Advances in Three-Dimensional Printing Technologies for Pharmaceutical Formulations: Transforming Personalized Drug Manufacturing and Engineering Controlled Release Systems for Precision Medicine

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Abstract
Three-dimensional (3D) printing, also termed additive manufacturing, has emerged as a transformative technology in pharmaceutical sciences, enabling the fabrication of complex drug delivery systems with unprecedented precision and customization. Conventional manufacturing processes are constrained by fixed dose strengths and standard geometries, limiting their capacity to address inter-patient pharmacokinetic variability. The present review aims to comprehensively examine the major 3D printing technologies applied in pharmaceutical formulations, including fused deposition modeling (FDM), inkjet printing, binder jetting, stereolithography (SLA), and selective laser sintering (SLS), evaluating their utility in designing personalized dosage forms and controlled-release systems. Key applications discussed encompass patient-specific oral dosage forms, polypill systems incorporating multiple active pharmaceutical ingredients (APIs), pediatric and geriatric formulations, and drug-eluting implants. The approval of Spritam (levetiracetam) by the U.S. Food and Drug Administration (FDA) in 2015 established a pivotal regulatory precedent that has accelerated translational research in this domain. Mechanisms of drug release from 3D printed matrices, including diffusion-controlled, erosion-mediated, and geometry-dependent release modulation, are critically evaluated. Despite remarkable advances, significant challenges remain in material biocompatibility, printing scalability, regulatory harmonization, and clinical validation. Future perspectives emphasize the integration of artificial intelligence in print parameter optimization, the development of pharmaceutical-grade printable biomaterials, and point-of-care manufacturing platforms. In conclusion, 3D printing holds immense potential to redefine pharmaceutical manufacturing toward individualized, patient-centric drug therapy.

Keywords: 3D printing; pharmaceutical formulations; personalized medicine; controlled drug release; additive manufacturing; polypill systems

1. Introduction

The emergence of 3D printing in pharmaceutical sciences represents a paradigm shift from traditional batch manufacturing toward digitally driven, patient-centric drug production. Additive manufacturing (AM) technologies facilitate layer-by-layer construction of dosage forms from computer-aided design (CAD) files, enabling unprecedented spatial control over drug distribution, geometry, and release kinetics [1, 2]. Unlike conventional tableting or capsule filling, 3D printing permits the incorporation of multiple APIs at individually programmed concentrations within a single dosage unit, paving the way for polypharmacy simplification and tailored therapeutic regimens [3].

The landmark FDA approval of Spritam (levetiracetam oral dispersible tablet) by Aprecia Pharmaceuticals in 2015, manufactured via the ZipDose binder jetting platform, validated the clinical and regulatory viability of 3D-printed pharmaceuticals [4]. This milestone catalyzed a surge in global research activity directed at exploiting AM for diverse drug delivery applications, including controlled-release oral dosage forms, transdermal patches, ophthalmic inserts, and biodegradable implants [5, 6].

The scope of this review encompasses a critical evaluation of clinically relevant 3D printing technologies, their mechanistic application to drug delivery design, and an assessment of therapeutic applications spanning personalized medicine, pediatric/geriatric pharmacotherapy, and complex drug delivery systems. Regulatory and translational challenges are discussed with reference to future directions for clinical implementation and pharmaceutical manufacturing innovation.

2. 3D Printing Technologies in Pharmaceutical Formulations

A diverse array of 3D printing modalities has been investigated for pharmaceutical applications. Each technology confers distinct advantages related to resolution, compatible materials, and drug processing conditions (Table 1; Figure 1).

