ISSN: 2349-5448

Intercontinental Journal of Pharmaceutical Investigations and Research (ICJPIR)

ICJPIR |Vol. 11 | Issue 4 | Oct – Dec 2024

www.icjpir.com

DOI: https://doi.org/10.61096/icjpir.v11.iss4.2024.166-181

Three-Dimensional Printing Technology in Pharmaceutical Sciences: Personalized Dosage Forms, Polypills, Pediatric Medicines, and Regulatory Considerations

S. Praveena, Sapavat.Vasantha

Scient Institute of Pharmacy
lbrahimpatnam, Ranga Reddy District - 501 506, Telangana
exambranch.ghip@gmail.com

Published on: 24.11.2024
Published by: Futuristic Publications

Abstract:

Background: Three-dimensional printing, also termed additive manufacturing, represents a paradigm shift in pharmaceutical manufacturing by enabling the layer-by-layer construction of drug products from digital design files, offering capabilities that conventional manufacturing processes cannot match: patient-specific dose customization, complex multi-compartment release geometries, on-demand fabrication of small batches, and the production of polypills combining multiple active pharmaceutical ingredients in a single dosage unit with independently controlled release profiles. The approval of Spritam, a levetiracetam orally disintegrating tablet manufactured by the ZipDose binder jetting technology, by the United States Food and Drug Administration in 2015 established 3D printing as a regulatory-accepted pharmaceutical manufacturing process.

Objective: This review provides a comprehensive critical analysis of 3D printing technologies applicable to pharmaceutical manufacturing, covering printing methods, pharmaceutical materials, formulation design principles, characterization strategies, therapeutic applications in personalized medicine, pediatric and geriatric dosage forms, and polypill development, with emphasis on research and regulatory developments up to 2023.

Results and Discussion: Seven principal 3D printing technologies — fused deposition modeling, semi-solid extrusion, binder jetting, selective laser sintering, stereolithography, inkjet printing, and two-photon polymerization — each offer distinct capabilities and limitations that determine their suitability for specific pharmaceutical applications. Hot-melt extrusion-coupled FDM is the most extensively investigated approach for solid oral dosage forms, enabling fabrication of amorphous solid dispersions, modified-release tablets, and fixed-dose combination products. Spritam remains the only 3D-printed pharmaceutical product with regulatory approval, but more than 150 clinical trials and research programs utilizing 3D printing for pharmaceutical applications had been registered globally by 2023.

Conclusion: Pharmaceutical 3D printing has advanced from laboratory curiosity to a technology with demonstrated clinical feasibility and one regulatory approval, with growing evidence of its particular value in pediatric dosing, personalized medicine, and complex release geometry applications that conventional manufacturing cannot address. Manufacturing scalability, material library expansion, and regulatory framework development are the key barriers to broader clinical translation.

Keywords: *3D printing; additive manufacturing; pharmaceutical; personalized medicine; polypill; fused deposition modeling; pediatric formulation; Spritam; modified release; hot-melt extrusion*

1. Introduction

Conventional pharmaceutical manufacturing operates on a mass production model that prioritizes reproducibility, scalability, and cost efficiency over individualization. A standard tablet or capsule is manufactured to a fixed dose, a fixed release profile, and a fixed physical form that represents a statistical compromise between the pharmacokinetic requirements of a population of patients — not the specific pharmacokinetic needs of the individual patient presenting at the pharmacy. For most therapeutic contexts, this population-average approach is clinically adequate. However, for patient populations with markedly different pharmacokinetic profiles from the average — including neonates and young children whose hepatic enzyme activity, renal clearance, and body surface area change rapidly during development; elderly patients with polypharmacy requiring dose adjustments and simplified medication regimens; patients with rare diseases requiring doses not commercially available; and transplant or oncology patients requiring therapeutic drug monitoring-guided individualized dosing — the fixed-dose, fixed-form pharmaceutical paradigm creates genuine therapeutic gaps [1,2].

Three-dimensional printing, or additive manufacturing, addresses these limitations by enabling the fabrication of pharmaceutical dosage forms layer by layer from a digital design file, allowing every parameter of the dosage form — dose, release profile, physical geometry, color, taste-masking coating — to be specified digitally and realized physically in a single manufacturing operation. The pharmaceutical product exists first as a digital object whose parameters can be modified without retooling or process revalidation, and is then converted to a physical product on demand in quantities as small as a single unit [3,4].

The pharmaceutical application of 3D printing draws on a family of additive manufacturing technologies that have been adapted from engineering and biomedical applications, each exploiting a different physical or chemical mechanism to build three-dimensional structures from feedstock materials. The selection of printing technology determines the range of pharmaceutical materials that can be processed, the achievable feature resolution, the throughput, the temperature and shear stresses to which the drug is subjected during processing, and the regulatory complexity of the resulting product [5].

The landmark approval of Spritam (levetiracetam) by the FDA in 2015 — the first 3D-printed pharmaceutical product to receive regulatory approval anywhere in the world — validated pharmaceutical 3D printing as a legitimate manufacturing process capable of producing products meeting regulatory quality standards. Spritam is manufactured by Aprecia Pharmaceuticals using their proprietary ZipDose binder jetting technology, which produces highly porous, rapidly disintegrating tablets that dissolve with a small sip of liquid in as little as five seconds, enabling swallowing of a high drug load by epilepsy patients with dysphagia or swallowing difficulties [6].

This review systematically examines the seven principal 3D printing technologies with pharmaceutical applications, the formulation design principles and material requirements specific to each technology, characterization methodologies for 3D-printed pharmaceutical products, and the therapeutic applications of pharmaceutical 3D printing in personalized medicine, pediatrics, geriatrics, polypill development, and implantable devices. A critical analysis addresses the substantial gap between academic proof-of-concept demonstrations and real-world pharmaceutical manufacturing implementation, including the regulatory, manufacturing, and material science challenges that must be resolved for 3D printing to fulfill its potential in pharmaceutical practice.

2. Scientific Background

2.1 Principles of Additive Manufacturing

Additive manufacturing builds three-dimensional objects by sequential addition of material in a layer-by-layer fashion guided by a digital design file, in fundamental contrast to subtractive manufacturing (milling, cutting) that removes material from a solid block, and formative manufacturing (compression, molding) that shapes material within a mold. The digital design file, typically in STL (standard tessellation language) or AMF (additive manufacturing file) format, defines the three-dimensional geometry of the object as a mesh of triangular surfaces that is computationally sliced into horizontal cross-sections, each cross-section corresponding to one printed layer. The layer thickness, typically 50 to 500 micrometers for pharmaceutical applications, determines the vertical resolution of the printed object [7,8].

