3D Printing in Pharmaceutics:Current Challenges and Future Directions

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***Abstract*—Three-dimensional (3D) printing, also termed additive manufacturing (AM), has emerged as a transformative technology in pharmaceutical sciences, offering unprecedented opportunities for personalized medicine, complex drug delivery architectures, and on-demand fabrication of dosage forms. Despite remarkable progress in the past decade—culminating in the FDA approval of the first 3D-printed tablet (Spritam®, 2015)—widespread clinical adoption remains constrained by unresolved technical, regulatory, and economic challenges. This review provides a structured analysis of the primary 3D printing modalities employed in drug product manufacturing, including fused deposition modeling (FDM), stereolithography (SLA), selective laser sintering (SLS), inkjet-based printing, and semi-solid extrusion (SSE). We critically examine their mechanistic foundations, pharmaceutical applications across therapeutic areas, and the current barriers impeding their translational progress. Key challenges discussed include material biocompatibility and regulatory compliance, print resolution limitations, scalability constraints, post-processing requirements, and the absence of pharmacopoeial standards. Looking forward, we identify convergent innovations—including artificial intelligence-driven formulation design, multi-drug polypills, bioprinted drug delivery scaffolds, and decentralized point-of-care manufacturing—as pivotal future directions. This review aims to serve as a comprehensive resource for pharmaceutical scientists, formulation engineers, and regulatory professionals navigating the evolving landscape of 3D-printed drug products.**

***Index Terms*—3D printing; additive manufacturing; fused deposition modeling; personalized medicine; drug delivery; pharmaceutical formulation; regulatory affairs; point-of-care manufacturing; polypill; bioprinting**

I. INTRODUCTION

The pharmaceutical industry has long relied on mass production techniques that generate standardized dosage forms designed for the average patient. While this model has served public health effectively at a population level, it fails to accommodate the considerable interpatient variability in pharmacokinetics, disease severity, body weight, age, comorbidities, and pharmacogenomics. Pediatric, geriatric, and oncology populations are particularly underserved by one-size-fits-all dosing regimens.

Three-dimensional (3D) printing—or additive manufacturing (AM)—offers a compelling paradigm shift: the ability to fabricate patient-specific dosage forms with precisely tailored drug content, release profiles, and physical attributes. By building objects layer-by-layer from digital models, 3D printing enables a degree of structural and compositional complexity that conventional pharmaceutical manufacturing cannot replicate. Tablets with internal compartments, multi-layered matrices, porous scaffolds, and graded drug concentration gradients are now routinely achievable in laboratory settings.

The pivotal regulatory milestone for pharmaceutical 3D printing arrived in 2015 when the U.S. Food and Drug Administration (FDA) approved Spritam® (levetiracetam), manufactured by Aprecia Pharmaceuticals using the ZipDose® binder-jet technology. Spritam® dissolves rapidly in the mouth with a small sip of water—a clinically meaningful advantage for epilepsy patients who may have difficulty swallowing—demonstrating that 3D-printed medicines can meet rigorous quality and safety standards.

Despite this landmark achievement, the field has not witnessed a cascade of subsequent commercial approvals. The gap between laboratory promise and

clinical reality reveals a complex interplay of material science limitations, process analytical technology (PAT) gaps, regulatory uncertainty, and economic barriers. Understanding these challenges is essential for charting a coherent path forward.

This review systematically addresses: (i) the major 3D printing technologies used in pharmaceutics and their underlying mechanisms; (ii) therapeutic areas where 3D printing has demonstrated clinical relevance; (iii) the critical challenges that limit broader adoption; and (iv) future directions that may overcome these barriers and accelerate translation to patient benefit.

II. MECHANISMS AND CLASSIFICATIONS OF 3D PRINTING TECHNOLOGIES

Several 3D printing modalities have been investigated for pharmaceutical applications. Each technology differs fundamentally in the physical and chemical principles by which material is deposited and consolidated, which in turn governs the types of excipients that can be used, the resolution achievable, and the drug classes that can be accommodated.