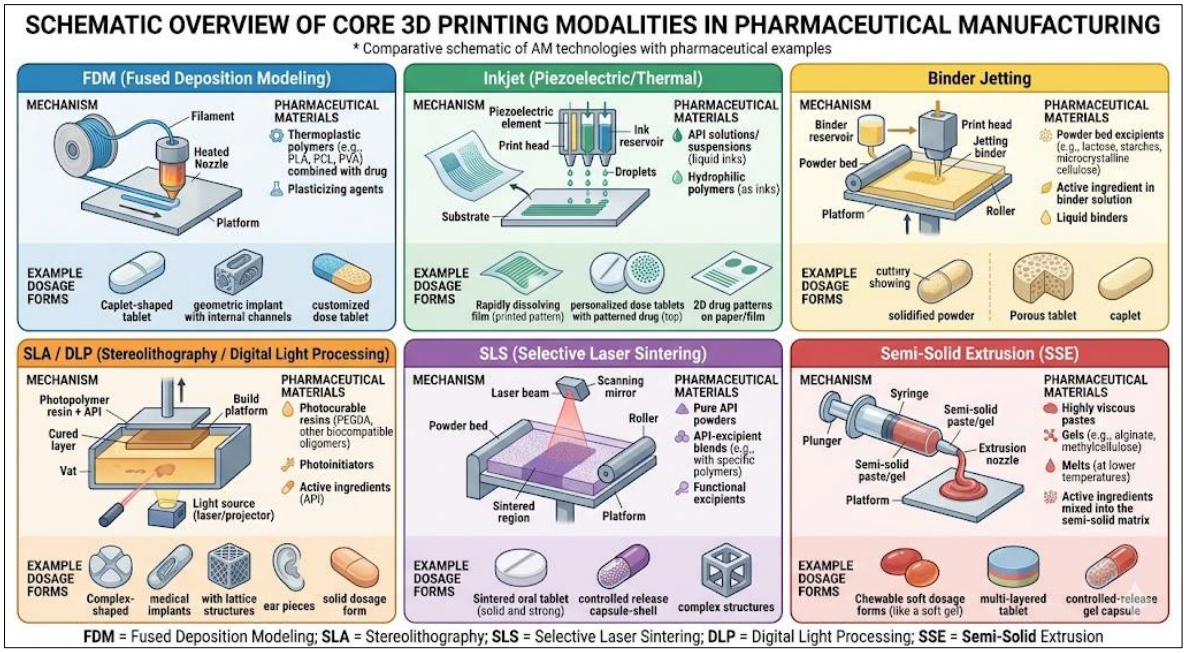

Fig 1: Overview of 3D Printing Technologies Used in Pharmaceutical Manufacturing

Table 1: Major 3D Printing Technologies Used in Pharmaceutical Formulations

Technology	Mechanism	Key Materials	Applications
FDM	Thermal extrusion of thermoplastic filaments	HPMC, PVA, PCL, PLA, Eudragit	Immediate/controlled release tablets, implants
Inkjet Printing	Droplet deposition of liquid formulations	Aqueous drug solutions, polymers	Orodispersible films, transdermal patches
Binder Jetting	Selective binder deposition onto powder bed	Drug powders, excipient blends	Fast-dissolving tablets (e.g., Spritam)
SLA/DLP	UV-photopolymerization of resin	Photopolymer resins, PEGDA	Controlled release, implantable devices
SLS	Laser sintering of powder layers	PVP, PLA, drug-polymer blends	Solid oral dosage forms, complex geometries
Semi-solid Extrusion	Extrusion of gels/pastes at room temp	Hydrogels, lipid bases, APIs	Suppositories, ophthalmic, topical forms

2.1. Fused Deposition Modeling (FDM)

FDM is the most extensively investigated 3D printing technology in pharmaceutical sciences, operating through the thermoplastic extrusion of drug-loaded filaments that are deposited layer-by-layer to construct the dosage form [7]. Drug-polymer filaments are typically prepared by hot-melt extrusion (HME) using pharmaceutical polymers such as hydroxypropyl methylcellulose acetate succinate (HPMCAS), polyvinyl alcohol (PVA), polyethylene glycol (PEG), and Eudragit copolymers [8]. The geometry of the printed structure—including infill density, shell thickness, and pore architecture—can be precisely programmed to modulate drug release kinetics [9]. FDM-produced tablets have demonstrated zero-order and sustained-release profiles through manipulation of internal lattice designs, making the technology suitable for chronopharmacological applications and time-controlled drug delivery [10].

A critical limitation of FDM is its requirement for elevated processing temperatures (typically 150–250°C), which may compromise thermolabile APIs and necessitate formulation screening for thermal stability [11]. Advances in low-temperature FDM variants, incorporating plasticizers and polymer blends with reduced glass transition temperatures, have partially addressed this constraint [12].