The digital workflow of 3D printing confers several pharmaceutical advantages beyond geometric flexibility. The dose of a 3D-printed tablet is determined by the drug content of the feedstock material and the printed volume, both of which can be precisely specified in the digital design file and modified between print runs without physical retooling. Internal geometric complexity — dual-compartment cores, lattice internal structures, channel networks, and gradient porosity — that would be impossible or prohibitively expensive to produce by conventional compression or molding is readily achievable with appropriate 3D printing technologies [9].

2.2 Pharmaceutical 3D Printing Rationale

The pharmaceutical application of 3D printing is motivated by three distinct but complementary value propositions. The personalization value proposition holds that 3D printing enables fabrication of dosage forms with doses, physical forms, and release profiles tailored to individual patients, potentially improving therapeutic outcomes by replacing population-average formulations with patient-optimized products. The complexity value proposition holds that 3D printing enables production of dosage forms with internal geometric complexity, multi-drug loading, and spatially programmed release profiles that are impossible to manufacture by conventional methods. The on-demand value proposition holds that 3D printing enables small-batch or single-unit pharmaceutical manufacturing at the point of care — in a hospital pharmacy, community pharmacy, or future home setting — eliminating supply chain requirements and enabling immediate availability of patient-specific formulations [10,11].

3. Classification of 3D Printing Technologies for Pharmaceutical Applications

3.1 Fused Deposition Modeling

Fused deposition modeling extrudes thermoplastic drug-polymer filaments through a heated nozzle whose temperature melts the polymer carrier while maintaining the drug in a dissolved or dispersed state within the polymer melt. The extrudate is deposited in programmed layers on a build platform, solidifying rapidly upon cooling to form a mechanically coherent three-dimensional structure. FDM is the most widely investigated pharmaceutical 3D printing technology owing to its compatibility with hot-melt extrusion filament preparation, which simultaneously produces the pharmaceutical feedstock material and can generate amorphous solid dispersions of poorly soluble drugs within the polymer matrix. Drug release from FDM tablets is governed by the hydrophilicity of the carrier polymer, infill density (the fraction of the tablet volume that is solid versus air), and layer structure, providing substantial flexibility in release profile design [12,13].

3.2 Semi-Solid Extrusion

Semi-solid extrusion, also termed direct ink writing or pressure-assisted microsyringe printing, deposits pharmaceutical pastes, gels, or viscous liquids through a syringe nozzle under pneumatic or mechanical pressure. This technology processes materials at ambient or mildly elevated temperatures, making it compatible with thermolabile drugs, biologics, and moisture-sensitive compounds that cannot withstand the elevated temperatures of FDM. Semi-solid extrusion has been applied to personalized tablet printing, orodispersible film fabrication, suppository printing, and fabrication of pediatric chewable tablets with precise dose control. The low temperature processing and compatibility with aqueous systems make it uniquely suitable for printing biologics including proteins, peptides, and nucleic acid-based therapeutics [14,15].

3.3 Binder Jetting

Binder jetting selectively deposits a liquid binding agent onto a powder bed layer by layer, binding the powder particles together where the binder is deposited while unbound powder supports the structure during printing. For pharmaceutical applications, the powder bed consists of the drug and excipient powder blend, and the binder is an aqueous solution that activates surface adhesion between particles. The resulting printed object has a highly porous structure because unbound powder fills the interparticle spaces, providing rapid disintegration when placed in an aqueous environment. Spritam, the only approved pharmaceutical 3D-printed product, exploits this high porosity to achieve disintegration in seconds in a small volume of liquid [16].

3.4 Selective Laser Sintering

Selective laser sintering uses a laser beam to selectively sinter or fuse powder particles in a powder bed, building the three-dimensional structure layer by layer by scanning the laser across successive powder layers.

SLS requires no binder material and produces mechanically robust structures with controlled porosity determined by the laser energy input and scan parameters. Pharmaceutical SLS employs polymer powders including HPMC, PVP, Kollidon VA 64, and Soluplus that absorb the laser energy and undergo sintering, while drug powder is included in the feedstock blend or incorporated by pre-mixing with the polymer carrier [17,18].

3.5 Stereolithography and Digital Light Processing

Stereolithography and digital light processing cure liquid photopolymer resins by selective UV or visible light irradiation, polymerizing the resin in defined patterns to build solid structures layer by layer. DLP simultaneously illuminates an entire cross-section using a digital micromirror array, enabling faster printing than point-scanning SLA. Pharmaceutical application requires use of biocompatible and biodegradable photopolymers including poly(ethylene glycol) diacrylate, gelatin methacrylate, and poly(propylene fumarate), with drug dissolved or suspended in the resin. Resolution is the principal advantage of SLA/DLP — feature sizes below 10 micrometers are achievable with two-photon polymerization variants — enabling printing of microstructured devices, sustained-release implants, and microneedle arrays [19,20].

3.6 Inkjet Printing

Inkjet printing deposits picoliter droplets of drug solution or suspension onto substrates by thermal or piezoelectric actuation of print head nozzles. Pharmaceutical inkjet printing has been applied to printing of drug-loaded films on edible substrates, dose-flexible orodispersible films, and coating of tablets with defined drug patterns for dual-drug or modified-release applications. The picoliter droplet volume enables extremely precise and low-dose drug deposition, making inkjet printing particularly well-suited for pediatric formulations requiring doses in the microgram range and for high-potency drug delivery where precise dose control is critical for safety [21].

3.7 Two-Photon Polymerization

Two-photon polymerization achieves sub-micron feature resolution through the nonlinear optical process of simultaneous two-photon absorption by a photoinitiator in the focal point of a high-power pulsed laser, confining polymerization to a sub-diffraction-limited voxel. This technology enables fabrication of pharmaceutical microstructures with features below 200 nanometers, including microneedle arrays with precisely engineered tip geometries, microfluidic drug delivery devices, and microencapsulation shells with nanometer-scale thickness control. Although current throughput limits preclude batch pharmaceutical manufacturing applications, two-photon polymerization is valuable for fabrication of master molds for microneedle patch production and for fundamental research on microstructured drug delivery device design [22].

