in murine models. Integration with imaging modalities such as MRI, ultrasound, or fluorescence-guided navigation further enables patient-specific monitoring and feedback, ensuring safe and accurate delivery. Despite their promise, microrobots face hurdles including scalable manufacturing, immune interactions, precise non-invasive tracking, and long-term biosafety. Translation into clinical practice requires optimization of navigation control, payload capacity, and biocompatible materials. Continued development of autonomous navigation, hybrid smart materials, and real-time imaging integration is expected to bridge preclinical findings with patient-specific therapies, enabling precise, adaptable, and clinically translatable micro robotic drug delivery [53-54].

Example- Inhalable Biohybrid Microrobots for Pulmonary Therapy

A promising innovation in pulmonary medicine is inhalable biohybrid microrobots, often algae-based, capable of penetrating deep lung regions post-aerosolization. These microrobots retain motility, evade immune clearance, and allow prolonged retention in alveoli, offering patient-specific therapeutic advantages such as adjustable dosing and site-targeted drug release [55-57]. In murine models of bacterial pneumonia, inhalable microrobots carrying vancomycin nanoparticles achieved over 10,000-fold reduction in bacterial load and complete survival, outperforming conventional intravenous therapy [58-59]. Such systems could be personalized based on lung morphology, disease severity, and pathogen profile, enabling precision respiratory medicine for conditions including asthma, COPD, tuberculosis, and viral infections [60]. Translational Considerations and Challenges in translation include optimization of nebulization devices, large-scale production, reproducibility, and thorough safety evaluation in human subjects [61]. Incorporating real-time imaging, patient-specific dosing strategies, and biocompatible payload design will be essential for clinical adoption. If successfully translated, inhalable biohybrid microrobots could revolutionize pulmonary therapeutics by providing targeted, adaptable, and patient-tailored interventions.[62-63]

8. Translational Barriers and Future Roadmap

While laboratory innovations in drug delivery systems (DDS) are progressing rapidly, clinical translation faces significant barriers. Addressing these challenges is essential for the successful implementation of advanced therapies [64-65].

8.1 Regulatory Frameworks

Current regulatory guidelines often lag behind novel platforms like nanomedicine, microrobotics, and AI-driven DDS. The emergency authorization of mRNA vaccines during COVID-19 demonstrated flexibility, but harmonized international standards are urgently needed to ensure the safety and efficacy of these advanced therapies. Recent reviews emphasize adaptive, internationally aligned frameworks [64,66].

8.2 Manufacturing and Scalability

Good Manufacturing Practice (GMP) production of complex nanocarriers remains challenging due to reproducibility, batch variability, and high costs. Continuous microfluidics, modular GMP approaches, and advanced biomanufacturing platforms have been proposed to enable large-scale, cost-effective production [65].

8.3 Safety and Long-Term Biocompatibility

Concerns such as immunogenicity, long-term toxicity, and off-target accumulation remain major hurdles. Organ-on-chip and advanced in vitro models are increasingly being used to predict human responses, providing better insights into nanomaterial–tissue interactions and potential toxicological risks [67].

8.4 Ethical and Accessibility Concerns

High costs risk widening healthcare disparities, especially in low-resource settings. AI-driven platforms also pose challenges related to data privacy, transparency, and accountability. Ethical frameworks and patient-centric designs are needed to ensure equitable access and responsible adoption [68-69]. To contextualize real-world adoption, Table 3 summarizes the major translational challenges, representative examples, and proposed solutions.

Table 7: Challenges and proposed solutions in next-generation drug delivery systems.

Challenge	Example/Context	Proposed Solutions	References
Formulation stability	Cold chain for mRNA vaccines	Thermostable lipids, lyophilized forms	[64]
GMP manufacturing scale-up	Complex nanocarrier production	Modular GMP, microfluidic platforms	[65]
Toxicity & immune response	Particle clearance issues	PEG alternatives, biomimetic coatings	[66-67]
Regulatory uncertainty	New tech lack guidelines	Adaptive international frameworks	[64,66]
Patient adherence	Wearable/device use	User-friendly design, patient education	[67]
High cost & poor access	CAR-T & gene editing costs	Streamlining production, insurance models	[68]
Data ethics in AI	Patient data risks	Blockchain, AI explainability	[69]

Future roadmap (2025–2030):

- ✧ Harmonized international regulatory guidelines for nanomedicine and AI-based DDS.
- ✧ Development of scalable, cost-effective manufacturing technologies.
- ✧ Integration of real-world data and AI analytics to personalize regimens.
- ✧ Inclusion of patient-centered outcomes in DDS evaluation.
- ✧ Strengthened global collaborations to improve access in resource-limited regions.
- ✧ Together, these steps will ensure that next-generation DDS move from innovation to patient benefit.