2.2. Inkjet and Binder Jet Printing

Inkjet printing deposits precise droplets of drug solution onto a substrate through thermal or piezoelectric actuator mechanisms, offering high-resolution dose placement with minimal material waste [13]. This technology is particularly suited for fabricating orodispersible films, transdermal patches, and low-dose pharmaceutical systems where droplet-level dose accuracy is critical [14]. Binder jetting, as employed in the ZipDose platform for Spritam production, selectively deposits liquid binder onto powder bed layers, creating highly porous tablets with rapid oral disintegration times of under 11 seconds—advantageous for patients with dysphagia or pediatric populations [4, 15].

2.3. Stereolithography (SLA)

SLA employs ultraviolet (UV) or visible light photopolymerization to cure liquid photopolymer resins into solid three-dimensional structures with submillimeter resolution [16]. In pharmaceutical applications, SLA has been used to fabricate complex geometries including torus-shaped, gyroid, and latticed drug delivery devices with highly predictable release profiles [17]. Lim *et al*. demonstrated the fabrication of controlled-release devices using pharmaceutical-grade poly(ethylene glycol) diacrylate (PEGDA) resins incorporating various APIs, achieving tunable release profiles by modifying resin composition and print parameters [18]. A primary challenge involves the limited availability of biocompatible, pharmaceutical-grade photopolymerizable resins, as well as potential cytotoxicity of unreacted monomers and photoinitiators [19].

2.4. Emerging Hybrid and Multi-Material Printing Technologies

Selective laser sintering (SLS) utilizes focused laser energy to sinter pharmaceutical-grade powder blends into solid dosage forms, eliminating the need for binders or solvents [20]. SLS-fabricated tablets have demonstrated excellent content uniformity and customizable porosity profiles. Semi-solid extrusion (SSE), also known as pressure-assisted microsyringe printing, operates at ambient temperatures and is compatible with hydrogel, lipid-based, and aqueous drug formulations, making it particularly relevant for biologic and thermolabile APIs [21]. Multi-material and hybrid printing platforms integrating FDM with inkjet or SLA with SSE are emerging as powerful tools for fabricating polypill systems and drug-eluting devices with spatially resolved drug domains and independent release kinetics [22].

3. Design of 3D Printed Drug Delivery Systems

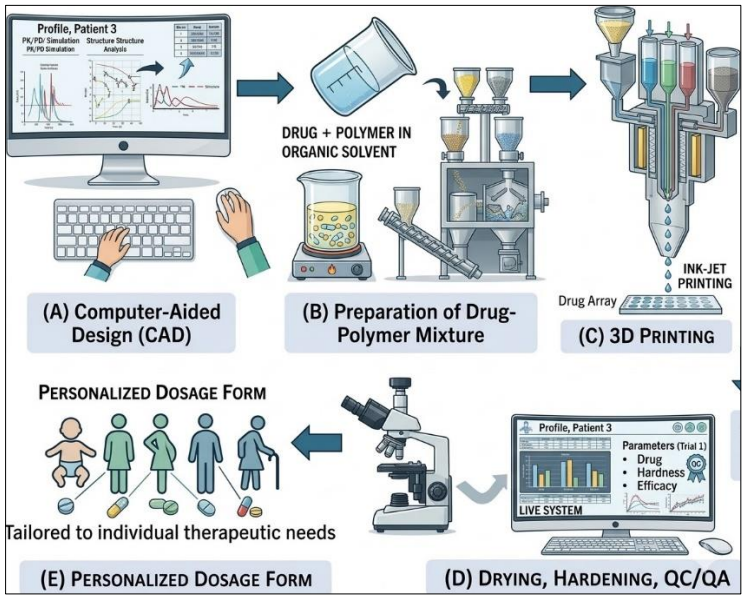

Fig 2: Workflow of 3D Printed Drug Formulation Development

3.1. Personalized Dosage Forms

Personalized pharmaceutical manufacturing through 3D printing allows dose individualization based on patient-specific pharmacokinetic parameters, genetic polymorphisms, body weight, age, renal/hepatic function, and comorbidities [23]. Patient-specific CAD files can be generated from pharmacokinetic modeling software and transmitted to point-of-care 3D printers in clinical or community pharmacy settings (Figure 2). Pediatric patients, who often require sub-milligram dose adjustments not achievable by tablet splitting or liquid dilution, represent a primary beneficiary population [24]. Similarly, geriatric patients requiring polypharmacy regimens can benefit from combined dosage forms with individually tailored API concentrations and release profiles.

