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Chapter 20

Device-, Nano-, and 3D-Printed Drug Delivery Systems

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Abstract: Drug delivery has entered an era defined by precision, personalization, and convergence of material sciences, nanotechnology, and engineering. Conventional formulations, while successful in addressing many therapeutic needs, often face bioavailability barriers, systemic toxicity, and lack of tissue specificity. The emergence of advanced delivery systems, including microneedle-based devices, nanocarriers, and 3D-printed pharmaceuticals, has revolutionized the field by enabling controlled, targeted, and patient-specific therapies. Transdermal microneedle platforms circumvent hepatic first-pass metabolism and improve patient compliance, whereas electroporation, iontophoresis, and jet injectors facilitate minimally invasive delivery. Nanocarrier technologies such as liposomes, niosomes, dendrimers, and PEGylated stealth systems have yielded clinically approved formulations including Doxil, Abraxane, and the mRNA-based lipid nanoparticle vaccines that demonstrated immense global impact during the COVID-19 pandemic. Similarly, biodegradable polymers such as PLGA microspheres, hydrogels, and electrospun fibers enable long-acting depots and tissue engineering applications. Meanwhile, additive manufacturing or 3D printing of polypills has unlocked personalized, on-demand pharmaceutical manufacturing. Despite these breakthroughs, regulatory, manufacturing, and nanotoxicology challenges persist, necessitating rigorous GMP compliance, standardized evaluation, and environmental safety assessments. Looking ahead, stimuli-responsive platforms integrated with artificial intelligence and wearable sensors represent the future of smart, adaptive drug delivery. This chapter provides an in-depth analysis of device-mediated, nanocarrier-based, and 3D-printed systems, highlighting their mechanisms, clinical applications, regulatory landscapes, and translational opportunities.

Keywords: microneedles, nanocarriers, 3D-printed pharmaceuticals, polymeric drug delivery, smart drug delivery.

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20.0 INTRODUCTION

Drug delivery science has evolved from simple formulations to sophisticated platforms designed to overcome physiological and pharmacokinetic barriers. The oral route, despite being the most widely used, suffers from issues such as enzymatic degradation, hepatic first-pass metabolism, and limited solubility of drugs, leading to suboptimal bioavailability. Similarly, parenteral routes, while bypassing some limitations, impose challenges related to patient compliance, invasiveness, and systemic toxicity. These limitations have spurred the development of advanced drug delivery systems that combine engineering innovations with nanoscience to ensure precise, sustained, and site-specific therapeutic action [1].

The contemporary drug delivery landscape is characterized by convergence. Devices such as microneedles offer minimally invasive self-administration, while nanocarriers engineered at the molecular scale provide targeted delivery with reduced off-target effects. Biodegradable polymers have enabled the creation of implants and depot formulations that sustain drug release over weeks or months. In parallel, additive manufacturing through 3D printing has redefined pharmaceutical manufacturing by enabling personalization, on-demand production, and complex dosage form geometries [2].

Clinical translation of these technologies has been substantial. For example, Doxil, the first FDA-approved liposomal formulation of doxorubicin, significantly reduced cardiotoxicity compared with free doxorubicin [3]. More recently, lipid nanoparticle formulations became the backbone of COVID-19 mRNA vaccines, showcasing the scalability and therapeutic relevance of nanomedicine [4]. Meanwhile, Aprecia's Spritam, the first FDA-approved 3D-printed oral dosage form, demonstrated the feasibility of additive manufacturing for commercial drug products [5].

However, integration of these platforms into mainstream medicine faces challenges including manufacturing scale-up, reproducibility, GMP compliance, and safety evaluations such as nanotoxicology. This chapter systematically explores the various categories of device-based, nano-enabled, and 3D-printed drug delivery systems, critically examining their mechanisms, clinical significance, limitations, and future prospects.