2.1 Fused Deposition Modeling (FDM)

FDM is the most widely studied pharmaceutical 3D printing technique due to its accessibility and compatibility with thermoplastic pharmaceutical-grade polymers. In FDM, a filament of drug-loaded polymer—typically prepared by hot-melt extrusion (HME)—is fed into a heated nozzle that melts and deposits material onto a build platform in successive layers. Common matrix polymers include hydroxypropyl methylcellulose acetate succinate (HPMCAS), polyvinyl alcohol (PVA), Eudragit® grades, and polylactic acid (PLA). The thermal history experienced during both HME and FDM must be carefully managed to prevent drug degradation and polymorphic transformation. FDM enables complex tablet geometries that modulate drug release kinetics through infill density, layer thickness, and shell thickness parameters.

2.2 Stereolithography (SLA) and Digital Light Processing (DLP)

SLA and DLP use photopolymerization to solidify liquid resin layers using UV or visible light. SLA traces the cross-section point-by-point with a laser, while DLP projects entire layers simultaneously using a digital micromirror device, offering superior throughput. Pharmaceutical applications have focused on incorporating drugs into photopolymerizable resins, though the choice of biocompatible and FDA-compliant photopolymers and photoinitiators remains limited. These technologies offer submillimeter resolution and are particularly suited for fabricating intricate drug-eluting implants, microneedle arrays, and oral films.

2.3 Selective Laser Sintering (SLS)

SLS employs a high-power laser to selectively fuse powder particles—typically polymers, waxes, or lipid-based materials—layer by layer. Unlike FDM, SLS does not require support structures, enabling more complex three-dimensional architectures. The solvent-free, room-temperature powder bed offers advantages for thermolabile drugs, though the laser energy still generates localized heat that must be controlled. SLS has shown particular promise for amorphous solid dispersions and has been used to fabricate porous, fast-dissolving oral dosage forms.

2.4 Inkjet and Binder Jetting

Inkjet printing deposits picoliter-volume droplets of drug solution onto substrates or powder beds. In binder jetting, a liquid binder selectively binds powder particles to consolidate each layer—the technology used in Spritam®. Inkjet approaches offer high precision and can deposit multiple drugs simultaneously, making them suitable for combinatorial dosage forms and transdermal patches. The primary constraint is the requirement that the drug formulation possess appropriate viscosity, surface tension, and droplet formation characteristics to ensure consistent jetting performance.

2.5 Semi-Solid Extrusion (SSE)

SSE, also known as direct powder extrusion or paste extrusion, dispenses semi-solid materials through a pressure-driven nozzle at near-ambient temperatures. This approach is particularly attractive for thermolabile APIs, biologics, and hydrogel-based formulations. SSE has been explored for personalized pediatric dosage forms, sustained-release suppositories, and implantable drug-eluting devices. Resolution is lower than photopolymerization-based methods, but the broad material compatibility represents a significant advantage.

2.6 Comparative Summary

The table below summarizes key attributes of these technologies to guide formulation scientists in technology selection:

Table 1. Comparative overview of 3D printing technologies in pharmaceutics. FDM = fused deposition modeling; SLA = stereolithography; SLS = selective laser sintering; SSE = semi-solid extrusion.

Technology	Resolution	Excipients	Scalability	Drug Types
FDM	250–500 µm	Thermoplastic polymers	High	Small molecules
SLA/DLP	25–100 µm	Photopolymers	Moderate	BCS I & II
Inkjet/Binder	30–100 µm	Binders, plasticizers	High	Broad spectrum
SLS	50–150 µm	Polymer powders	Moderate	Proteins, peptides
Extrusion (SSE)	200–600 µm	Semi-solid carriers	Moderate	Hydrophilic drugs

III. CLINICAL APPLICATIONS

The versatility of 3D printing has enabled its exploration across a broad spectrum of therapeutic areas, from oral solid dosage forms to sophisticated implantable devices.

3.1 Personalized Oral Dosage Forms

Personalized oral dosage forms represent the most extensively studied pharmaceutical application. The ability to fine-tune drug dose, tablet geometry, and release profile facilitates patient-centric pharmacotherapy. Polypills—single tablets containing multiple active pharmaceutical ingredients (APIs)—have been fabricated by 3D printing for cardiovascular disease management, offering a strategy to simplify complex medication regimens and improve adherence. Multi-layered tablets with spatially separated incompatible drugs, pulsatile release systems that mimic chronotherapeutic dosing needs in conditions such as rheumatoid arthritis and hypertension, and orodispersible films for dysphagic patients have all been demonstrated in preclinical and early clinical research.