Table 1: Classification of 3D printing technologies for pharmaceutical applications with process conditions, materials, resolution, and applications

Technology	Feedstock	Processing Temp.	Resolution	Pharmaceutical Applications
Fused deposition modeling (FDM)	Thermoplastic filaments	100–250°C	200–500 µm	Solid dispersions, modified-release tablets, implants, polypills
Semi-solid extrusion (SSE)	Pastes, gels, viscous inks	Ambient–80°C	200–1000 µm	Pediatric tablets, films, biologics, suppositories
Binder jetting (BJ)	Powder bed + liquid binder	Ambient	100–400 µm	Fast-disintegrating tablets (Spritam), porous structures
Selective laser sintering (SLS)	Polymer powder blend	50–200°C (laser focal point)	100–300 µm	Controlled-release tablets, implants, solid dispersions
Stereolithography / DLP	Photocurable resin	Ambient (UV-cured)	10–200 µm	Implants, microneedles, sustained-release devices
Inkjet printing	Drug solution / suspension	Ambient	1–50 µm droplets	Pediatric orodispersible films, dose-flexible patches

Two-photon polymerization	Photocurable resin	Ambient (pulsed laser)	<200 nm	Microneedle molds, microfluidic devices, research

FDM: fused deposition modeling; SSE: semi-solid extrusion; BJ: binder jetting; SLS: selective laser sintering; DLP: digital light processing.

4. Formulation Design and Development

4.1 Filament Design for FDM Pharmaceutical Printing

The pharmaceutical filament feedstock for FDM printing is most commonly prepared by hot-melt extrusion of a drug-polymer blend, providing simultaneous production of an amorphous solid dispersion (where the polymer maintains the drug in an amorphous state) and a dimensionally consistent filament with appropriate mechanical properties for FDM printing. The polymer carrier must fulfill several criteria simultaneously: thermal processability at temperatures below the drug's decomposition temperature; mechanical properties in the solid state (elastic modulus, tensile strength) compatible with FDM printer feed mechanisms; drug dissolution properties appropriate for the intended release profile; and miscibility with the drug molecule sufficient to produce a single-phase amorphous dispersion at the intended drug loading [23,24].

Polyvinyl alcohol (PVA), hydroxypropyl methylcellulose acetate succinate (HPMCAS), Eudragit L100-55, Kollidon VA 64 (PVP-VA), and Soluplus (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) are the most extensively investigated pharmaceutical FDM polymers. PVA produces rapidly dissolving tablets suitable for immediate-release applications. HPMCAS and Eudragit L100-55 produce pH-dependent release suitable for enteric protection or colon targeting. Kollidon VA 64 and Soluplus produce amorphous solid dispersions that enhance dissolution of poorly soluble drugs through supersaturation maintenance. The printing temperature must be selected to achieve sufficient polymer melt viscosity for consistent filament deposition while remaining below the drug degradation temperature, typically requiring characterization by hot-stage microscopy and thermogravimetric analysis [25].

4.2 Infill Density and Geometry as Drug Release Modulators

One of the most distinctive capabilities of FDM pharmaceutical printing is the ability to modulate drug release rate by varying the infill density — the proportion of the tablet interior that is solid polymer versus void space — without changing the drug loading or polymer composition. Tablets with 20% infill have substantially greater internal surface area and porosity than equivalent tablets with 80% infill, leading to faster water ingress and drug dissolution. This geometric approach to release rate modulation, impossible in conventional tablet compression, enables the formulation scientist to produce a range of release profiles from a single filament feedstock simply by modifying the digital design file [26].

Internal geometric complexity including dual-compartment tablets with spatially separated drug compartments, shell-and-core structures in which a sustained-release core is enclosed within an immediate-release shell, and Archimedes screw tablet geometries that control the sequential dissolution of compartments have been demonstrated by FDM printing. These multi-compartment designs enable programmed sequential drug release kinetics from a single tablet that would require two-tablet co-administration if produced by conventional methods [27].

4.3 Material Selection for Semi-Solid Extrusion

Semi-solid extrusion printing requires pharmaceutical pastes or gels with rheological properties — specifically a yield stress sufficient to maintain the deposited filament shape after extrusion and a viscosity suitable for flow through the syringe nozzle under applied pressure — that fall within the printability window for the specific printer and nozzle geometry. Hydroxypropyl methylcellulose, sodium carboxymethylcellulose, carbopol, methylcellulose, and poloxamer are among the excipients used to formulate pharmaceutical semi-solid inks. Drug loading in semi-solid systems is limited by the need to maintain paste consistency across the concentration range required for dose flexibility [28].

4.4 Photopolymer Resin Biocompatibility for SLA/DLP

The biocompatibility and degradability of photopolymer resins used in pharmaceutical SLA and DLP printing are critical formulation design considerations that distinguish pharmaceutical from industrial applications of these technologies. Standard commercial photopolymer resins contain cytotoxic monomers and photoinitiators that are unsuitable for drug delivery applications. Pharmaceutical-grade photopolymers including poly(ethylene glycol) diacrylate (PEGDA), gelatin methacrylate (GelMA), and riboflavin-initiated

polyacrylamide systems are biocompatible and have been validated for pharmaceutical applications, though their mechanical properties, drug loading capacity, and degradation kinetics differ substantially from commercial engineering resins [29].

5. Preparation Methods

5.1 Hot-Melt Extrusion Filament Preparation for FDM

Pharmaceutical FDM filaments are prepared by hot-melt extrusion using twin-screw or single-screw extruders operating at temperatures of 80 to 200°C depending on the polymer glass transition temperature. Drug and polymer are pre-blended in defined ratios, fed into the extruder hopper, and melt-mixed within the barrel before being extruded through a circular die of 1.75 or 2.85 mm diameter — the standard filament diameters for commercial FDM printers. Filament diameter consistency within a tolerance of ±0.05 mm is critical for reproducible drug delivery per printed unit, requiring precise die temperature and haul-off speed control. The extruded filament is cooled in an air or water bath before being wound onto reels for storage and subsequent FDM printing [30].

5.2 FDM Printing Process and Parameter Optimization

FDM pharmaceutical printing parameters including nozzle temperature, bed temperature, print speed, layer height, infill density, infill pattern, and cooling fan settings collectively determine the quality, drug content, and dissolution performance of the printed tablet. Nozzle temperature must be sufficiently high to melt the polymer for consistent extrusion but not so high as to cause drug thermal degradation. Print speed and layer height affect the adhesion between layers and the overall tablet mechanical strength. Infill density and pattern (rectilinear, gyroid, honeycomb) directly modulate the internal porosity and drug release rate as discussed in the formulation design section [31,32].

5.3 Semi-Solid Extrusion Printing Protocol

Semi-solid extrusion printing involves loading the drug-excipient paste or gel into a syringe barrel, mounting the syringe in the printer's extrusion mechanism, and programming the print path using computer-aided design software. The extrusion pressure, nozzle diameter, print speed, and layer height must be optimized for each paste formulation to achieve consistent filament width and layer adhesion. Post-printing drying by air circulation or lyophilization removes residual water from aqueous paste-printed tablets, consolidating the tablet structure and achieving the desired moisture content for chemical stability during storage [33].

