Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Review Article

Next – Generation Drug Delivery System: Bridging Innovation and Therapeutic Needs

PRATHAMESH NIVAS THORAT [1], JAMEEL AHMED S MULLA[1]*, MILIND DILIP PHANSE[2]

[1] Department of Pharmaceutics, Shree Santkrupa College of Pharmacy, Ghogaon- Karad, Maharashtra - 415111, India

[2] Department of Pharmaceutics, Arvind Gavali College of Pharmacy, Jaitapur, Satara, Maharashtra -415004, India

ARTICLE DETAILS

Article history:
Received on 13 December 2025
Modified on 21 December 2025
Accepted on 23 December 2025

Keywords:
Next-Generation Drug Delivery Systems (NGDDS),
Controlled Release,
Nanotechnology,
Biomaterials Technology,
3D Printing,
Microfluidic Devices,
AI Guidance Models,
Precision Medicine,
Personalized Drug Delivery,
Biocompatible Carriers,
Biodegradable Systems,
Targeted Delivery.

ABSTRACT

"Next-Generation Drug Delivery Systems: A Controlled Release Concept" is a groundbreaking book, self-contained and fully integrated in its treatment of next-generation nano systems employed in controlled release of drugs." Through implementation of nanotechnology, biomaterials technology, 3D printing, microfluidic device technologies and AI guidance models as well as precision medicine methodology incorporated NGDDS could provide the controlled and targeted delivery along with personalized patient specific treatment. Biocompatible, biodegradable, and active/passive targeting capabilities along with controlled release and stimuli-responsiveness are core design features for intelligent carriers such as nanoparticles, liposomes, polymeric micelles, hydrogels, microneedles, implantable systems and bioinspired vesicles. They improve the pharmacokinetics, stabilise fragile biologics and enable programmable site-specific release of drug in situ. Therapeutic uses range from oncology, neurological diseases and infectious endemics (e.g., m RNA based vaccines), to autoimmune disorders and gene/nucleic-acid therapies. But there are still hurdles to overcome in the areas of mass production, long-term safety, biodistribution, immunogenicity and regulatory complexity. Novel trends including personalized nanomedicine, combined with digital health and wearable sensors, green biomaterials and ethical consideration are paving the way for NGDDS in a new direction. In general, NGDDS represent a revolution by bringing technological discoveries to meet medical challenges in the context of predictable, preventive, personalized, and participatory (P4) medicine that are more accurate, safer and cheaper overall.

INTRODUCTION

The main idea of NGDDS is to bypass the pharmacokinetic, chemical, and biological limitations of conventional medicines. Conventional dosage forms are often inefficient because they are poorly targeted, have low solubility and not well controlled distribution. Alternatively, through the application of biomaterials, AI and nanotechnology, NGDDS aims to offer patient specific-directed treatment with precision [1].

1. Evolution of Drug Delivery System

Drug delivery the concept of drug delivery has evolved from a simple administration of active pharmaceutical ingredients (APIs) to complex systems that control the release rate, time point, and site of action [2].

These two generations of medicine were 1) The first generation (1950-1980s): focus on traditional dosage forms, such as tablets, capsules, and injections. These resulted in immediate release but plasma levels were uncontrolled to produce variable therapeutic effects.

To achieve uniform levels of the drug, controlled-release devices such as matrix tablets, osmotic pumps and transdermal patches were developed in the second generation (1980–2000s) [3]. In contrast to the first-generation systems with challenges in achieving net drug delivery and the second-generation carrier and implant-based systems, which generally suffer from systemic exposure, the third generation of precision

Author for Correspondence:
Email: jameelahmed5@gmail.com

medicine -- an era focusing on targeted and stimulus-responsive formulations such as hydrogels, liposomes and microneedles or nanoparticles responding to pH, enzymes or temperature [4] - have enabled patient-specific dose forms with tunable pharmacokinetics achievable by recent advances in 3D printing/deposition and microfluidic manufacturing [5]. It is therefore not surprising that intelligent, responsive and programmable therapeutic systems have surpassed passive administration in drug delivery.

2. Limitation of Conventional Method

Conventional routes of administration, particularly oral and parenteral, suffer a variety of limitations that limit the efficacy with which treatment can be applied.

1. Low Bioavailability: Marked hepatic metabolism results in low systemic concentrations. Metabolism and poor solubility [6].
2. Limited Ability to Target: Drugs course through the body and cause collateral damage to healthy tissue as well as diseased [2].
3. Rapid Elimination and Short HL: Patient adherence is often poor because of multiple administrations.
4. Inability to Cross Biological Barriers: Most medicines cannot penetrate the blood–brain barrier and/or tumor core physique defense mechanisms, since peptides, proteins, and nucleic acids are sensitive to enzyme degradation which is unsecure in treatment of administration [7, 8].

For example, systemic toxicities and off-target delivery limit the application of anticancer drugs such as doxorubicin and paclitaxel while protecting payloads is a prerequisite for efficient targeting of biologics including insulin and mRNA vaccines.

NGDDS encapsulation, surface modification and [9] stimulus-responsive process to solve these problems reduces bioavailability and safety.

3. Scope and Objective of the Review

Rationale: The review of NGDDS is intended to provide information about the state of the art platforms, materials and supporting technologies that vehicles for drugs are in face with now a day clinically.

The scope consists of:

1. Key design considerations: physicochemical optimization, biocompatibility and biodegradability.
2. Nanoparticles, microneedles, liposomes and implantable devices are some of the emerging systems for delivery.
3. Among technology enablers are AI-enabled modelling, microfluidics and 3D printing for personalized treatment [10].
4. Applications range from gene/nucleic acid delivery to cancer therapy, neurological and autoimmune diseases.
5. Regulatory, ethical, and translational implications remain for guaranteeing repeatability, safety, and patient consent [11].