20.1 Transdermal and Microneedle Delivery

The skin, with its large surface area and accessibility, is an attractive site for drug delivery, but the stratum corneum poses a formidable barrier to most therapeutics. Traditional transdermal patches rely on passive diffusion, which restricts their use to lipophilic, low-molecular-weight drugs. To overcome these limitations, microneedle (MN) technology has emerged as a transformative innovation. MN arrays consist of micron-scale projections that painlessly penetrate the stratum corneum, creating microchannels that facilitate drug diffusion into dermal capillaries [6].

There are several microneedle designs, including solid MNs coated with drug layers, hollow MNs for fluid injection, dissolving MNs fabricated from biodegradable polymers, and hydrogel-forming MNs that swell to release encapsulated drugs. Clinical studies have demonstrated successful MN delivery of vaccines, insulin, and biologics, highlighting improved patient compliance and reduced dependence on healthcare personnel [7]. For instance, dissolving MN patches for influenza vaccination have shown equivalent immunogenicity to intramuscular injections, while offering a pain-free and needle-free alternative [8].

Complementary device-based methods also enhance skin permeation. Electroporation involves transiently increasing skin permeability using short electrical pulses, enabling the passage of macromolecules such as DNA and peptides. Iontophoresis uses low electrical currents to drive charged

molecules through the skin, while jet injectors deliver drugs at high velocity without needles, reducing cross-contamination risks [9]. Despite their promise, these approaches face challenges in terms of dose uniformity, stability of biologics in MN matrices, and manufacturing scalability. Regulatory pathways for microneedle patches are still evolving, with requirements for mechanical robustness, sterility, and patient safety assessments. Nonetheless, the painless, self-administrable, and scalable nature of MN systems positions them as key players in the next generation of drug delivery technologies [10].

20.2 Liposomes, Niosomes, and Nanocarriers

Nanocarriers, engineered at dimensions between 10–500 nm, offer unique physicochemical advantages including large surface area-to-volume ratios, tunable surface chemistry, and the ability to encapsulate both hydrophilic and hydrophobic drugs. Among these, liposomes and niosomes are the most extensively studied. Liposomes are vesicular carriers composed of phospholipid bilayers, while niosomes utilize non-ionic surfactants, offering improved stability and cost-effectiveness [11]. PEGylation, or surface modification with polyethylene glycol, has been pivotal in prolonging circulation half-life by reducing opsonization and clearance by the reticuloendothelial system. Targeting ligands, such as antibodies, peptides, and aptamers, can be conjugated to nanocarriers to achieve site-specific delivery. For instance, trastuzumab-conjugated liposomes target HER2-positive breast cancer cells, enhancing therapeutic efficacy while minimizing systemic toxicity [12].

Several FDA-approved nanomedicines exemplify clinical translation. Doxil, a PEGylated liposomal doxorubicin, significantly reduced cardiotoxicity compared to free drug administration [3]. Abraxane, an albumin-bound paclitaxel nanoparticle, eliminated the need for toxic solvents and improved therapeutic outcomes in breast and pancreatic cancers [13]. Most notably, lipid nanoparticles (LNPs) served as the delivery vehicle for mRNA vaccines during the COVID-19 pandemic, underscoring the scalability and public health relevance of nanocarriers [14].

Emerging carriers such as dendrimers, polymeric micelles, and exosomes further expand the scope of nanomedicine. However, concerns regarding immunogenicity, unpredictable biodistribution, and cost of large-scale production remain hurdles. Strategies such as microfluidic manufacturing and continuous-flow systems are being developed to enhance reproducibility and scalability [15]. Overall, nanocarriers represent one of the most impactful innovations in modern drug delivery, bridging the gap between molecular therapeutics and clinical efficacy, while continuously evolving toward safer and smarter systems.

20.3 Polymeric and Biodegradable Systems

Biodegradable polymers have become essential tools for controlled and sustained drug release. Poly(lactic-co-glycolic acid) (PLGA), approved by the FDA, is one of the most widely used due to its predictable degradation into lactic and glycolic acids, which are metabolized via natural pathways. PLGA-based microspheres and nanoparticles can provide release profiles ranging from days to months, making them ideal for chronic therapies such as hormone replacement, cancer treatment, and psychiatric medications [16]. Implantable polymeric systems represent another clinically validated modality. For example, the Norplant contraceptive implant utilized levonorgestrel-loaded polymer rods, providing sustained release for up to five years [17]. More recent innovations include hydrogel-based delivery systems, which can encapsulate proteins, peptides, and cells while providing biocompatible, hydrated matrices that mimic native tissue environments [18].