3.2 Pediatric and Geriatric Formulations

Children and the elderly represent populations with the greatest unmet need for dose flexibility and alternative dosage forms. Regulatory guidance (EMA Paediatric Regulation, FDA PREA) demands age-appropriate formulations, yet the economics of small-batch pediatric drug development have historically been prohibitive. 3D printing offers an economically viable route to small-batch, flexible-dose pediatric medicines. Chewable, palatable mini-tablets, gummies, and liquid-filled capsules containing individually calculated doses have been prototyped. For elderly patients with dysphagia, orodispersible tablets fabricated by inkjet or SLS offer a clinically meaningful alternative to crushing commercial tablets—a practice associated with dose inaccuracy and drug-excipient interactions.

3.3 Oncology and Dose-Banding

Oncology pharmacotherapy is highly individualized, with dosing frequently calculated on body surface area or weight. 3D printing could enable hospital pharmacies or compounding centers to produce precisely dosed anticancer tablets on demand, reducing the compounding errors associated with manual preparation of liquid formulations. Additionally, dose-banding—the use of standardized dose ranges approximating calculated doses—could be complemented by printed tablets offering finer dose granularity, potentially improving therapeutic outcomes while reducing toxicity.

3.4 Controlled Drug Delivery and Implants

3D-printed implantable devices for sustained local drug delivery represent a high-impact application. Biodegradable poly(lactic-co-glycolic acid) (PLGA) scaffolds loaded with antibiotics for localized orthopedic infection prophylaxis, intravaginal rings delivering antiretroviral agents for HIV pre-exposure prophylaxis, and drug-eluting stents with

geometrically optimized strut profiles have been reported. The ability to program drug release through scaffold architecture—rather than relying solely on polymer chemistry—opens new avenues for spatiotemporally controlled therapeutic delivery.

3.5 Transdermal and Microneedle Systems

Dissolving and hollow microneedle arrays fabricated by SLA and two-photon polymerization have been explored for vaccine delivery, insulin administration, and cosmeceutical applications. The precise geometric control enabled by high-resolution printing permits optimization of needle dimensions for minimal pain, maximal skin penetration, and controlled drug release. Printed transdermal patches with drug-loaded reservoirs and rate-controlling membranes offer an alternative to conventional cast-and-peel manufacturing.

3.6 Ophthalmology and Specialty Drug Products

3D-printed ocular inserts and contact lens-based drug delivery systems have been investigated for glaucoma, dry eye, and posterior segment diseases. The ocular route demands extreme precision in dose delivery given the small volumes involved and the sensitivity of ocular tissues. Printed devices can achieve drug loadings and release durations unattainable with conventional eye drops, potentially improving both therapeutic efficacy and patient compliance.

IV. CHALLENGES AND BARRIERS TO ADOPTION

Despite the compelling scientific rationale for pharmaceutical 3D printing, its transition from bench to bedside is impeded by a constellation of interrelated technical, regulatory, and commercial challenges.

4.1 Material Limitations and Biocompatibility

The palette of pharmaceutical-grade excipients compatible with each 3D printing modality remains restricted. FDM requires thermoplastic polymers with suitable melt viscosities and thermal stability windows that may not coincide with those of the target API. SLA and DLP demand photopolymers and photoinitiators that must be biocompatible, non-cytotoxic, and fully characterized for extractable and leachable (E&L) profiles—a catalog that is currently limited and expensive to expand. SLS powders must possess flowability characteristics and sinterability profiles that pharmaceutical excipients do not always naturally exhibit, necessitating complex powder engineering. The incorporation of moisture-sensitive, hygroscopic, or otherwise reactive APIs into printed dosage forms introduces additional compatibility challenges not encountered in conventional film coating or direct compression.