Ultimately, the study raises questions about where NGDDS may fit into the realm of predictive, preventative, personalized and participatory (P4) medicine through linking novelty to therapeutic need [12].

Design Paradigms of Drug Delivery System of Next Generation:

1. Biocompatibility and Biodegradability:

Biocompatibility and biodegradability are two key factors of the NGDDSs which means that the carrier should have minimal interaction with biological tissue, it can be predictably degrade and eliminates from body. Biocompatible materials do not cause immune, toxic or inflammatory responses upon onset and degradation [13]. Some biodegradable polymers, such as polylactic acid (PLA), polyglycolic acid (PGA), and (lactic-co-glycolic acid) (PLGA), have been widely used because of their low toxic potential and hydrolytic degradation yielding lactic and glycolic acids which are metabolizable [14]. Biodegradability eliminates the need for surgical explantation of implant, decreasing chronic implantation-related problems over time [15]. Polymer chemistry has now been advanced to this level that kinetics of degradation, surface charge, and hydrophilicity of resorbable systems are controlled more precisely so that drug release kinetics and tissue compatibility can be defined [16]. Additionally, polymers of natural origin including chitosan, alginate and collagen constitute biodegradable eco-friendly alternatives with the capacity to target receptors on endogenous cells [17].

2. Targeting Strategies: Passive and Active Targeting:

Targeting methods determine the specificity and therapeutic effect of NGDDSs. Examples of passive targeting include EPR effect that allows nano vehicles (10–200 nm) to accumulate in the tumor because of leaky vasculature and disturbed lymphatic drainage, in diseased tissues [18, 19]. Morphological and physicochemical appearance is considered to be optimal when particle size, surface charge, and hydrophilicity are optimized for the best biodistribution and systemic circulation [20, 21]. In contrast, active targeting is based on molecular recognition for the conjugation with oligonucleotides to the surfaces of carriers (ligands: antibodies, peptides or aptamers), which selectively bind such end-overexpressed receptors at diseased cells [3, 22, 23]. This increases the receptor-mediated uptake and reduces off-target toxicity. Passive targeting: a chemically-prepared nanocarrier supersedes the need for cargo to be protected in a biologically derived particle with accumulation at sites enhanced over healthy tissue [1-3] Doxil® (PEGylated liposomal doxorubicin) is such passively targeted nano formulation that has had clinical success, however newer ligand-decorated particles take advantage of both active and passive processes for better site-specific delivery [24-26].

3. Sustained and Controlled Delivery Systems:

Controlled and sustained release systems are developed to retain therapeutic concentrations at the level of action for prolonged periods, reducing fluctuations or potential toxicity [27]. These systems control drug release by diffusion, polymer degradation or osmotic pressure mechanisms based on the physical and chemical nature of the material and drug properties [28]. Polymeric implants, hydrogels and microspheres typically act as sustained delivery matrices and release kinetics are controlled by both polymer degradation and molecular diffusion [29]. Controlled drug release represents a beneficial treatment in terms of increased patient compliance due to decrease dosing frequency and avoiding peak-trough plasma concentrations [30, 31]. Recent developments allow for "programmable" systems, where release can be controlled by environmental signals or internal feedback loops [32]. Smart hydrogels and nanocomplexes that dynamically respond to biological signals are becoming the basis for the wave of new generation precision therapeutics [33, 34].

4. Smart and Stimuli-Responsive Systems:

Smart or stimuli responsive systems represent the degrees of NGDDS develop that respond to some physiological extrinsic trigger to release drug in a targeted manner at the right time and site. These systems are generally based on materials that experience physical or chemical changes in response to signals, including pH, temperature, redox potential, enzymes and magnetic field or light stimulation [35]. For example, pH-sensitive nanoparticles release their payload in the acidic environment of the tumor microenvironment and thermosensitive liposomes have been designed to release drug following local heating [36]. Enzyme-sensitive hydrogels and magnetically directed nanoparticles have exhibited a sanctioned site-specific precision without substantial systemic toxicity [37]. Multistimuli responsive platforms coupling two or more triggers (e.g., pH + enzyme, temperature + magnetic field) allow precise and complex modulation over therapeutic performance [38]. These are the technologies, which constitute the cornerstone of theranostics -- integration of drug delivery with diagnostic imaging to monitor in real time the treatment response [39, 40].

Classes and Platforms of NGDS:

1. Nanoparticles and Nanocarriers:

Nanoparticles (NPs) continue to be a cornerstone in NGDDS as they possess tunable physicochemical properties (size, shape, and surface chemistry) that influence their circulation, biodistribution, cellular uptake and clearance [41, 42]. Polymeric nanoparticles, lipid-based particles (including LNPs, solid lipid nanoparticles, inorganic NPs (gold, silica), and nanocrystals have been designed for the following purposes: (i) enhancing solubility of poorly water-soluble drugs; (ii) safeguarding labile molecules such as peptides, proteins and nucleic acids; and (iii) achieving passive and active targeting by EPR effects or ligand medsiated processes [43, 44]. Design parameters (e.g., PEGylation, ionizable lipids for facilitating endosomal escape and targeting ligands) impact directly on immune recognition (protein corona formation), pharmacokinetics and therapeutic index [45]. Translational hurdles include consistent scale-up, intense physicochemical and biological characterization, and manipulation of toxicologic/immunogenic profiles documented

in the maturing nanotoxicology field [46, 47]. There are clinical success stories (such as liposomal chemotherapeutics and LNPs for mRNA vaccines) showing that carrier engineering has implications on PK/PD and safety, but also challenges associated with regulatory concerns, and manufacturing bottlenecks towards introducing new nanoparticle varieties into the clinics [48].