CONCLUSION AND FUTURE PERSPECTIVES

Next-generation drug delivery systems are moving beyond experimental concepts to clinically relevant solutions across oncology, infectious diseases, genetic disorders, and chronic illnesses. Stimuli-responsive nanocarriers, biopolymer matrices, AI-assisted models, nanogels, and microrobotics demonstrate how personalization can be embedded directly into therapeutic design. Yet, fewer than 15% of advanced DDS currently progress beyond early trials, underscoring the urgent need for scalable manufacturing, harmonized regulation, and predictive safety testing. By 2030, the convergence of nanotechnology, digital health, and advanced biomaterials is expected to deliver adaptive, intelligent ecosystems capable of real-time personalization. The next critical step lies in translating these personalized platforms into everyday clinical practice, ensuring accessibility, safety, and patient-centered outcomes. If achieved, drug delivery will evolve from passive carriers to dynamic systems, redefining the very foundation of precision medicine.

Ethical approval: Not applicable, as this study is a review of published literature.

Conflict of Interest: The authors declare no conflict of interest.

ACKNOWLEDGMENTS: The authors received no specific funding for this work

REFERENCES

1. Sun T. Stimuli-responsive drug delivery systems triggered by intracellular microenvironments. J Control Release. 2023;370:25–40.
2. Zhang H, Wang X, Xu J, et al. pH-responsive nanomedicine for tumor therapy: recent progress and clinical outlook. J Control Release. 2023;360:485–500.
3. Zhao Z, Yu H, Wang Z, et al. Enzyme-triggered drug delivery systems in cancer therapy. Acta Pharm Sin B. 2023;13(8):3578–96.
4. Li J, Liu P, Zhou Y, et al. Stimuli-responsive nanocarriers for precision drug delivery: recent advances and translational prospects. Adv Mater. 2024;36(7):2308654.
5. Huang X, Wang Y, Zhang C, et al. Advances in ultrasound-responsive drug delivery systems for cancer treatment. Adv Drug Deliv Rev. 2024;205:114338.
6. Xu Y, Chen Q, Guo X, et al. Multi-stimuli responsive nanocarriers for on-demand drug release and precision cancer therapy. Nano Today. 2023;52:101940.
7. Wang Y, Lin J, Tang L, et al. Smart nanomedicine platforms for imaging-guided