Electrospun fibers fabricated from polymers such as polycaprolactone and PLGA allow the creation of drug-loaded mats with tunable porosity, high surface area, and the ability to deliver drugs

locally at surgical sites or wounds. Similarly, shape-memory polymers can be engineered to change form in response to stimuli, offering spatiotemporal control over drug release [19]. Despite these advantages, polymeric systems face limitations including burst release, incomplete degradation, and challenges in ensuring batch-to-batch reproducibility at industrial scale. Biocompatibility, sterilization, and long-term safety assessments are critical for regulatory approval. Yet, the flexibility of polymer chemistry, coupled with advances in fabrication techniques such as 3D printing and electrospinning, continues to expand the therapeutic potential of biodegradable systems [20].

20.4 3D-Printed Drug Products

Additive manufacturing, or 3D printing, has disrupted conventional pharmaceutical manufacturing by enabling highly customizable dosage forms. Unlike mass production of tablets and capsules that rely on uniformity, 3D printing allows for individualized formulations tailored to patient-specific needs such as pediatric dosing, polypharmacy, and rare diseases [21]. Several printing techniques are used in pharmaceutics, including fused deposition modeling (FDM), inkjet printing, stereolithography (SLA), and selective laser sintering (SLS). Each method offers unique advantages in terms of resolution, speed, and compatibility with different drug-excipient systems.

A landmark achievement in this domain was the FDA approval of Aprecia Pharmaceuticals' Spritam (levetiracetam) in 2015. Manufactured using ZipDose® technology, Spritam dissolves rapidly in water due to its porous structure, providing a safe and effective option for patients with swallowing difficulties [22]. Beyond orodispersible formulations, 3D printing has facilitated the development of polypills containing multiple active pharmaceutical ingredients (APIs) in spatially separated layers. This approach allows the controlled release of different drugs from a single tablet, simplifying regimens for patients with chronic diseases [23]. 3D printing also enables geometry-driven control of drug release. For example, torus-shaped tablets and honeycomb matrices exhibit different dissolution kinetics compared to conventional flat compacts. Moreover, 3D-printed implants can be customized to fit anatomical defects while simultaneously delivering antibiotics or chemotherapeutics locally [24].

However, regulatory challenges loom large. Current frameworks are designed around batch-based manufacturing, whereas 3D printing emphasizes on-demand, small-scale production. Issues of quality assurance, reproducibility, and Good Manufacturing Practice (GMP) compliance must be addressed before widespread adoption. The U.S. FDA and European Medicines Agency have initiated workshops to develop regulatory guidance, but harmonized global standards remain elusive [25]. As costs decline and portable 3D printers become available, point-of-care manufacturing in hospitals and pharmacies may soon become feasible. This could transform healthcare delivery by providing personalized formulations at the bedside, bridging the gap between pharmacogenomics and real-world patient needs.

20.5 Inhalable Nanocarriers

Pulmonary delivery has long been used for asthma and chronic obstructive pulmonary disease (COPD), but recent advances in inhalable nanocarriers have broadened its applications to oncology, infectious diseases, and even gene therapy. The lung offers several advantages: a large absorptive surface area (~70 m^2), extensive vascularization, and thin epithelial barriers that allow rapid systemic absorption [26]. However, challenges such as mucociliary clearance and alveolar macrophage uptake require sophisticated design of carriers.