4.2 Regulatory Framework and Quality by Design (QbD)

No dedicated regulatory guidance exists for 3D-printed drug products beyond the FDA's 2017 draft guidance on technical considerations, which focuses primarily on device applications. Pharmaceutical 3D printing sits at the intersection of drug and device regulations, creating jurisdictional ambiguity. Critical quality attributes (CQAs) such as content uniformity, dissolution performance, and physical integrity must be demonstrated through validated analytical methods, but the non-traditional geometries and internal architectures of 3D-printed dosage forms challenge conventional pharmacopoeial testing (e.g., USP <711> dissolution for tablets with complex porous structures). A QbD framework that maps Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) to CQAs through design spaces is essential but has been elaborated for only a handful of 3D printing platforms to date.

4.3 Scalability and Manufacturing Economics

Most 3D printing platforms in pharmaceutical research operate at laboratory scale, producing single units or small batches over extended print times. Scaling to production volumes relevant for commercial distribution presents significant engineering challenges. Print speed, nozzle fouling, build platform homogeneity, and inter-batch variability all intensify as throughput demands increase. Continuous manufacturing concepts—increasingly favored by regulators for their PAT integration and real-time release testing (RTRT) potential—have been difficult to reconcile with the inherently batch-like nature of layer-by-layer deposition. Economic analyses suggest that 3D printing is cost-competitive with conventional manufacturing only for low-volume specialty products or truly personalized medicines where the elimination

of intermediary dosage strengths justifies the higher unit cost.

4.4 Process Analytical Technology and Real-Time Quality Control

In-line and at-line PAT tools capable of monitoring 3D printing processes in real time are insufficiently developed. Drug content and polymorphic form of printed tablets, layer adhesion integrity, porosity, and geometric fidelity are typically assessed post-manufacture using destructive or offline analytical techniques such as near-infrared spectroscopy (NIR), Raman imaging, X-ray powder diffraction (XRPD), and micro-computed tomography (μCT). The absence of closed-loop control systems that can detect and correct print deviations in real time impedes the implementation of RTRT strategies demanded by modern pharmaceutical quality systems. Developing non-destructive, rapid, and process-compatible analytical methods for printed dosage forms is a pressing unmet need.

4.5 Intellectual Property and Data Security

Point-of-care 3D printing—where digital drug formulation files are transmitted to decentralized printers in hospitals, pharmacies, or even patient homes—introduces novel intellectual property, data security, and diversion risks. The ability to replicate a dosage form from a digital blueprint raises concerns about counterfeit medicine production, unauthorized dose manipulation, and cybersecurity vulnerabilities in connected manufacturing devices. Blockchain-based verification systems and cryptographically secured formulation files have been proposed as potential safeguards, but their practical implementation in regulated pharmaceutical environments remains nascent.

4.6 Drug Stability During Printing

Thermal, photochemical, and mechanical stresses inherent to 3D printing processes can compromise API stability. In FDM, the thermal energy required to melt the polymer filament may exceed the degradation threshold of heat-sensitive drugs, alter solid-state form, or accelerate moisture uptake. In SLA, photosensitive drugs may undergo photodegradation during UV curing. In SLS, localized laser-induced heating can drive crystalline-to-amorphous transitions or induce oxidative degradation. Systematic pre-formulation screening of API thermodynamic stability, solid-state compatibility with selected excipients, and stress-specific degradation pathways is therefore indispensable but adds significantly to development timelines.

V. FUTURE DIRECTIONS

Overcoming the barriers described above will require coordinated advances across materials science, process engineering, digital technology, and regulatory science. Several promising trajectories are beginning to converge.

5.1 Artificial Intelligence and Machine Learning in Formulation Design

Artificial intelligence (AI) and machine learning (ML) approaches are increasingly being applied to accelerate the formulation development of 3D-printed dosage forms. Predictive models trained on physicochemical property datasets can identify optimal polymer-drug combinations for FDM filament preparation, reducing the experimental burden of formulation screening. Generative AI algorithms can propose novel tablet geometries that achieve target dissolution profiles, while reinforcement learning frameworks can optimize printer parameters in a closed-loop manner. The integration of high-throughput experimental data with physics-based models of heat transfer, mass transport, and crystallization kinetics holds promise for establishing mechanistic digital twins of printing processes—potentially enabling in silico prediction of CQAs from CMAs and CPPs.