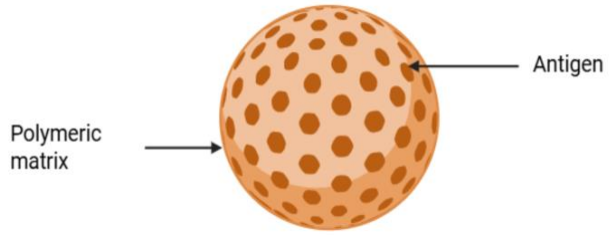

Figure 1: Structure of Nanoparticle

2. Liposomes and Lipid-Based Systems:

Liposomes (phospholipid bilayer vesicles) are still the most clinically advanced type of nanocarriers [49]. They sequester hydrophilic drugs into aqueous cores and water-insoluble ones inside bilayers, and LNPs (ionizable lipid systems) have become a significant part of nucleic acid delivery due to their ionizable lipids, which enable endosomal escape [50, 51]. Advantages include biocompatibility, the ability to carry a variety of cargo (small molecules, peptides, siRNA and mRNA) and known manufacturing processes [52] Lipid composition, presence of cholesterol or helper lipids to increase stability and surface modification to modify RES uptake are key engineering levers [53]. Limitations Artifacts concerningrom the NT-E were physical stability, storage, drug leakage and batch comparability all of which are essential for regulatory approval and clinical translation [54].

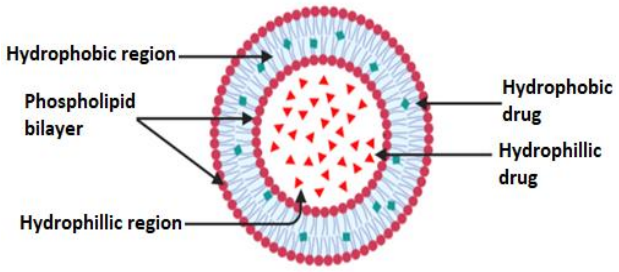

Figure 2: Structure of Liposome

3. Polymeric Micelles and Hydrogels:

Polymeric micelles are nanoparticles based on self-assembled amphiphilic block copolymers with a hydrophobic core able to solubilize poorly soluble drugs and hydrophilic corona, thus conferring steric stabilization [55, 56]. Micelles are able to penetrate the tumors passively through EPR, but also can be functionalized to actively target and/or respond to stimuli (pH or redox) [57]. Hydrogels and covalently crosslinked hydrophilic polymer networks in three dimensions can be used for local depot delivery, injectable sustained release "platforms," and tissue engineering scaffolds [58]. Injectable/self-healing and stimuli-responsive (ex: thermosensitive, pH-sensitive, enzyme-degradable) hydrogels are allows to release on-demand or environmental stimulated release [59]. Furthermore, D-L hydrogels (micelle-loaded gels) for high drug loading with local retention and sustained release in (post-surgical or for example intratumoral therapy) [60, 61]. Mechanical properties, sterilization and predictable in vivo release as well as the preservation of bioactivity with labile cargos are fundamental issues [62, 63].

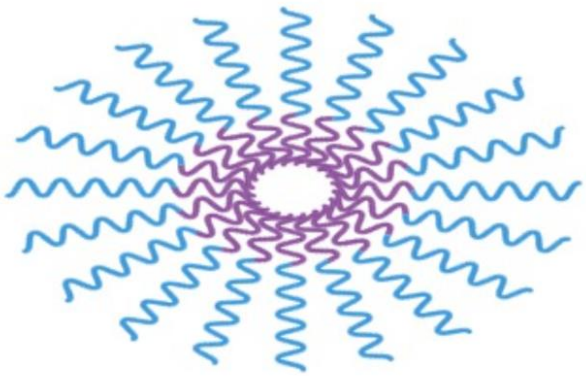

Figure 3: Structure of Polymeric Micelle (a)

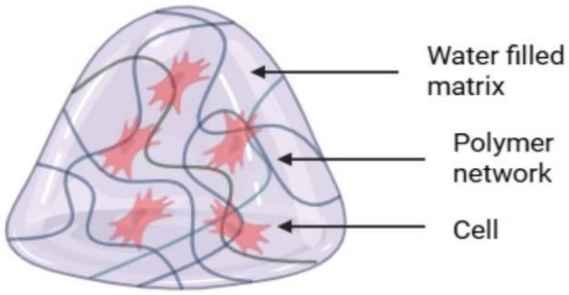

Figure 3: Structure of Hydrogel (b)

4. Implantable and Transdermal Systems:

Implantable systems (biodegradable polymer rods, reservoir catheters or programmable pumps) sustain long-term therapy and have a low variance, precise drug release suitable for chronic indications (contraception, chronic pain

management and hormone replacement) [64]. They provide clear advantages of prolonged retention and local high concentrations, but have concerns regarding surgical risk, foreign-body response and infection, while device biocompatibility and predictable polymer degradation are vital [65, 66]. Transdermal carriers (patches, iontophoresis, chemical enhancers) offer a non-invasive systemic route of delivery but are restricted by the stratum corneum barrier. Until recently, transdermal administration was limited to small and lipophilic molecules; however, new innovative methods particularly that of microneedle arrays are able to overcome this issue by temporally disrupting the stratum corneum impermeable barrier for delivery of small molecules, macromolecules and particles with improved patient acceptance. Smart functionalities are also being added to implantable systems (wireless control, refilling ports), bridging medicinal product engineering and drug formulation science [67, 68].