combination cancer therapy. Small. 2024;20(5):2306782
8. Hsu CY. Recent advances in polysaccharide-based drug delivery systems. Drug Deliv Transl Res. 2024;14:1835–1849.
9. Sreena R, et al. Biodegradable biopolymeric nanoparticles for biomedical applications. Int J Nanomedicine. 2023;18:1877–92.
10. Yu B, et al. Silk fibroin as a drug delivery carrier: biocompatibility, mechanical properties, biodegradability, and safety. Front Pharmacol. 2023;14:1071868.
11. Azimizonuzi H, et al. Hybrid liposome-nanoparticle structures for theranostic drug delivery. Nanoscale Adv. 2025;7:1050–1063.
12. Wang Z, Huang Z, Zhang H, et al. Artificial intelligence in drug delivery systems: opportunities and challenges. Adv Drug Deliv Rev. 2024;205:114342.
13. Sharma A, Patel V, Singh R, et al. AI-enabled cancer imaging and precision therapy planning: recent trends. Front Oncol. 2023;13:1224875.
14. Li J, Hu W, Tang Y, et al. Wearable sensors and AI-assisted drug delivery for chronic disease management. Biosens Bioelectron. 2024;243:115731.
15. Xie Y, Wang S, Xu H, et al. Integration of AI and EHR for predictive pharmacology. NPJ Digit Med. 2023;6:65.
16. Gupta R, Bender A, Schneider P, et al. Generative AI in drug design and delivery: current applications and future outlook. Nat Rev Drug Discov. 2024;23(2):89–108.
17. Serrano DR, Luciano FC, Anaya BJ, et al. Artificial intelligence in drug delivery: moving toward personalized nanomedicine. Pharmaceutics. 2024;16(10):1328.
18. Satheeskumar R, et al. Enhancing drug discovery with AI: Predictive modeling of drug release kinetics using machine learning algorithms. Sci Rep. 2025;15(1):1234.
19. Teplytska O, et al. Machine learning methods for precision dosing in anticancer drug therapy. Pharmaceutics. 2024;16(3):123–134.
20. Wang Y, et al. A machine learning approach to personalized medicine: Predicting optimal drug delivery parameters. Preprints. 2025;2025042570.
21. Alhnan MA, Okwuosa TC, Sadia M, Wan KW, Ahmed W, Arafat B. Emergence of 3D printed Dosage Forms: Opportunities and Challenges. Pharm Res. 2020;37(2):34.
22. Li J, Wu C, Chu PK, Gelinsky M. 4D printing of hydrogels: Innovation in biomedical applications. Mater Today. 2020;35:88-100.
23. Wan X, Li Z, Luo D, Wang K, Yang H, Chen X. Stimuli-responsive 4D printed hydrogels for biomedical applications. Adv Sci (Weinh). 2021;8(3):2002027.
24. Seoane-Viaño I, Trenfield SJ, Basit AW, Goyanes A. Translating 3D printed pharmaceuticals: From hype to real-world clinical applications. Adv Drug Deliv Rev. 2021;174:553-74.
25. Zhu C, Warner J, Han J, Li T, Gogotsi Y, Kumbur EC. The role of advanced manufacturing in next-generation drug delivery and tissue engineering. Adv Drug Deliv Rev. 2022;188:114434.
26. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: An updated review. Pharmaceutics. 2022;14(2):389.
27. Danaei M, Dehghankhold M, Ataei S, Hasanzadeh Davarani F, Javanmard R, Dokhani A, et al. Impact of particle size and surface modification on the cellular uptake and biodistribution of polymeric nanoparticles. Int J Nanomedicine. 2021;16:731–746. doi:10.2147/IJN.S284720.
28. Singh R, Lillard JW Jr. Nanoparticle-based targeted drug delivery. Exp Mol Pathol. 2021;118:104573.

29. Ventola CL. Progress in nanomedicine: Approved and investigational nanodrugs. pt. 2020;45(1):41–51. PMID:31930277.
30. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: An update. Bioeng Transl Med. 2021;6(3):e10246.
31. Bulbake U, et al. Challenges in manufacturing and scale-up of nanocarriers for clinical translation. Pharmaceutics. 2022;14(6):1153.
32. Singh S, et al. Stimuli-responsive nanogels for personalized drug delivery in oncology. Adv Drug Deliv Rev. 2023;196:114703.
33. Vashist A, Sharma S, Kumar R, et al. Recent advances in nanogels for drug delivery and biomedical applications. J Control Release. 2024;345:123–145.
34. Ashwani PV, Gupta S, Singh R, et al. Stimuli-Responsive and Multifunctional Nanogels in Drug Delivery. Chem Biodivers. 2023;20(9):e202301009.
35. Chakroborty S, Ghosh S, Saha S, et al. Stimuli-responsive nanogels: A smart material for targeted drug delivery. J Drug Deliv Sci Technol. 2024;69:103436.
36. Tsimberidou AM, Kurzrock R. Precision medicine in oncology—2025 outlook. J Clin Oncol. 2024;42(5):423–34.
37. Parums DV. First regulatory approvals for CRISPR-Cas9 therapeutic exagamglogene autotemcel (Casgevy) for sickle cell disease and transfusion-dependent β-thalassemia. Am J Med. 2024;137(2):100-2.
38. Bagley SJ, O'Rourke DM, Desai AS, et al. Dual-target CAR-T cell therapy in recurrent glioblastoma: early clinical results. Nat Med. 2025;31(3):455-63.
39. Weber JS, Atkins MB, Schadendorf D, et al. Personalized neoantigen vaccine (mRNA-4157) plus pembrolizumab in resected melanoma: results from a randomized Phase IIb trial. N Engl J Med. 2023;389(25):2304-15.
40. Rosenblat JD, McIntyre RS, Rodrigues NB, et al. Psilocybin-assisted psychotherapy for treatment-resistant depression: efficacy and safety outcomes from a randomized clinical trial. Lancet Psychiatry. 2024;11(3):215-27.
41. Wang C, Torous J, Chan S, et al. Digital therapeutics for chronic disease and mental health management: current status and future perspectives. NPJ Digit Med. 2023;6(1):120.
42. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 2020;383:2603–15.
43. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403–16.
44. Ray KK, Wright RS, Kallend D, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med. 2020;382:1507–19.
45. Lancet Haematol. VYXEOS® (liposomal daunorubicin/cytarabine) approval summary. Lancet Haematol. 2022;9:e100-5.
46. Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia. N Engl J Med. 2023;388:252–64.
47. Neelapu SS, Locke FL, Bartlett NL, et al. Obecabtagene autoleucel: CAR-T therapy in lymphoma. Blood. 2023;141:122–35.
48. Sahin U, Karikó K, Türeci Ö. Personalized mRNA vaccines for cancer immunotherapy. Nat Rev Drug Discov. 2024;23:215–36.
49. Li X, Gao W, Zhang L, et al. Inhalable biohybrid microrobots for targeted pulmonary therapy. Adv Mater. 2025;37:2405678.
50. Chen X, Hoop M, Mushtaq F, et al. Magnetically driven micro- and nanorobots for biomedical applications. Appl Mater Today. 2023;32:101025.