Nanocarriers engineered for pulmonary delivery include liposomes, polymeric nanoparticles, solid lipid nanoparticles, and dendrimers. Inhaled liposomal formulations of amikacin (Arikayce) have

been FDA-approved for treatment of Mycobacterium avium complex lung disease, demonstrating the translational success of this strategy [27]. Nanocarriers can encapsulate chemotherapeutic drugs, enabling localized delivery for lung cancer while reducing systemic toxicity. Preclinical models have shown that inhaled paclitaxel-loaded nanoparticles exhibit enhanced tumor retention and reduced systemic exposure compared to intravenous administration [28].

Gene therapy applications are also emerging, with lipid nanoparticles being adapted for aerosolized delivery of mRNA and siRNA. For instance, inhalable formulations targeting cystic fibrosis transmembrane conductance regulator (CFTR) mutations are being explored in clinical trials [29]. Advanced models such as lung-on-chip microfluidic devices simulate physiological airflow, mechanical stretching, and immune cell interactions, offering predictive platforms for nanoparticle testing [30].

Despite these advances, stability of nanocarriers in nebulization, potential immunogenicity, and dose standardization remain significant hurdles. Particle size distribution (1–5 µm aerodynamic diameter) is critical for alveolar deposition, and manufacturing methods must ensure narrow dispersity. Furthermore, regulatory evaluation of inhalable nanomedicines must include long-term pulmonary safety, given concerns of fibrosis and chronic inflammation [31]. Overall, inhalable nanocarriers exemplify the intersection of nanotechnology and respiratory medicine, holding promise not only for treating pulmonary diseases but also for enabling systemic therapy through the lungs.

20.6 Ocular, Otic, and Intranasal Systems

Drug delivery to the eye, ear, and brain presents unique challenges due to specialized barriers such as the blood-retinal barrier, round window membrane, and blood-brain barrier (BBB). Nanotechnology and device-based strategies are increasingly being deployed to overcome these anatomical and physiological constraints. In ophthalmology, topical eye drops are the most common dosage form, but less than 5% of instilled drug reaches intraocular tissues due to tear turnover and corneal barriers. Nanoparticle-loaded eye drops, such as liposomes, dendrimers, and polymeric nanoparticles, have demonstrated improved corneal penetration and sustained drug retention in preclinical and clinical studies [32]. Ocular iontophoresis, which applies a mild electrical current to drive charged drugs across the cornea or sclera, has been investigated for corticosteroids and antibiotics with promising results [33]. Additionally, sustained-release intravitreal implants, such as dexamethasone (Ozurdex), have validated the concept of biodegradable ocular drug delivery [34].

In otology, local delivery to the inner ear is hindered by the impermeability of the round and oval windows. Nanoparticle suspensions and hydrogels applied to the middle ear cavity can facilitate diffusion into the cochlea, enabling treatment of sensorineural hearing loss and tinnitus. Experimental studies using growth factor-loaded nanoparticles have shown potential for regenerating cochlear hair cells [35]. Intranasal delivery has gained tremendous attention for its ability to bypass the BBB and deliver drugs directly to the brain via the olfactory and trigeminal nerve pathways. Nanocarriers such as chitosan nanoparticles and solid lipid nanoparticles enhance mucosal adhesion and prolong residence time, improving brain uptake of peptides and neurotherapeutics [36]. Intranasal delivery of neuroprotective agents, insulin, and even stem cell-derived exosomes is under investigation for Alzheimer's and Parkinson's diseases [37].

Nevertheless, patient acceptability, mucosal irritation, and dose reproducibility are concerns for intranasal and ocular/otic systems. Additionally, long-term safety data are scarce, requiring rigorous clinical trials. Despite these challenges, the integration of nanocarriers and device-assisted strategies offers promising avenues for treating ophthalmic, auditory, and neurological disorders.

20.7 Regulatory and Manufacturing Issues

The translation of advanced drug delivery systems from bench to bedside requires stringent adherence to regulatory and manufacturing standards. Good Manufacturing Practice (GMP) compliance is central to ensuring consistency, safety, and reproducibility. Nanomedicines, unlike conventional small-molecule drugs, present unique challenges due to their complex structures, multicomponent formulations, and size-dependent behavior [38]. Regulatory agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan have established preliminary frameworks for evaluating nanomedicines, but harmonization remains incomplete [39].