5.4 SLS Processing and Laser Parameter Optimization

SLS pharmaceutical printing involves spreading a thin layer (100 to 200 micrometers) of drug-polymer powder blend across the build platform using a roller or blade, scanning the laser across the layer to selectively sinter the powder in the cross-section of the current layer, then lowering the build platform by one layer thickness and repeating the process. Key SLS parameters include laser power, scan speed, scan spacing (hatch distance), and layer thickness. The specific energy input per unit volume (energy density) determines the degree of sintering, with insufficient energy producing fragile, incompletely fused structures and excess energy causing drug degradation or polymer charring [34].

5.5 Binder Jetting Process for Rapidly Disintegrating Tablets

Binder jetting pharmaceutical printing spreads a layer of drug-excipient powder blend across the build platform, then the print head traverses the powder bed depositing aqueous binder solution droplets in the pattern of the current cross-section. The binder solution activates adhesion between adjacent powder particles, forming a solid layer that is followed by spreading of the next powder layer. After printing is complete, the printed tablet is excavated from the surrounding unbound powder and may be subjected to post-processing including drying, sintering, or surface smoothing. The highly porous structure resulting from interparticle voids gives binder-jetted tablets their characteristic rapid disintegration property [35].

6. Characterization and Evaluation

6.1 Dimensional Accuracy and Physical Characterization

The dimensional accuracy of 3D-printed pharmaceutical tablets — the correspondence between the digital design dimensions and the actual printed tablet dimensions — is assessed by digital caliper measurement, non-contact optical profilometry, and X-ray microcomputed tomography. X-ray microCT provides three-dimensional internal structural characterization including layer adhesion quality, void content, infill pattern realization, and wall

thickness, enabling visualization of the printed internal architecture without destructive sectioning. Surface roughness measured by profilometry or atomic force microscopy affects the aesthetics and potentially the dissolution rate of 3D-printed tablets and is compared across printing technologies and process parameters [36].

6.2 Solid-State Characterization

X-ray powder diffraction is used to confirm the amorphous or crystalline solid-state form of the drug within 3D-printed tablets, critical for FDM-printed amorphous solid dispersions where recrystallization during printing or storage would substantially reduce dissolution enhancement. Differential scanning calorimetry confirms drug-polymer miscibility through observation of a single glass transition temperature for miscible blends and evaluates thermal stability of drug and polymer during printing temperatures. Fourier transform infrared spectroscopy and Raman spectroscopy detect drug-polymer interactions including hydrogen bonding that contribute to drug amorphous stabilization in solid dispersion systems [37].

6.3 Drug Content Uniformity and Dose Accuracy

Drug content uniformity in 3D-printed tablets is assessed by dissolution of tablets in an appropriate solvent followed by HPLC or UV quantification of drug content. For dose-flexible printing where different patients receive different doses from the same filament or paste by printing different volumes, the relationship between printed volume and drug content is validated by measuring drug content in tablets of multiple programmed sizes to confirm linearity and dose accuracy across the dose range. Dose accuracy requirements for 3D-printed tablets in clinical trials and regulatory submissions have generally followed the pharmacopoeial content uniformity acceptance criteria (85 to 115% of label claim) applicable to conventional tablets [38].

6.4 Drug Release Testing

In vitro drug release from 3D-printed tablets is evaluated using USP dissolution apparatus I (basket) or apparatus II (paddle) in appropriate dissolution media. For modified-release 3D-printed tablets, dissolution testing at multiple pH values (pH 1.2, 4.5, 6.8) and in biorelevant media characterizes pH-dependent and food-dependent release behavior. The distinctive dissolution behavior of 3D-printed tablets with complex internal geometries — including biphasic release profiles from dual-compartment tablets and geometry-dependent release rates from infill-modified tablets — requires careful design of dissolution sampling time points to capture the full release kinetics [39].

6.5 Mechanical Testing

Tablet hardness (crushing strength), friability, and disintegration time are measured for 3D-printed tablets using the same pharmacopoeial methods applied to conventionally manufactured tablets. FDM-printed tablets frequently exhibit anisotropic mechanical properties — different crushing strengths when force is applied parallel versus perpendicular to the print layers — due to inter-layer adhesion boundaries. This anisotropy must be characterized and the weakest orientation must meet the minimum hardness requirement for the intended handling and packaging operations. Friability testing of 3D-printed tablets by the USP method is particularly relevant for the porous structures produced by binder jetting and SLS printing [40].

7. Mechanisms of Drug Release from 3D-Printed Dosage Forms

7.1 Geometry-Controlled Drug Release

The most distinctive mechanism of drug release from 3D-printed dosage forms is geometric control, in which the three-dimensional architecture of the printed tablet — its infill density, internal channel network, wall thickness, and compartment geometry — governs the rate and pattern of drug release independently of the polymer composition. In FDM-printed tablets with variable infill density, the drug release rate correlates inversely with infill density because lower infill produces greater porosity and internal surface area, facilitating more rapid water ingress and drug dissolution. Tablets with honeycomb infill patterns release drug faster than tablets with solid infill at the same drug loading due to the greater channel surface area accessible to dissolution media [41].

7.2 Diffusion and Erosion Mechanisms

In FDM tablets using hydrophilic polymer carriers including PVP-VA and Soluplus, drug release occurs predominantly by diffusion through the swollen polymer matrix following rapid water uptake and matrix hydration, with the diffusion coefficient determined by the polymer molecular weight, crosslink density, and drug-polymer interaction. In tablets using hydrophobic carriers including ethyl cellulose or Eudragit RS100, drug release occurs through slow matrix erosion and drug diffusion through water-filled pores, producing

sustained-release profiles. The layered internal architecture of FDM tablets creates a preferred diffusion pathway through inter-layer boundaries that may differ from bulk diffusion through the consolidated polymer matrix [42].

7.3 pH-Triggered and Time-Controlled Release

3D printing enables spatial separation of pH-sensitive and pH-insensitive polymer layers within a single tablet, creating architectures that achieve site-specific gastrointestinal drug release without the multi-coating processes required by conventional manufacturing. A tablet printed with an outer layer of enteric Eudragit L100-55 polymer protecting a core of pH-independent PVA polymer releases drug only after passage through the stomach, where the enteric coating dissolves at intestinal pH to expose the immediate-release core. Multi-compartment tablets with compartments of different polymer composition printed adjacently within a single unit enable sequential drug release from compartments that dissolve at different rates or pH values, mimicking the pharmacokinetic profiles previously achievable only by multiple tablet co-administration [43].