3.2. Controlled Drug Release Structures

The three-dimensional spatial control afforded by AM enables the engineering of sophisticated internal architectures that govern drug release behavior independently of material composition. Hollow-core tablets, Torus geometries, and gradient-density matrices allow programmable release profiles ranging from pulsatile to extended zero-order kinetics [25]. Shell-core structures fabricated by FDM, comprising an immediate-release drug-loaded shell surrounding a controlled-release core, have demonstrated biphasic pharmacokinetic profiles suitable for chronotherapy [10]. Digital design modifications require no changes to printing materials or equipment, enabling rapid prototyping and release profile optimization.

3.3. Multi-Drug and Polypill Systems

The polypill concept—combining multiple drugs for cardiovascular, metabolic, or infectious disease management within a single dosage unit—is uniquely enabled by 3D printing's multi-material fabrication capability [3]. Printed polypill systems incorporating antihypertensive agents (atenolol, ramipril, hydrochlorothiazide) at individualized doses with independent release rates have been demonstrated in FDM studies [26]. The clinical implications include simplified dosing regimens, improved patient adherence, and potential reduction of cardiovascular events in high-risk populations. SSE-based multi-nozzle printing systems enable simultaneous deposition of incompatible drug compartments within the same dosage unit, addressing physicochemical incompatibilities encountered in conventional fixed-dose combinations.

4. Mechanisms of Drug Release from 3D Printed Dosage Forms

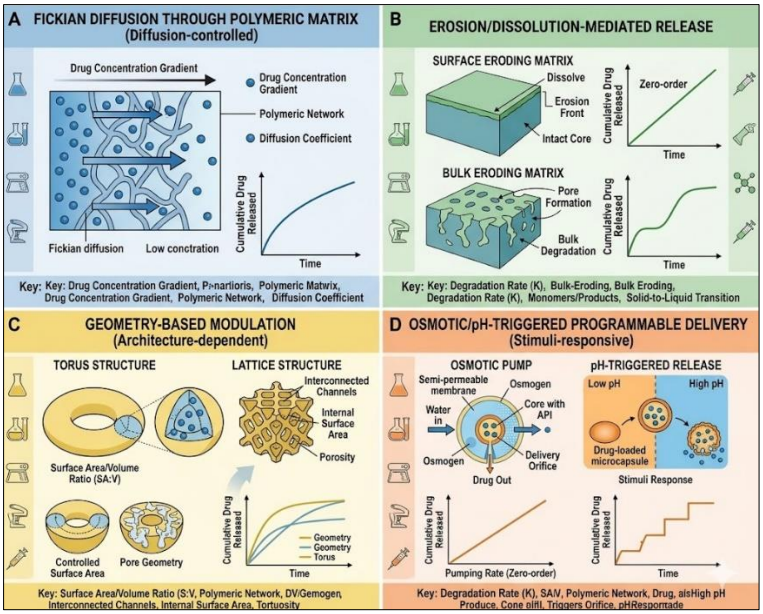

Fig 3: Mechanisms of Controlled Drug Release from 3D Printed Dosage Forms

4.1. Diffusion-Controlled Release

The predominant release mechanism from polymeric 3D printed matrices is Fickian diffusion, governed by the concentration gradient across the drug-polymer matrix and the diffusion coefficient of the API through the selected excipient [27]. In FDM-printed tablets utilizing hydrophilic polymers such as PVA or HPMC, drug release follows Higuchi kinetics, correlating with the square root of time. Modification of infill density, layer height, and shell permeability directly modulates diffusivity, enabling empirical release rate optimization without reformulation.