Manufacturing scalability is another hurdle. While microfluidics and continuous-flow synthesis have improved reproducibility in nanoparticle fabrication, scaling up these processes while maintaining uniformity in particle size, drug loading, and surface modifications is difficult. Sterilization and biocompatibility testing further complicate manufacturing, as conventional methods such as autoclaving or gamma irradiation can destabilize nanocarriers or degrade sensitive biologics [40].

For 3D-printed pharmaceuticals, regulatory pathways are still evolving. Quality control must address layer-by-layer variability, mechanical strength, and dissolution performance of printed products. The FDA has issued draft guidance on additive manufacturing, but questions remain regarding decentralized or point-of-care printing, where pharmacies or hospitals may manufacture personalized formulations onsite [41].

Thus, regulatory science is playing a critical role in shaping the development of advanced delivery systems. Cross-agency collaborations and international consortia are essential to establish standardized characterization, toxicological evaluation, and GMP requirements that will enable global approval and patient access.

20.8 Nanotoxicology and Immunogenicity

While nanocarriers and device-assisted delivery systems promise enhanced efficacy, their interaction with biological systems introduces new safety concerns. Nanotoxicology, the study of nanoparticle-induced toxicity, has emerged as a vital discipline in evaluating biodistribution, clearance, and long-term effects [42]. The fate of nanoparticles in vivo is dictated by their size, shape, surface charge, and chemical composition. For instance, particles smaller than 5 nm are rapidly cleared by renal filtration, while larger particles may accumulate in the liver and spleen, raising concerns of hepatosplenic toxicity [43]. Similarly, positively charged nanoparticles tend to disrupt cell membranes more readily than neutral or PEGylated counterparts, contributing to cytotoxicity.

Immunogenicity is another critical issue. While PEGylation prolongs circulation half-life, repeated administration of PEGylated formulations can induce anti-PEG antibodies, leading to accelerated blood clearance and hypersensitivity reactions [44]. Moreover, nanoparticles may trigger unintended immune activation via Toll-like receptor signaling, potentially causing inflammation or autoimmunity [45].

Genotoxicity and reproductive toxicity assessments are still limited, particularly for chronic use of nanocarriers. Environmental safety is also a concern, as the large-scale production of nanomaterials may result in unintended release into ecosystems, where their long-term ecological effects remain poorly understood [46]. Standardization of toxicological testing, including in vitro assays, advanced imaging, and in vivo biodistribution studies, is essential. Newer tools such as organ-on-chip models and advanced computational simulations may improve predictive power and reduce reliance on animal testing.

Table 1: Advantages and Limitations of Inhalable Nanocarrier Platforms

Nanocarrier Type	Advantages	Limitations
Liposomes	Biocompatible, can encapsulate hydrophilic & lipophilic drugs	Stability during nebulization, high cost
Polymeric Nanoparticles	Controlled release, versatile chemistry	Clearance by macrophages, manufacturing challenges
Solid Lipid Nanoparticles	High drug loading, physical stability	Polymorphic transitions, aggregation risk
Dendrimers	High drug payload, functionalizable surface	Potential cytotoxicity, high production cost

Table 2: Key Regulatory Considerations for Advanced Drug Delivery Systems

Regulatory Domain	Nanomedicines	3D-Printed Pharmaceuticals
Quality Control	Particle size, zeta potential, drug loading consistency	Layer uniformity, mechanical strength, dissolution profiles
Sterility	Difficult for nanosuspensions; must avoid degradation	Challenging for in situ printing
Scalability	Continuous flow and microfluidic systems under development	On-demand, decentralized printing raises reproducibility issues
Regulatory Guidance	EMA Nanomedicine Reflection Paper (2019), FDA draft guidelines	FDA additive manufacturing guidance (2017), EMA consultations
Clinical Challenges	Biodistribution unpredictability, immunogenicity	Decentralized GMP compliance, point-of-care oversight