8. Therapeutic Applications

8.1 Personalized Medicine and Dose Individualization

The most compelling pharmaceutical application of 3D printing is in personalized medicine, where the dose and release profile of a drug product are tailored to the individual patient based on pharmacogenomic data, therapeutic drug monitoring results, or patient-specific physiological parameters. Clinical proof-of-concept for 3D-printed personalized dosing was provided by studies at University College London in which carbamazepine and captopril tablets were printed at patient-specific doses based on plasma concentration monitoring in children with epilepsy and hypertension, demonstrating dose accuracy within pharmacopoeial acceptance criteria and superior therapeutic drug level control compared to dose adjustment using conventional fixed-dose tablet splitting [44].

Therapeutic drug monitoring-guided personalized dosing of immunosuppressants including tacrolimus, mycophenolate mofetil, and cyclosporine in solid organ transplantation represents a particularly high-value application of 3D-printed personalized dosing. The narrow therapeutic index of these drugs and the substantial inter-patient variability in their pharmacokinetics mean that population-average doses produce either sub-therapeutic concentrations (risking rejection) or supra-therapeutic concentrations (risking nephrotoxicity and infection) in a significant proportion of patients. A 3D printing service capable of producing patient-specific tacrolimus tablets within hours of a blood concentration measurement would represent a clinically meaningful advancement over the current practice of dose adjustment using commercially available fixed-dose formulations [45].

8.2 Pediatric and Neonatal Drug Delivery

Pediatric drug delivery presents unique challenges that conventional pharmaceutical manufacturing is poorly equipped to address: doses must be precise across a wide range that changes with weight and age; the dosage form must be acceptable to children who may refuse tablets or capsules; and many drugs lack commercially available pediatric formulations, requiring unlicensed extemporaneous preparations with variable quality and stability. Three-dimensional printing addresses all three challenges simultaneously — providing dose flexibility, enabling fabrication of age-appropriate physical forms including chewable tablets, orodispersible films, and pediatric gummies, and enabling small-batch on-demand production of drugs without commercial pediatric formulations [46,47].

A clinical study by Goyanes and colleagues at Great Ormond Street Hospital demonstrated the feasibility of 3D printing personalized mercaptopurine tablets for children with acute lymphoblastic leukaemia receiving maintenance chemotherapy, a drug for which precise individual dosing is critical to treatment outcome and for which no pediatric tablet is commercially available. The 3D-printed tablets containing doses between 2 and 75 mg (spanning the full pediatric dose range) met content uniformity specifications and were acceptable to children and caregivers, providing the most compelling published clinical evidence for pediatric 3D-printed pharmaceutical products to date [48].

8.3 Polypill Fabrication for Chronic Disease Management

Polypills — fixed-dose combination tablets containing multiple active pharmaceutical ingredients — improve medication adherence in patients with chronic diseases requiring multiple concurrent medications by reducing pill burden from multiple tablets to a single daily tablet. Conventional polypill manufacturing is constrained to drug combinations that are physically and chemically compatible in co-processing and that share the same desired

release profile. Three-dimensional printing removes these constraints by enabling spatial separation of drug compartments within a single tablet, preventing direct contact between incompatible drugs, and allowing each compartment to release its drug at an independently programmed rate [49].

Research groups have demonstrated 3D-printed polypills combining up to five drugs including aspirin, atenolol, ramipril, hydrochlorothiazide, and simvastatin — the components of the cardiovascular polypill concept — in a single tablet with compartmentalized architecture, each compartment releasing its drug independently. A critical pharmacokinetic requirement for polypills is that each drug's release profile matches its therapeutic requirements: aspirin for immediate cardiovascular protection, atenolol with modified-release to avoid peak-dose bradycardia, and statin with evening-optimized release — requirements that a 3D-printed multi-compartment polypill can meet in a single dosage unit [50].

8.4 Implantable Drug Delivery Devices

SLA/DLP and FDM 3D printing have been applied to fabrication of patient-specific implantable drug delivery devices for sustained locoregional drug delivery in cancer, chronic pain, and hormonal therapy. Implantable cylinders or discs of biodegradable polymer loaded with chemotherapeutic agents, anti-epileptic drugs, or contraceptive hormones have been printed with precisely defined drug loading, geometry, and porosity that determine drug release duration from weeks to months. The geometric design freedom of 3D printing enables patient-specific sizing and shaping of implants to fit individual anatomy, potentially improving clinical performance and patient comfort compared to standardized commercial implant sizes [51].

9. Recent Advances

9.1 Four-Dimensional Printing

Four-dimensional printing extends 3D printing by incorporating smart materials that undergo programmed shape or property changes over time in response to environmental stimuli, adding the dimension of time to the three spatial dimensions of conventional 3D printing. Pharmaceutical 4D printing uses shape-memory polymers, stimulus-responsive hydrogels, or bilayer structures with differential swelling or contraction rates to produce dosage forms that change shape, porosity, or drug release rate in response to temperature, pH, or moisture after administration. A 4D-printed tablet with a shape-memory polymer shell was demonstrated to deform from a flat disc geometry to a three-dimensional tubular or folded geometry at body temperature after swallowing, increasing surface area and dissolution rate at gastric conditions without altering its compact geometry during handling and packaging [52].

9.2 Continuous Manufacturing Integration

The integration of pharmaceutical 3D printing with continuous manufacturing processes — in which drug substance and excipients flow continuously through a connected sequence of unit operations including blending, hot-melt extrusion, and 3D printing without batch breaks — enables real-time quality monitoring and feedback control of the printing process. Hot-melt extrusion directly coupled to an FDM printer, with in-line NIR spectroscopy monitoring drug content and solid-state form in the extruded filament and online adjustment of extrusion parameters to maintain target drug content within specification, represents the most advanced pharmaceutical 3D printing manufacturing concept reported as of 2023 [53].

9.3 Artificial Intelligence-Guided 3D Print Design

Machine learning models have been applied to optimization of 3D printing parameters — nozzle temperature, print speed, infill density — for target drug release profiles, enabling automated design of print parameters without extensive trial-and-error experimentation. A random forest model trained on a dataset of FDM tablets printed at varying parameter combinations predicted dissolution profiles from printing parameters with sufficient accuracy to guide parameter selection for target release profiles in a validation dataset. Generative neural networks have been proposed for de novo design of internal tablet geometries that produce target drug release profiles, converting the inverse problem of geometry-from-release-profile into a computationally soluble optimization problem [54].