51. Li J, Gao W, Wang J, Zhang L. Micro/nanorobots for targeted drug delivery: advances and challenges. Nat Rev Mater. 2023;8:215–32.
52. Park BW, Zhuang J, Yasa O, et al. Biohybrid microswimmers for targeted drug delivery. ACS Nano. 2024;18(1):112–23.
53. Medina-Sánchez M, Xu H, Schmidt OG. Emerging microrobotic systems for drug delivery. Nat Rev Bioeng. 2024;2:67–82.
54. Zhang Y, Wang L, Xu T, et al. Intelligent microrobots for precision cancer therapy. Adv Mater. 2023;35(12) :2208745.
55. Li J, Esteban-Fernández de Ávila B, Gao W, et al. Micro/nanorobots for targeted delivery and sensing. Adv Mater. 2020;32(14):1906766.
56. Gao W, Wang J. The environmental impact of microrobots: from bench to bedside. ACS Nano. 2020;14(5):5799–816.
57. Sitti M, Ceylan H, Hu W, et al. Biohybrid microrobots. Nat Rev Mater. 2021;6(5):5–26.
58. Li S, Fan Y, Liu H, et al. Challenges and prospects of microrobotics in biomedical applications. Adv Funct Mater. 2022;32(12):2109351.
59. Chen Y, Dong R, Zhao X, et al. Imaging-guided navigation for microrobot-mediated drug delivery. Small. 2023;19(4):2205578.
60. Esteban-Fernández de Ávila B, Angsantikul P, Li J, et al. Micromotor-based delivery for respiratory therapy. Adv Funct Mater. 2022;32(18):2109873.
61. Angsantikul P, Li J, Esteban-Fernández de Ávila B, et al. Algae-driven microrobots for targeted antibiotic delivery in lungs. Sci Adv. 2021;7(18):eabd7483.
62. Wu Z, Wang H, Zhang Q, et al. Biohybrid microrobots for targeted respiratory therapy: preclinical applications. Adv Healthc Mater. 2022;11(5):2102415.
63. Li J, Angsantikul P, Esteban-Fernández de Ávila B, et al. Translation challenges of inhalable microrobots for lung diseases. Nano Today. 2022;42:101325.
64. Mangla B, Rehan F, Greish K, Torchilin VP. Regulating nanomedicines: challenges, opportunities, and strategies. Nat Rev Drug Discov. 2023;22(7):453–470.
65. Rehan F, Zhang M, Fang J, Greish K. Therapeutic applications of nanomedicine: recent developments and future perspectives. Molecules. 2024;29(9):2073.
66. Rodríguez-Gómez FD, Monferrer D, Penon O, Rivera-Gil P. Regulatory pathways and guidelines for nanotechnology-enabled health products: a comparative review of EU and US frameworks. Front Med. 2025;12:1544393.
67. Liu Y, Zhang Y, Li H, Hu TY. Recent advances in the bench-to-bedside translation of cancer nanomedicines. Acta Pharm Sin B. 2025;15(1):97–122.
68. Havelikar U, Ghorpade KB, Singh M, Patel A, Gupta PN. Comprehensive insights into nanotoxicity mechanisms, assessment methods, and regulatory challenges of nanomedicines. Discover Nano. 2024;15:41.
69. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25:44–56.

HOW TO CITE: Tekumatla Gowthami, K. S. Vaishnavi, Nazneen Kausar, Oruganti Manaswi, Madishetty Raghavi, Usha Rani Peddaboina*, Next-Generation Drug Delivery Systems (2020–2025): Translating Personalization into Practice, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 9, 1516-1535 https://doi.org/10.5281/zenodo.17115597