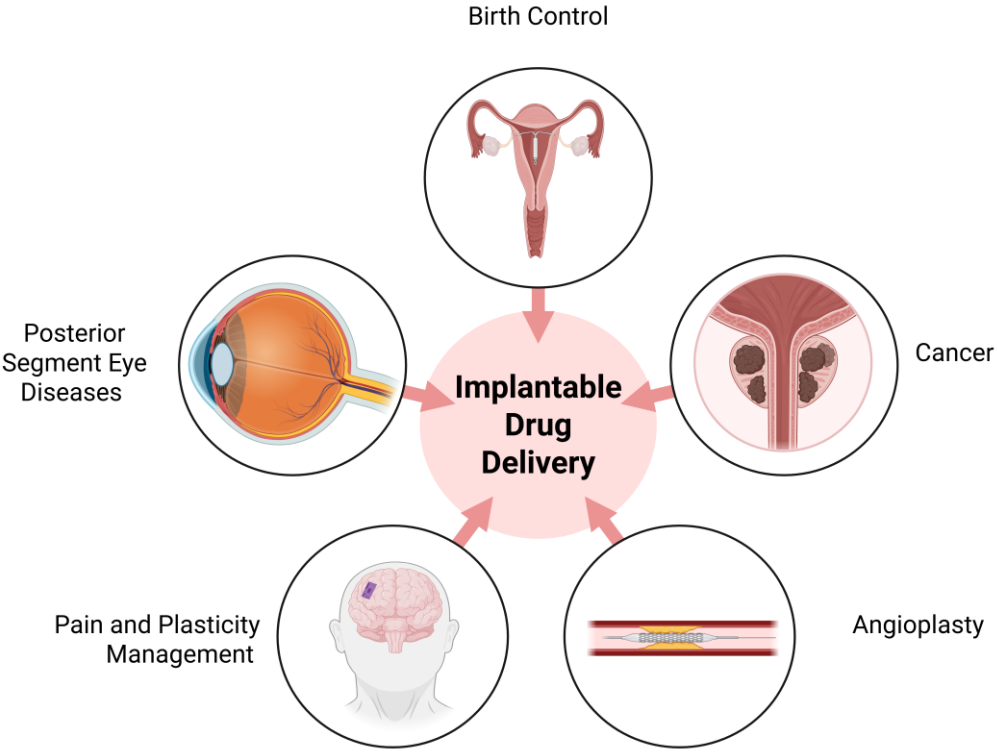

Figure 4: Implantable Drug Delivery

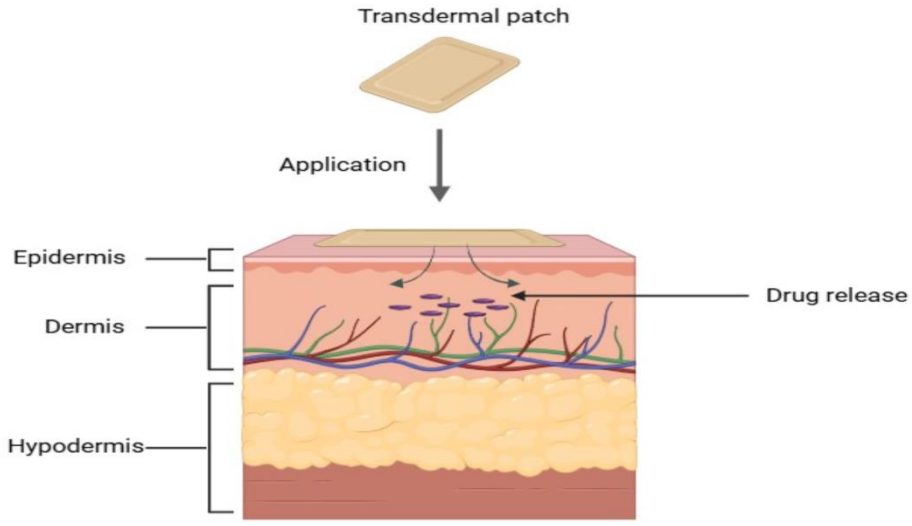

Figure 5: Transdermal Drug Delivery System

5. Microneedles and Oral-Delivery Innovations:

In particular, microneedles (MNs) as an emergent platform: micrometer-dimension projections arrays (solid, coated, dissolving, hollow, hydrogel-forming) in which painless and minimally invasive epidermal/dermal deliveries take place—antigen-presenting cells enriched—they are arising interest for vaccine delivery and biologics administration. Biodegradable polymer MNs are able to dissolve and elicit thermostable, self- administered vaccines as wells as single visit prime boost regiments through multistaged release [69-71]. For oral administration, the focus of progress is the protection of biologics from gastric conditions with rationally designed enteric coats, enzyme inhibitors, mucoadhesive polymers, and gut-targeted nanoparticles or devices (e.g., gastroretentive systems) [67, 72]. Oral delivery of proteins/peptides has continued to be challenging but advances in permeation enhancers, protease inhibitors and carrier development have bridged the gap [68].