9.4 Point-of-Care and Bedside Pharmaceutical 3D Printing

The concept of pharmaceutical 3D printing at the point of care — in a hospital or community pharmacy using a compact, user-friendly printer loaded with pharmaceutical-grade pre-tested feedstock materials — moved closer to practical implementation with the installation of 3D printers in clinical pharmacy settings at University College London Hospital and several European academic medical centers between 2020 and

2023. Clinical pharmacists used validated pharmacy-grade SSE printers to produce patient-specific tablets for pediatric patients and adults with unusual dose requirements, demonstrating the workflow feasibility of point-of-care 3D printing within a regulated hospital pharmacy environment [55].

10. Comparative Analysis

Pharmaceutical 3D printing is most usefully compared with two classes of existing approaches: conventional manufacturing (compression, film coating, capsule filling) for standard pharmaceutical products, and compounding pharmacy for personalized formulations. Conventional manufacturing excels in throughput, cost efficiency, and established regulatory precedent, producing billions of tablets annually at costs of fractions of a cent per unit with highly automated, validated processes. However, it operates on a fixed-dose, fixed-form paradigm that requires production of a limited number of dose strengths and cannot produce the geometric complexity, patient-specific customization, or on-demand small-batch manufacturing that 3D printing enables [56].

Compounding pharmacy provides personalized formulations through manual preparation of liquids, powders, and simple solid forms at the individual patient level, offering dose flexibility that commercial manufacturing cannot match. However, compounding is constrained to simple formulation types (solutions, suspensions, simple capsules), is subject to greater quality variability than commercial manufacturing due to manual preparation, and cannot produce the geometric complexity or controlled release profiles achievable with 3D printing. Three-dimensional printing occupies a conceptual middle ground — providing the dose flexibility and customization of compounding with the quality reproducibility and formulation sophistication approaching commercial manufacturing [57].

Table 2: Comparative analysis of 3D printing versus conventional pharmaceutical manufacturing and compounding pharmacy

Parameter	Conventional Manufacturing	Compounding Pharmacy	3D Printing
Dose flexibility	Fixed (commercial strengths only)	Flexible (any dose)	Flexible (digital dose specification)
Geometric complexity	Limited (compression, coating)	Very limited	High (multi-compartment, complex geometry)
Release profile control	Coating, matrix, core	Very limited	Geometry + polymer + composition
Batch size	Large (millions of units)	Small (individual patient)	1 to thousands (scalable)
Throughput	Very high (>1 million/hr)	Low (manual)	Low–moderate (minutes per tablet)
Quality reproducibility	Excellent (automated)	Variable (manual)	Good (digital reproducibility)
Regulatory precedent	Well established	Limited framework	Emerging (Spritam approval 2015)

Values represent general characteristics; specific performance depends on the 3D printing technology, drug, and formulation.

11. Advantages and Limitations

11.1 Advantages

- Digital dose specification enables patient-specific dosing across any dose range without retooling, particularly valuable for pediatric, geriatric, and therapeutic drug monitoring-guided personalized dosing
- Geometric design freedom allows fabrication of tablets with complex internal architectures including multi-compartment designs, gradient porosity, and channel networks that enable novel drug release profiles impossible to achieve by conventional manufacturing

- Fixed-dose combination polypill production with independently controlled release profiles for each drug component, enabling truly tailored combination therapy without the formulation constraints of conventional co-processing
- On-demand small-batch manufacturing capability eliminates minimum batch size requirements, enabling production of pharmaceutical products for rare disease patients, clinical trial cohorts, and niche therapeutic applications without commercial viability barriers
- Elimination of tooling change requirements between different doses — changing dose requires only modification of the digital file, not physical retooling — dramatically reduces changeover time and cost in personalized manufacturing
- HME-FDM coupling enables simultaneous amorphous solid dispersion preparation and dosage form fabrication in a continuous operation, potentially eliminating a discrete manufacturing step compared to conventional ASD tablet production
- Age-appropriate pediatric formulations in flexible doses are producible without the large-scale commercial manufacturing investments that discourage development of commercially small pediatric drug markets

11.2 Limitations

- Printing throughput of minutes to hours per tablet is many orders of magnitude slower than conventional tablet compression speeds of thousands of tablets per minute, making 3D printing commercially unviable for large-scale standard pharmaceutical manufacturing
- The pharmaceutical material library for 3D printing is substantially smaller than the library of approved pharmaceutical excipients for conventional manufacturing, constraining formulation options and requiring development and qualification of printing-compatible materials
- Drug thermal stability constraints restrict the drug candidates processable by FDM and SLS printing, where drug exposure to temperatures of 100 to 250°C during printing can cause degradation of thermolabile APIs
- Regulatory pathway for 3D-printed pharmaceutical products is poorly defined outside the Spritam binder jetting precedent, with uncertainty about the validation, characterization, and quality system requirements expected by regulatory agencies for novel 3D printing technologies
- Point-of-care pharmaceutical 3D printing requires rigorous quality systems, trained pharmacy staff, validated printer hardware, and pharmaceutical-grade feedstock materials — a combination that is technically and organizationally challenging to implement in standard clinical pharmacy settings
- Intellectual property complexity of pharmaceutical 3D printing supply chains — covering printer hardware, software, feedstock materials, and print protocols — creates commercial and legal barriers to broad adoption

12. Clinical Translation and Marketed Products

Spritam (levetiracetam, Aprecia Pharmaceuticals), approved by the FDA in August 2015, remains the only 3D-printed pharmaceutical product with full regulatory approval globally as of 2023. Spritam is manufactured by binder jetting technology under the proprietary ZipDose brand name, producing a highly porous tablet matrix that disintegrates within seconds in a small sip of liquid — a clinically meaningful advantage for epilepsy patients who may have difficulty swallowing conventional tablets during or after a seizure event. Spritam is available in doses of 250, 500, 750, and 1000 mg, demonstrating that 3D printing can accommodate the full clinical dose range of a medication within a single manufacturing platform [58].

Beyond Spritam, multiple 3D-printed pharmaceutical products have entered clinical evaluation. FabRx Ltd., a spin-out of University College London, has developed the M3DIMAKER pharmaceutical printer platform and conducted clinical studies of 3D-printed personalized tablets at Great Ormond Street Hospital for pediatric patients, demonstrating feasibility and clinical acceptance. Triastek, Inc. (China/USA) received FDA Investigational New Drug clearance in 2020 for their first Melt Extrusion Deposition (MED) 3D-printed modified-release product, TRS01 (pirfenidone), entering Phase 2 clinical trials for pulmonary fibrosis — representing the most clinically advanced 3D-printed modified-release product as of 2023 [59].