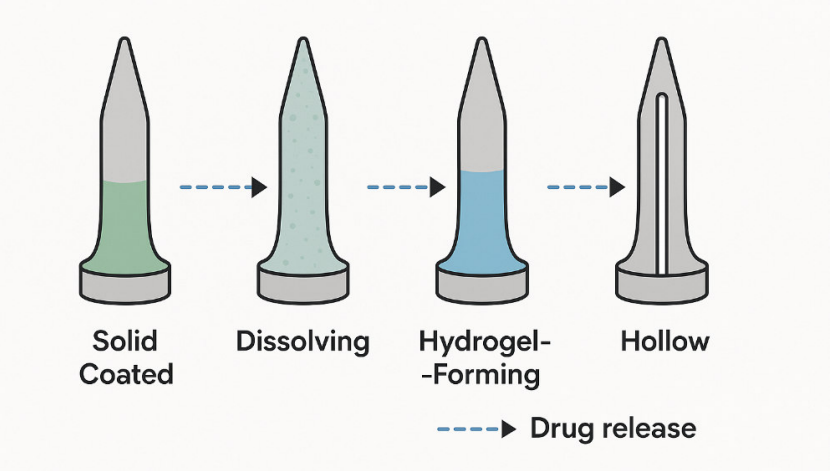

Figure 1: Microneedle designs

20.9 Future of Smart Drug Delivery

The future of drug delivery lies in systems that can sense, respond, and adapt dynamically to physiological signals. Stimuli-responsive platforms, also known as "smart" delivery systems, are engineered to release drugs in response to environmental triggers such as pH, temperature, redox potential, enzymes, or external stimuli like light, ultrasound, or magnetic fields [47]. For instance, pH-sensitive nanoparticles release drugs in acidic tumor microenvironments, sparing healthy tissues.

Thermoresponsive hydrogels can undergo sol-gel transitions at body temperature, enabling injectable depots for sustained delivery. Enzyme-responsive carriers exploit disease-specific enzymes, such as matrix metalloproteinases in cancer, to trigger localized release [48].

Integration with digital technologies further expands possibilities. AI-driven formulation design leverages machine learning algorithms to optimize excipient selection, release kinetics, and patient-specific dosing. Wearable-integrated delivery systems, such as glucose-responsive insulin pumps and microneedle patches connected to smartphone applications, exemplify the convergence of biotechnology and digital health [49]. In the long term, closed-loop drug delivery systems—where biosensors detect physiological signals and trigger real-time drug release—may revolutionize management of chronic diseases like diabetes, epilepsy, and cardiovascular disorders. Quantum computing, though nascent, may one day accelerate predictive modeling of complex drug–excipient–tissue interactions [50]. The combination of bioresponsive materials, computational intelligence, and personalized manufacturing (via 3D printing) will define the next frontier of drug delivery, enabling safer, more effective, and more patient-centric therapies.

CONCLUSION

Device-mediated, nanotechnology-enabled, and 3D-printed drug delivery systems represent a paradigm shift in modern pharmacology. These platforms collectively address the long-standing challenges of bioavailability, tissue specificity, and patient compliance. Clinical milestones such as Doxil, Abraxane, Spritam, and mRNA vaccine formulations demonstrate the translational impact of these innovations. At the same time, emerging applications in pulmonary, ocular, otic, and intranasal delivery expand therapeutic frontiers, especially for oncology, infectious diseases, and neurological disorders.

Despite significant progress, hurdles remain in regulatory harmonization, large-scale manufacturing, toxicological evaluation, and long-term safety. Nanotoxicology and immunogenicity concerns highlight the need for rigorous preclinical and clinical assessments, while environmental safety issues underscore the importance of sustainable production. Looking forward, the integration of smart materials, AI-assisted formulation design, and wearable technologies will enable dynamic, patient-specific therapies that redefine the practice of medicine. By bridging material science, nanotechnology, regulatory science, and digital health, the future of drug delivery is poised to move beyond static formulations toward adaptive, intelligent, and personalized systems.

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