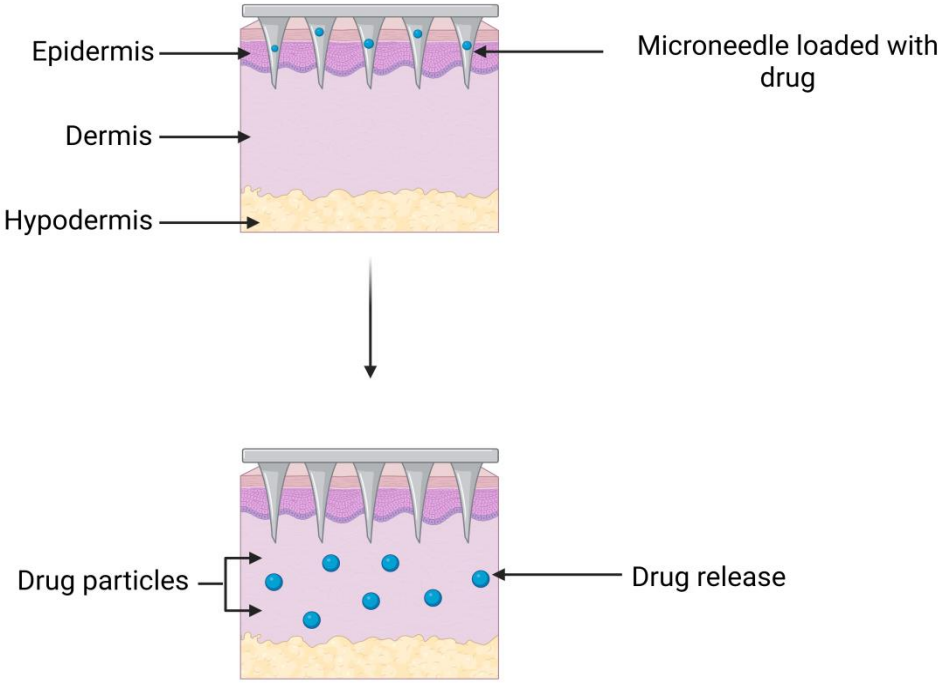

Figure 6: Microneedle Drug Delivery System

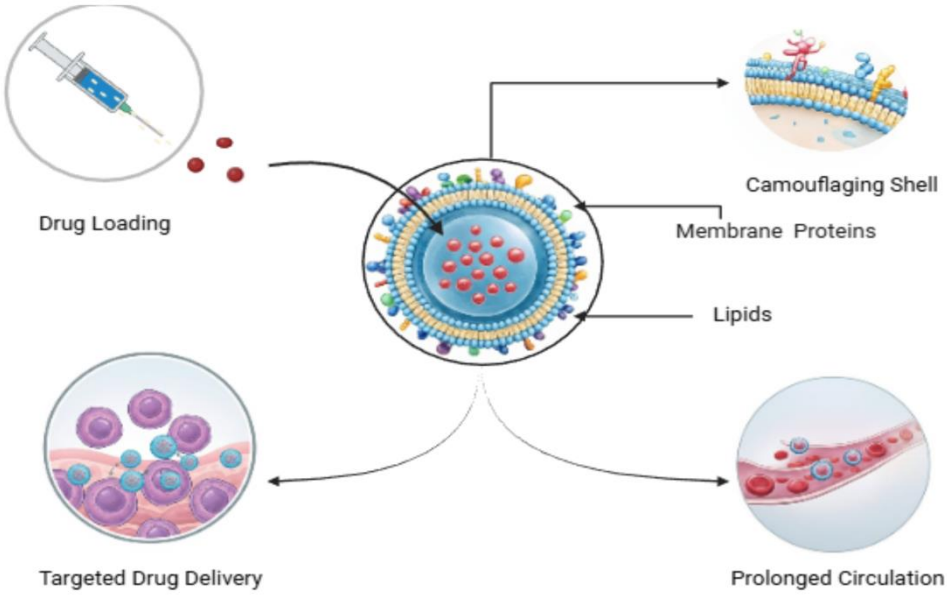

Figure 7: Bioinspired and Cell-Mimicking Carriers

6. Bioinspired and Cell-Mimicking Carriers:

Immunological barriers inspired carrier systems (cell membrane-coated nanoparticles, exosomes, and virus-like particles) take advantages of natural materials and mechanisms to avoid immune recognition, target native targeting pathways and regulation intracellular traffic. Exosomes and designer extracellular vesicles provide inherent biocompatibility, endogenous molecular signalling and safety-background yet encounter major obstacles in large-scale isolation techniques, loading accuracy as well as rigorous safety profiling. NPs cloaked with cell membranes (e.g., RBC or platelet membrane coatings) can provide "self" markers to lower clearance and may express targeting moieties in their natural orientation. Additional translational barriers are batch-to-batch variability, rigorous definition and regulations (biologic /device/combination product). Nevertheless, the bioinspired approach is heading towards translational studies on account of the promising properties of such highly efficient and low-immunogenic carriers [73, 74].

Technology Enables and Innovations:

1. 3D Printing for Drug Delivery Applications:

3D printing (additive manufacturing) is capable of producing custom drug-delivery systems with tablets, implants, microneedles and extended-release formulations on a layer-by-layer basis. Methods such as fused deposition modelling (FDM), inkjet printing and selective laser sintering (SLS) permit fine tuning of geometry, porosity, infill density and multi-drug compartment designs which directly affect drug release rates [75]. DO GOT A TO 3D printing allows dose tailoring, combination therapy formulation of drugs with complex release kinetics and manufacturing on-site at hospitals or pharmacies. Such technologies have been used to fabricate androspheroids, polypills, paediatric formulations, gastroretentive dosage forms and rapid prototypes of implantable drug reservoirs. Remaining challenges include API stability at high temperatures, limited pharmaceutically approved printable polymers and lack of regulatory guidelines for point-of-care production [76].

2. Artificial Intelligence and Computational Modelling:

AI advances drug delivery by predicting how a formulation will behave, and optimizing nanoparticle composition while at the same time predicting release kinetics as well providing support to PK/PD modelling. In the above gate, machine learning tools process large datasets to determine best-in-class combinations of excipients and predict material properties and in vitro as well as in vivo performance. AI reduces the design time of lipid nanoparticles for mRNA delivery, optimizes 3D printing parameters, and predicts personalized dosages based on patient physiology and genetic profile. Computational models eg.(PBPK and CFD) further our understanding of drug transport, absorption and tissue distribution. Challenges are due to training data biases, interpretable models, and the regulatory approval of AI-driven decisions [77].

3. Microfluidics and Lab-on-a-Chip Devices:

For example, microfluidics has facilitated the controlled environment to produce nanoparticles such as liposomes and lipid nanoparticles having uniform size and shape. They are able to control flow rate, mixing and solvent exchange leading to NPs with low polydispersity, good encapsulation efficiency and stable reproducibility. Microfluidic chips are also compatible with organ-on-chip platforms such as blood–brain barrier and gut-on-chips or vascular models, enabling in vivo like assessment of permeability, toxicity and response to treatment. Since microfluidics operate at the microliter scale, waste is greatly minimized and high-throughput screening can be performed. However, undertaking production at larger scales, compatibility with chip materials and harmonization with platforms for regulatory use are challenges [78].