4.2. Geometry-Based Release Modulation

A distinctive advantage of 3D printing over conventional manufacturing is the capacity to engineer drug release through geometric design rather than chemical modification of excipients. Studies have demonstrated that tablets with gyroid and diamond infill architectures exhibit significantly different release rates compared to solid matrices of identical composition [25, 28]. Surface area-to-volume ratio, accessible porosity, and tortuosity of the diffusion pathway—all directly determined by the CAD design—serve as primary determinants of release kinetics. This geometry-pharmaceutical interface represents a paradigmatic shift in formulation science, where release profiles are digitally programmed rather than chemically engineered.

4.3. Sustained and Programmable Drug Delivery

Beyond diffusion and geometry, 3D printing enables the engineering of osmotic, pH-dependent, and stimuli-responsive release systems with high reproducibility [29]. Enteric-coated SLA devices fabricated with pH-sensitive methacrylate resins exhibit site-specific colonic release, applicable for inflammatory bowel disease therapy. Dual-layer FDM tablets incorporating an external hydrophobic barrier and an inner hydrophilic drug core achieve osmotically driven zero-order delivery. Programmable time-delayed pulsatile systems, achieved through concentric shells of varying polymer dissolution rates, enable chronopharmacological dosing aligned with circadian pharmacodynamics of conditions such as hypertension and asthma.

5. Therapeutic and Clinical Applications

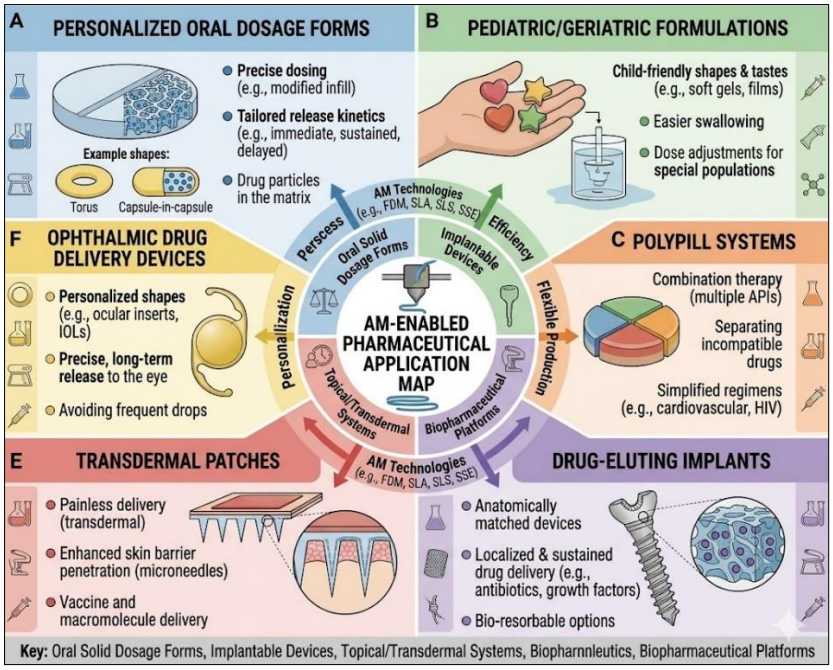

Fig 4: Applications of 3D Printing in Personalized Medicine and Drug Delivery

5.1. Personalized Medicine and Patient-Specific Dosing

The integration of 3D printing with pharmacogenomics, therapeutic drug monitoring, and clinical decision-support systems creates a framework for genuinely individualized drug therapy [23]. Dose printing systems integrated with electronic health records can automatically generate patient-specific dosage units adjusted to real-time pharmacokinetic parameters. In oncology, where narrow therapeutic index drugs such as methotrexate and capecitabine require dose modifications based on body surface area and toxicity profiles, 3D printing enables precise fractional dosing currently unachievable with commercial formulations [30].

5.2. Pediatric and Geriatric Drug Formulations

Pediatric pharmacotherapy is constrained by the scarcity of age-appropriate dosage forms, necessitating off-label manipulation of adult formulations with associated risks of dose inaccuracy and contamination [24]. Inkjet-printed orodispersible films and FDM-printed mini-tablets with age-appropriate flavoring excipients provide pediatric-compliant drug delivery with verifiable dose uniformity. For geriatric patients, who commonly present with polypharmacy burdens and swallowing difficulties, 3D-printed polypills and rapidly disintegrating tablets fabricated by binder jetting offer substantial compliance advantages. Orodispersible FDM mini-tablets with customized API loading have demonstrated acceptance in patient-centric pediatric trials, supporting their pharmaceutical development [15].