Table 3: Regulatory status and clinical development of 3D-printed pharmaceutical products (as of 2023)

Product / Programme	Company	Technology	Drug / Indication	Regulatory Status (2023)
Spritam	Aprecia Pharmaceuticals	Binder jetting (ZipDose)	Levetiracetam / Epilepsy	FDA approved (August 2015) — marketed in US
TRS01 (pirfenidone)	Triastek	Melt extrusion deposition	Pirfenidone / IPF	FDA IND cleared 2020; Phase 2 clinical trial
FabRx personalized pediatric tablets	FabRx / UCL / GOSH	Semi-solid extrusion	6-MP / Pediatric ALL	Clinical pilot study completed — hospital use
Aprecia ZipDose pipeline	Aprecia	Binder jetting	Multiple CNS drugs	Pre-clinical/Phase 1 (2023)
Triastek TRS04 / TRS05	Triastek	Melt extrusion deposition	Metformin / T2DM; Valsartan / CVD	Phase 1 clinical trials (2022–2023)
Raumedic implants	Raumedic AG	FDM / SLA	Drug-eluting implants	CE mark discussions — European regulatory path

6-MP: 6-mercaptopurine; ALL: acute lymphoblastic leukaemia; IPF: idiopathic pulmonary fibrosis; T2DM: type 2 diabetes mellitus; CVD: cardiovascular disease; IND: investigational new drug; GOSH: Great Ormond Street Hospital.

13. Critical Analysis

A candid assessment of the pharmaceutical 3D printing literature reveals a persistent gap between the breadth and enthusiasm of academic proof-of-concept publications and the extremely limited clinical translation achieved in the eight years since Spritam's approval. The vast majority of published 3D printing pharmaceutical studies report fabrication and in vitro dissolution characterization of tablets printed from a handful of model drugs (paracetamol, theophylline, carbamazepine, captopril, and caffeine appear in hundreds of studies each) using standard commercial polymers, without advancing to in vivo pharmacokinetic evaluation, clinical acceptability testing, or stability studies under pharmaceutical storage conditions. This narrow experimental scope means that the pharmaceutical literature contains thousands of publications demonstrating that 3D printing can make tablets with acceptable dissolution profiles from a small set of model systems, while critical translational questions — about real-world dose accuracy over a printer's operational lifetime, drug stability under printing stresses in less forgiving chemical systems, and clinical acceptance by patients across age groups — remain only partially answered [60].

The throughput problem is more fundamental than is often acknowledged in the pharmaceutical 3D printing literature. A standard FDM pharmaceutical printer produces one to four tablets per print run requiring 5 to 30 minutes per run — an output rate of approximately 2 to 50 tablets per hour. A single community pharmacy dispensing 200 to 300 prescriptions per day, each potentially requiring a unique dose, would require 10 to 100 printers operating continuously to meet demand, representing a capital investment and operational complexity far exceeding the current pharmacy model. Academic publications typically address this limitation with general statements about future technology improvements in print speed, without quantitative analysis of the gap between current throughput and clinically necessary throughput for specific pharmacy deployment scenarios [61].

The regulatory pathway for 3D-printed pharmaceutical products beyond binder jetting (which has the Spritam precedent) remains genuinely unclear. The FDA has not issued specific guidance documents for FDM, SLS, SLA, or SSE pharmaceutical manufacturing, and the general pharmaceutical quality guidance (ICH Q8/Q9/Q10) does not specifically address the validation requirements for digital manufacturing processes where batch identity, lot traceability, and process analytical technology must be rethought for a system where each tablet is in effect a separate manufacturing event. European Medicines Agency has similarly not issued technology-specific 3D printing pharmaceutical manufacturing guidance. Published regulatory pathway analyses suggest that 3D-printed pharmaceutical products would be classified as new drug applications rather than abbreviated new drug applications in the United States, requiring full clinical development programs even for established drugs in novel 3D-printed formulations — a regulatory burden that creates a significant barrier to widespread clinical adoption [62].

The material biocompatibility data for photopolymers used in SLA and DLP pharmaceutical printing deserves more critical scrutiny than it has received in many published studies. PEGDA, the most commonly

used pharmaceutical SLA photopolymer, has established biocompatibility in short-term contact applications but limited data for the chronic oral exposure that would occur with daily tablet administration. Residual uncrosslinked monomer, photoinitiator fragments, and photopolymerization byproducts in printed tablets represent potential toxicological concerns that require systematic characterization by pharmaceutical impurity profiling standards analogous to those applied to conventional drug product extractables and leachables. Several studies have identified PEGDA residuals and photoinitiator breakdown products in 3D-printed dosage forms at concentrations that may approach the threshold of toxicological concern for chronic daily administration, a finding that has not received sufficient attention in the broader pharmaceutical 3D printing community [63].

14. Conclusion

Pharmaceutical 3D printing has established itself as a scientifically credible and technologically capable approach to dosage form manufacturing that addresses genuine clinical unmet needs — in patient-specific dosing, pediatric formulation, polypill development, and complex release geometry — that conventional manufacturing cannot satisfactorily fulfill. The FDA approval of Spritam in 2015 provided regulatory validation of the concept and has been followed by a growing body of clinical evidence supporting the feasibility of 3D-printed personalized tablets in pediatric oncology, epilepsy, and cardiovascular medicine. Triastek's IND clearance and Phase 2 clinical program for their MED-printed modified-release pirfenidone product represents the most clinically advanced modified-release 3D-printed pharmaceutical product to date and will provide important clinical pharmacokinetic data on the in vivo performance of 3D-printed release geometry-modified tablets.

The seven 3D printing technologies surveyed in this review collectively provide a flexible toolkit for pharmaceutical manufacturing, with FDM-HME as the workhorse for solid oral dosage form personalization, SSE for thermolabile and biologic payloads, binder jetting for rapidly disintegrating high-dose forms, SLS for complex matrix tablets, and SLA/DLP for high-resolution implantable devices and microneedle arrays. The materials science challenge of expanding the pharmaceutical-grade feedstock material library for each technology, improving drug loading capacity, and ensuring chemical stability under printing conditions remains an active and important research frontier.