4. Advanced Imaging for Tracking of Delivery:

Novel imaging modalities (e.g., PET, quantum dot-based NIR fluorescence imaging, photoacoustic and magnetic resonance imaging) could be employed for real-time tracking of carriers in vivo. These platform tools can provide real-time tracking of biodistribution, on-target accumulation, drug release and therapeutic response in situ without invasive intervention. Fluorescent dye, contrast agent or radionuclide-labeled nanoparticles facilitate with the evaluation of can dendrimer-based delivery vehicles in vivo and optimization. Imaging also facilitates image-guided therapy. Theranostic targeted nanoparticles that integrate imaging and therapy into a single platform enhance early detection and treatment monitoring. Drawbacks

include expensive equipment, regulatory difficulties of imaging agents and potential alteration of nanoparticle behavior upon labeling [79].

Therapeutic Applications:

1. Cancer Therapy:

Cancer treatment is more and more delivered through sophisticated drug-delivery systems that allow drugs to reach tumours more effectively while sparing healthy tissues. Nanoparticles, including those based on lipids (i.e., liposomes), polymers (polymeric nanoparticles) and inorganics (dendrimers, micelles and nanocarriers), passively accumulate in tumors due to the enhanced permeability and retention (EPR) effect, that is leakage of tumor blood vessels enabling particles to enter more readily than normal tissue [80]. This is called passive targeting.

Ligand active targeting is additionally applied in more sophisticated systems, where nanoparticles are functionalized with ligands (antibodies, peptides, aptamers) which recognize tumor-specific receptors (targeting the drug specifically to the cells of interest). Another advantage is co-delivery, so that a single nanoparticle can contain two or more drugs (e.g., chemotherapy + siRNA for drug resistance reversal) [81]. Only few nanoparticles are currently designed to be responsive to the tumor microenvironment (acidic, high glutathione) with respect to stimuli-controlled release within cancer cells.

Clinically, a few nanomedicines are already approved (acetildenafil), and many more are in clinical trials. The major hurdles are scalability, stability, immune-clearance and tumor biology variabilities from patient to patient [82, 83].

2. Neurological Disorders (Alzheimer's, Parkinson's):

The blood–brain barrier (BBB) is a major obstacle to drug delivery to the brain, as this physiological structure inhibits most therapeutics from accessing the central nervous system. Nanotechnology provides novel methods to deliver drugs, proteins and nucleic acids across BBB.

Synthetic NPs employ various mechanisms such as receptor mediated transcytosis by which some ligands (e.g., transferrin and insulin) can allow them to pass through BBB endothelial cells. Exosome-like vesicles, lipid nanoparticles and polymeric carriers are under investigation for the delivery of therapies for AD (e.g., anti-amyloid antibodies, siRNA against tau protein) and PD (e.g., neurotrophic factors, dopamine-releasing systems).

Certain nanoparticles can also enable sustained and controlled release that, in turn, provides extended therapeutic effects with less doses. Although animal studies have shown promising outcomes such as improved memory, reduced plaque formation and neuroprotection (translation to humans is slow due to the more complex heterogeneity of human BBB structure and immune responses) [84, 85].

3. Infectious Disease and Vaccines (mRNA Delivery)

mRNA therapeutics, in particular vaccination, have redefined the modern medicine. The problem with mRNA is that it is unsteady and readily broken down by enzymes. Lipid nanoparticles (LNPs) address this issue by shielding the mRNA, facilitating uptakes into cells and aiding its release from the endosome to the cytoplasm where proteins are made [86].

The success of LNP-based COVID-19 mRNA vaccines proved the advantages of LNP platforms in fast development, strong immunogenicity and great scalability. The LNPs are comprised of ionizable lipids, cholesterol, helper phospholipids and PEG-lipids that contribute to up stability, delivery and safety. This technology is currently being applied to influenza, RSV, HIV and therapeutic cancer vaccines.

Current scientific endeavors aim at adressing challenges such as improving thermostability (to avoid maintaining deep-cold storage), reducing immune reactogenicity and re-dosing the antigen without eliciting robust anti-PEG responses. mRNA–LNPs are emerging as a central platform in next-generation antiviral and immuno-therapy products [87, 88].

4. Autoimmune and Chronic Inflammatory Disorders:

Autoimmune diseases result when the immune system attacks healthy tissue by mistake. Conventional treatments broadly dampen the immune system, with side effects and infections. Nanomedicine targets immunomodulation treatment action only to immune cells implicated in the disease.

Nanoparticles can gather at sites of inflammation (in, say, a joint affected by rheumatoid arthritis or an inflamed intestine) and release drugs in a controlled way. More sophisticated strategies involve tolerogenic nanoparticles, which can re-educate the immune system to quit fighting its own tissues, either by training regulatory T cells (Tregs) or tamping down inflammatory macrophages.

Other approaches are to use cell membrane coated nanoparticles (imitation of immune cells) aiming at better specificity for delivery. In preclinical animal models, there is less inflammation, lower toxicity and better disease control. The key is to getting the long-term immune safety demonstrated while having consistent results in such a variety of autoimmune conditions [89].

5. Gene and Nucleic-Acid-Based Therapies:

Gene and nucleic-acid therapies attempt to control the expression of genes or to directly modify defective genes. These range from siRNA and antisense oligonucleotides (ASOs), to mRNA therapeutics, to CRISPR/Cas gene editing. Their effectiveness hinges on delivery systems that shield the nucleic acids and deliver them into certain cellular interiors [90].