5.3. Complex Drug Delivery Systems and Implants

Beyond oral formulations, 3D printing has demonstrated significant utility in fabricating drug-eluting implants, intravaginal rings, ophthalmic inserts, and biodegradable scaffolds for localized drug delivery [21]. FDM and SSE-printed biodegradable poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) implants incorporating chemotherapeutic agents have been investigated for post-surgical local tumor recurrence prophylaxis, achieving sustained drug release over weeks to months at tumor-bed concentrations exceeding systemic delivery levels [6]. Ophthalmic 3D-printed drug delivery devices incorporating anti-glaucoma and anti-inflammatory agents offer sustained ocular delivery, reducing the compliance burden of multiple daily eye drop administrations.

6. Challenges and Future Perspectives

Despite considerable progress, the clinical translation of 3D printed pharmaceuticals encounters multifaceted challenges spanning regulatory, material, manufacturing, and clinical domains.

Regulatory challenges represent the foremost barrier to widespread pharmaceutical adoption of AM. The FDA and European Medicines Agency (EMA) have issued initial technical considerations for AM devices and medicines; however, no comprehensive, harmonized pharmaceutical Good Manufacturing Practice (GMP) framework specific to 3D printed dosage forms has been established [5]. The inherent on-demand, patient-specific nature of 3D printing conflicts with conventional batch-based quality assurance paradigms, necessitating development of new real-time process analytical technologies (PAT) and continuous quality verification strategies.

Material limitations present a parallel challenge. The currently available library of pharmaceutical-grade, printable excipients is substantially narrower than conventional formulation materials, particularly for SLA and SLS technologies where specialized resins and sinterable polymers are required [19]. The thermal requirements of FDM impose compatibility constraints on thermolabile APIs, and the photopolymer resins used in SLA must undergo rigorous biocompatibility evaluation to ensure absence of cytotoxic leachables [16, 17].

Manufacturing scalability remains a critical unresolved issue, as the inherently sequential, layer-by-layer printing process limits production throughput compared to high-speed conventional tableting equipment. Industrial-scale

pharmaceutical 3D printing will require advances in multi-nozzle parallel printing, continuous-flow AM processes, and integrated quality control systems [22]. Clinical translation challenges include the need for prospective pharmacokinetic/pharmacodynamic studies confirming the bioequivalence and *in vivo* performance of 3D printed formulations relative to established reference products. The integration of 3D printing into community pharmacy and point-of-care settings requires standardized printer validation protocols, formulation databases, and pharmacist training frameworks. Future directions include AI-driven formulation optimization, development of multi-responsive smart materials, and regulatory sandbox frameworks to accelerate clinical evaluation of innovative AM dosage forms.

7. Conclusion

Three-dimensional printing has irrevocably transformed the conceptual and practical landscape of pharmaceutical formulation science, enabling a transition from standardized, population-averaged drug manufacturing toward individualized, digitally driven therapeutic systems. The diverse portfolio of AM technologies—spanning FDM, binder jetting, inkjet printing, SLA, and SLS—provides formulation scientists with versatile platforms to engineer dosage forms with precisely programmed drug release kinetics, patient-specific doses, and multi-drug configurations unattainable by conventional manufacturing. The clinical validation of the first FDA-approved 3D-printed drug product (Spritam) has established a regulatory framework that continues to evolve alongside the technology. Particular promise exists in pediatric, geriatric, and oncology applications where dose individualization is clinically imperative. Overcoming current barriers in regulatory harmonization, pharmaceutical-grade material development, and manufacturing scalability will be essential to realizing the full potential of 3D printing in precision medicine. With continued interdisciplinary convergence of pharmaceutical sciences, materials engineering, digital manufacturing, and clinical pharmacology, 3D printing is poised to redefine future drug manufacturing paradigms toward truly personalized, patient-centric therapy.

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