5.2 Multi-Drug Polypills and Combinatorial Dosage Forms

The polypill concept—a fixed-dose combination targeting multiple cardiovascular risk factors simultaneously—has demonstrated improved adherence and outcomes in clinical trials. 3D printing uniquely enables the co-fabrication of multiple APIs within a single dosage form, each potentially in a spatially distinct compartment with an independently tailored release profile. Future work should focus on demonstrating clinical equivalence of 3D-printed polypills to co-administered monocomponent tablets, navigating the complex regulatory pathway for fixed-dose combinations, and expanding the polypill

concept to therapeutic areas beyond cardiology, including infectious disease (e.g., antiretroviral polypills), mental health, and metabolic syndrome.

5.3 Bioprinting and Personalized Drug-Eluting Implants

The convergence of 3D printing with biological materials—bioprinting—opens the possibility of drug-loaded scaffolds that can simultaneously support tissue regeneration and deliver therapeutics in a spatiotemporally controlled manner. Bioprinted bone substitutes loaded with bone morphogenetic proteins (BMPs), cartilage scaffolds containing anti-inflammatory agents, and vascularized tumour models for in vitro drug testing are among the most advanced preclinical demonstrations. As bioink formulations mature and the regulatory pathway for combination products clarifies, bioprinted drug-tissue constructs may transform regenerative medicine and targeted oncology therapy.

5.4 Point-of-Care and Decentralized Manufacturing

The vision of pharmacy-based or even bedside 3D printing of personalized medicines is predicated on the development of closed, validated, pharmacy-grade printing units analogous to automated compounding devices. Several academic and industrial consortia are advancing this concept, with pilot programs in hospital pharmacy settings demonstrating feasibility for selected drug products. Regulatory bodies will need to develop a dedicated framework governing the qualification of pharmacy 3D printing equipment, the validation of digital formulation files, the training of operators, and the scope of products amenable to point-of-care fabrication. If these frameworks can be established, decentralized 3D printing could transform the supply chain for personalized medicines, eliminating storage and distribution of slow-moving dosage strengths and enabling truly on-demand manufacturing.

5.5 Continuous Manufacturing Integration

Integrating 3D printing into continuous pharmaceutical manufacturing lines—where raw materials flow continuously through interconnected unit operations monitored by PAT—would address scalability and quality control limitations simultaneously. Extrusion-based printing modalities are most readily compatible with continuous upstream processes (e.g., twin-screw hot-melt extrusion followed by direct FDM printing). Embedding Raman or NIR probes at the print head to monitor drug content in real time, coupled with automated rejection of out-of-specification units, would satisfy RTRT requirements. This integrated approach could substantially reduce manufacturing cycle times and working capital tied up in batch intermediates.

5.6 Expansion of the Pharmaceutical Excipient Toolkit

Broadening the portfolio of pharmaceutical-grade excipients qualified for each 3D printing modality is a prerequisite for wider application. Industry consortia such as the International Pharmaceutical Excipients Council (IPEC) and regulatory bodies have a role to play in expediting the characterization and qualification of novel excipients—including photo-curable biopolymers, printable lipid-based carriers, and biocompatible support materials.

VI. CONCLUSIONS

Three-dimensional printing stands at an inflection point in pharmaceutical sciences. The scientific community has convincingly demonstrated its potential to deliver personalized medicine, simplified polypharmacy regimens, and novel drug delivery architectures that are impossible to achieve with conventional manufacturing. The approval of Spritam® provided proof of regulatory viability, yet the decade that followed has been characterized more by incremental laboratory advances than by transformative clinical translation.

The path forward demands a multi-disciplinary response: material scientists must expand the excipient toolkit; process engineers must embed PAT for real-time quality assurance; regulatory agencies must develop fit-for-purpose guidance that neither stifles innovation nor compromises patient safety; and health economists must rigorously evaluate the cost-effectiveness of personalized printing in specific therapeutic contexts. Simultaneously, digital infrastructure—including secure file transfer, AI-driven formulation design, and digital twins of printing processes—must mature to support the decentralized manufacturing paradigm.

When these advances converge, 3D printing has the potential to move from a niche compounding tool to a cornerstone of twenty-first century pharmaceutical

practice—delivering the right drug, in the right dose, in the right form, for the right patient, at the right time.

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