Lipid nanoparticles (LNPs) are the most advanced non-viral delivery systems in clinical use Be it patisiran (siRNA), mRNA vaccines. In gene editing, nanoparticles are engineered to deliver Cas9 mRNA or protein + guide RNA and transiently express it to lower off-target risks.

Other carriers, like polymeric nanoparticles, lipid–polymer hybrid and engineered exosomes are being engineered for targeting non-liver organs (lungs, muscle, immune cells) by improving liver targeting. Prominent among the challenges are immunogenicity, off-target effects, long-term safety and tunability of editing activity. However, despite these difficulties, the field of nucleic-acid based medicines is growing rapidly and represents one of the most exciting potential areas for therapeutic interventions [91, 92].

Clinical Translation and Regulatory Landscape:

1. Preclinical Assessment and In-Vivo Models:

The success in translation requires an extensive preclinical validation ranging from target engagement to biodistribution, efficacy and safety. Typical preclinical investigations conducted with next-generation drug delivery systems typically include: (a) in vitro physicochemical stability and testing (size, zeta potential and release profile), (b) cell-based uptake, toxicity and mechanism studies; (c) small animal pharmacokinetics (PK), biodistribution and efficacy models; and objective d. Related to scaling/targeting or immunogenicity necessitates. Imaging (optical, PET/SPECT, MRI) and quantitative biodistribution (radiolabelling, LC–MS/MS) are the most often applied techniques to follow carrier fate and relate exposure to effect. Traditional factors such as selection of disease model (orthotopic vs subcutaneous grafts, genetically engineered models); reproducibility; relevance of route of administration and dose regimens to translation, are all important aspects which good preclinical design attends to. Finally, preclinical safety analysis should not be limited to the active ingredient itself, but should include carrier materials such as lipids or polymers and impurities arising through the manufacturing process [93, 94].

2. Scale-up and Manufacturing Challenges:

Transitioning from bench to clinic highlights issues around reproducible manufacturing, process control and batch-to-batch variability. challenges include: mastering critical quality attributes (particle size distribution, encapsulation efficiency, residual solvents), the process transfer from small laboratory scale methods (thin-film hydration, microfluidics and nanoprecipitation) to scalable technologies (continuous microfluidic mixing and high-pressure homogenization) as well as developing robust in-process analytics for real-time release testing. Regulatory standards call for validated GMP processes and proof that scale up does not impact product potency of safety. Environmental, supply-chain and cost criteria (variability of raw material supplies, sterile fill/finish, cold-chain requirements for lipid nanoparticles) are frequently determinative of feasibility. Continuous Manufacturing and Modular, Closed Systems – the way forward for reproducibility and supply management Novel aspects of products can also require new manufacturing approaches [95, 96].

3. Regulatory Considerations for NGDDS:

NGDDS regulatory frameworks combine the classic pharmaceutical questions of quality,

safety and efficacy- with issues on how this carrier modifies ADME, toxicity+ immunogenicity. Regulators anticipate a well-defined CQA (critical quality attribute) profile, comprehensive substance recoveries or retention (drug substance) and characterization data for both drug substance and drug product as well as comparative effectiveness when filing 'follow-on/generics' versions. Regulatory (FDA, EMA) guidance and horizon-scanning documents have been issued on nanotechnology medicinal products and both agencies run scientific-advice pathways to support early discussions. In the case of advanced modalities (lipid nanoparticles, gene-carriers), health authorities will typically demand comprehensive preclinical studies including biodistribution, immune activation, and especially complement activation-related pseudoallergy (CARPA) and life-time trace. Harmonization is a process in progress and early dialogue (pre-IND/ATU/Scientific Advice) is essential to harmonize studies avoiding last minute unexpected comments [97, 98].

4. Case Studies: Bench to Bed Side:

Lessons learnt are from both approved and clinically advanced NGDDS. These include (i) liposomal chemotherapies (e.g., Doxil®), where a modified PK/toxicity profile necessitated new safety monitoring and manufacturing control; (ii) silencing therapies in lipid nanoparticles (Onpattro®) due to the requirement for robust LNP manufacture, understanding of PK/biodistribution as well as immunogenecity assessment; and finally. iii) mRNA COVID-19 vaccines where rapid up-scaling, stability requirements (cold-chain), and regulatory considerations have facilitated their unprecedented deployment. These cases reveal common themes – the need for cross-discipline teams (formulation, process engineering, analytics and regulatory), early and iterative discussion with regulators, investment in scalable, control-able manufacturing and transparent documented comparability and stability data [99, 100].

Future Perspectives and Emerging Trends:

1. Personalized and Precision Drug Delivery:

Personalized drug delivery is a key development direction of NGDDS in the future, which requires the type and amount of drugs delivered, release behavior and designed carriers to be tailored for an individual's genetic profile, disease phenotype and physiological conditions. Thanks to advances in pharmacogenomics (i.e., CYP450 polymorphisms), real-time biomarker readouts, and computational modelling, nanoparticles, hydrogels and implantable devices can be custom modified to meet the patient's specific requirements.

Nanocarriers including LNPs, polymeric nanoparticles, and exosome-mimetic vesicles are designed to have tunable PK kinetics which enable clinicians for the first time to estimate and manage drug exposure very precisely.

Many reviews emphasise that AI mediated modelling (machine learning based prediction of nanoparticle–tissue interactions, biodegradation and immune response) will accelerate personalized system design. Combining genomic and proteomic markers will further support "precision targeting" for cancer, autoimmune diseases, and neurological conditions [101].

2. Digital Health and Wearables Integration:

Digital therapeutics and wearable technologies revolutionize NGDDS in terms of real-time control, feedback-regulated drug presentation and smart hybrids. Examples include:

- Microneedle arrays linked to glucose detectors for closed loop insulin delivery.
- Wearable patches including microheaters, pH sensor or motion sensors for drug release on demand.
- IoT based remote health monitoring systems transmitting physiological parameters to modulate the drug release from implants or nanocarriers.

These systems can be coupled with smart biomaterials (thermo responsive, pH-responsive, magnetically responsive) for dynamically tunable configurations. Integration with mobile health systems should cause a reduction in hospital visits, facilitate the management of chronic diseases and support the individualized data-driven administration of drugs [102].

3. Sustainable and Green Delivery Systems:

A growing trend in NGDDS is the selection of environmentally safe, degradable and renewable biomaterials due to safety and environmental issues. Examples include:

- Polysaccharide carriers (chitosan, alginate and cellulose derivatives).
- Bio-sourced polymers (PLA, PHA).

- Plant extract and enzyme mediated synthesis of nanomaterials.
- Biodegradable microneedles that break down into harmless byproducts.

Such systems minimize the amount of ecological burden over a period of time, avoid long-term plastic waste residues and exhibit low-toxicity metabolic degradation. Pharmaceutical industry is slowly moving in the direction of 'green' synthesis, using energy-efficient operations and minimum solvent use [103].

4. Ethical and Societal Considerations:

The swift development of the field of next-generation drug delivery presents key ethical and social issues including:

- Data privacy-related issues around digital-health–connected delivery systems (e.g., wearables that collect ongoing health information).
- Access to advanced nanomedicines in a fair and affordable manner, particularly for developing areas.
- Safety transparency, particularly the effects over the long-term of biodegradation, accumulation in nanoparticles and rare immune responses.
- Hybrid systems (drug + device + software) are driving the complexity of regulation.
- Challenges presented by consent to the use of AI personal dosing systems.

Practical guidelines concentrate on responsibility in innovation, education of patients and ongoing surveillance for risk management. Trust in nanomedicines on the part of the public relies on clear reporting, open access to technologies and rigorous regulatory scrutiny [104].

CONCLUSION

1. Summary of Key Insights:

The next-generation of drug delivery systems (NGDDS) mechanically increase the bioavailability, accuracy and therapeutic index of drugs by overcoming challenges presented by traditional delivery modalities including rapid clearance from the circulation, hydrophobicity or off-target toxicities. Among all kinds of open-access reviews, it seems that agreement has been reached on NGDDS—including lipid nanoparticles (LNPs), polymeric nanoparticles, micelles, dendrimers, hydrogels, microneedles and bioinspired carriers—attributing to the advantages of targeted delivery, controlled release and protection for such fragile biologics (e.g., siRNA and mRNA) [28–30]. Ventola (2017) indicates that nanocarriers improves the system's pharmacokinetics as well as minimising systemic toxicity particularly in oncology and antiviral therapy [105].

Additionally, AI-guided nanoparticle design, microfluidic fabrication, advanced imaging techniques and computational tools further facilitate the development process by predicting nano–bio interactions and improving formulation reproducibility. Mitchell et al. (2021), precision nanoparticles enhance tissue specificity, lower the dose burden and enable personalized therapy through receptor-mediated uptake and programmable release mechanisms [106].

In general, the literature concurs NGDDS are moving medicines towards predictable, target oriented, patient specific medicine and provide a robust technological platform for their eventual clinical application in future.

2. Challenges and Opportunities Ahead:

Translation of NGDDS into clinical practice is, however, an ambitious goal that presents its own significant challenges. Several reviews have noted that manufacturing and scalability are the most significant hurdles, with lab-scale nanoprecipitation or microfluidics systems consistently not meeting Good Manufacturing Practice (GMP) standards for reproducibility in particle size, polydispersity, surface ligand density and sterility. Shi et al. (2017) and state that discrepancy as one of the major reasons for late-stage failures in many nanocarriers [107].

Long-term safety and biodistribution is again another big hurdle. Nanoparticles can be deposited in the liver, spleen, lymph nodes, or kidney and are considered a potential for chronic toxicity, immunogenicity, as well as inflammatory activation. A number of the authors stress long-term toxicology studies, PBPK models and pan-specific biodistribution assays. Regulatory hurdles are significant as well: NGDDS commonly straddle the line between drug, device, and biologic with unclear avenues to approval. Pignatello et al. Stress level The importance of early contact with agencies and harmonization of regulations to provide predictability of translation pathways (2020).

However, literature has high prospects: AI driven formulation, sustainable materials, green route of synthesis and wearable integrated smart delivery carriers. Mitchell et al. (2021) highlights that precision nanomedicine will be one of the main future driving forces with the use of multi-omics profiling, enabling a personalized targeting strategy [108]. Together, these opportunities provide a route to bypass the current translational valleys.

3. Concluding Ideas on Connecting I with N:

A recurring theme in the literature is that and NGDDS will only reach clinical fruition if scientific innovation dovetails with the reality of clinical, regulatory, and patient-centered needs. These NGDDS should not only show enhanced drug performance but also be scalable manufacturing, storage stability, low costs and regulatory/patient acceptance. Hua (2023) stresses that the application of principle of precision medicine to delivery system design including matching ligand density to biomarker expression and dosing individualised in response to genetic variability will be essential for clinical significance [101].

Some reviews also emphasize the need to develop NGDDS with patient access in mind. Further equity issues occur if next-level delivery technologies are costly or need special storage, as in the early distribution of mRNA vaccines. To help foster the marriage of innovation with necessity, the authors suggest that attention be paid to biodegradable materials, room temperature-stable formulations, ease of manufacture and early dialogue with regulators. Tinkle et al. (2020) emphasize that long-term monitoring, open communication, and the public confidence will be pivotal in securing clinical application of nano-based therapies.

Simply put, bringing innovation to need requires an integrated approach that considers scientific validity, regulatory strategy, manufacturability, sustainability and patient-centered design. However, when these dimensions intersect rare is the potential that NGDDS can provide safer, smarter and accessible therapies on a global scale [104].

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