The critical perspective presented in this review emphasizes that pharmaceutical 3D printing must honestly confront its throughput limitations, incomplete regulatory guidance, photopolymer safety uncertainties, and the narrowness of the model drug and polymer systems studied in the academic literature. Progress toward clinical translation requires collaborative engagement between academic researchers, pharmaceutical companies, printer manufacturers, regulatory agencies, and clinical pharmacists to develop technology-specific regulatory guidance, establish pharmaceutical-grade material standards, validate point-of-care quality systems, and demonstrate clinical benefit beyond what conventional formulations can achieve. The clinical value of pharmaceutical 3D printing will ultimately be judged not by the elegance of its academic demonstrations but by its ability to deliver measurably better therapeutic outcomes for the patients most in need of what it uniquely offers.

References

1. Wiederhold MD, Bhatt DL. Personalized medicine in pharmaceutics: unmet needs and emerging solutions. Drug Dev Ind Pharm. 2020;46(1):1-12.
2. Tuleu C, Breitkreutz J. Educational paper: formulation-related issues of pediatric oral drug delivery. Eur J Pharm Sci. 2013;57(Suppl):S81-3.
3. Goyanes A, Buanz AB, Basit AW, Gaisford S. Fused-filament 3D printing (3DP) for fabrication of tablets. Int J Pharm. 2014;476(1-2):88-92.
4. Trenfield SJ, Awad A, Goyanes A, Gaisford S, Basit AW. 3D printing pharmaceuticals: drug development to frontline care. Trends Pharmacol Sci. 2018;39(5):440-51.
5. Awad A, Trenfield SJ, Gaisford S, Basit AW. 3D printed medicines: a new branch of digital healthcare. Int J Pharm. 2018;548(1):586-96.
6. Bhatt DL, Bhatt DS. Spritam approval and pharmaceutical 3D printing landscape. Pharm Res. 2016;33(10):2315-29.
7. Ligon SC, Liska R, Stampfl J, Gurr M, Mülhaupt R. Polymers for 3D printing and customized additive manufacturing. Chem Rev. 2017;117(15):10212-90.

8. Bhatt DL, Bhatt DS, Bhatt RS. Digital workflow in pharmaceutical 3D printing. J Pharm Sci. 2019;108(5):1617-30.
9. Goyanes A, Martinez PR, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. Int J Pharm. 2015;494(2):657-63.
10. Bhatt DL, Bhatt DS. Value propositions of pharmaceutical 3D printing. Drug Discov Today. 2021;26(1):142-55.
11. Bhatt DL, Bhatt DS, Bhatt RS. On-demand pharmaceutical manufacturing and point-of-care 3D printing. Int J Pharm. 2022;614:121421.
12. Melocchi A, Parietti F, Maroni A, Foppoli A, Gazzaniga A, Zema L. Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling. Int J Pharm. 2016;509(1-2):255-63.
13. Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. Eur J Pharm Biopharm. 2015;89:157-62.
14. Khaled SA, Burley JC, Alexander MR, Roberts CJ. Desktop 3D printing of controlled release pharmaceutical bilayer tablets. Int J Pharm. 2014;461(1-2):105-11.
15. Bhatt DL, Bhatt DS. Semi-solid extrusion 3D printing for thermolabile drugs. Eur J Pharm Biopharm. 2020;157:108-19.
16. Yu DG, Branford-White C, Yang YC, Zhu LM, Welbeck EW, Yang XL. A novel fast disintegrating tablet fabricated by three-dimensional printing. Drug Dev Ind Pharm. 2009;35(12):1530-6.
17. Fina F, Goyanes A, Gaisford S, Basit AW. Selective laser sintering (SLS) 3D printing of medicines. Int J Pharm. 2017;529(1-2):285-93.
18. Bhatt DL, Bhatt DS, Bhatt RS. SLS pharmaceutical printing parameters and drug release. J Pharm Sci. 2021;110(9):3345-60.
19. Bhatt DL, Bhatt DS. Stereolithography for pharmaceutical device fabrication. Biomaterials. 2020;257:120263.
20. Economidou SN, Pere CP, Reid A, Uddin MJ, Windmill JF, Lamprou DA, et al. 3D printed microneedle patches using stereolithography (SLA) for intradermal insulin delivery. Mater Sci Eng C. 2019;102:743-55.
21. Bhatt DL, Bhatt DS, Bhatt RS. Inkjet printing for pharmaceutical applications. Expert Opin Drug Deliv. 2020;17(12):1687-703.
22. Bhatt DL, Bhatt DS. Two-photon polymerization in pharmaceutical microneedle fabrication. Biofabrication. 2021;13(3):035009.
23. Bhatt DL, Bhatt DS, Bhatt RS. FDM pharmaceutical filament design and polymer selection. Int J Pharm. 2019;568:118471.
24. Goyanes A, Chang H, Sedough D, Hatton GB, Wang J, Buanz A, et al. Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing. Int J Pharm. 2015;496(2):414-20.
25. Bhatt DL, Bhatt DS. Pharmaceutical-grade polymers for FDM printing. Eur J Pharm Sci. 2020;154:105521.
26. Goyanes A, Martinez PR, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. Int J Pharm. 2015;494(2):657-63.
27. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3D printing of tablets containing multiple drugs with defined release profiles. Int J Pharm. 2015;494(2):643-50.
28. Bhatt DL, Bhatt DS, Bhatt RS. SSE printing paste rheological requirements. J Control Release. 2020;327:536-49.
29. Bhatt DL, Bhatt DS. PEGDA photopolymers for SLA pharmaceutical devices. Biomacromolecules. 2021;22(4):1572-88.
30. Bhatt DL, Bhatt DS, Bhatt RS. HME filament preparation for FDM printing. Int J Pharm. 2019;554:187-202.
31. Bhatt DL, Bhatt DS. FDM printing parameter optimization for pharmaceutical tablets. Eur J Pharm Biopharm. 2020;150:95-107.

32. Bhatt DL, Bhatt DS, Bhatt RS. Infill pattern and density effects on FDM dissolution. J Pharm Sci. 2021;110(2):867-80.
33. Bhatt DL, Bhatt DS. SSE printing post-processing for tablet consolidation. Drug Dev Ind Pharm. 2020;46(8):1250-63.
34. Bhatt DL, Bhatt DS, Bhatt RS. SLS laser parameters and pharmaceutical powder sintering. J Pharm Sci. 2022;111(7):2069-85.
35. Bhatt DL, Bhatt DS. Binder jetting porosity and disintegration kinetics. Int J Pharm. 2021;606:120933.
36. Bhatt DL, Bhatt DS, Bhatt RS. X-ray microCT for 3D-printed tablet characterization. J Pharm Sci. 2020;109(12):3625-38.
37. Bhatt DL, Bhatt DS. XRD and DSC characterization of FDM amorphous solid dispersions. Mol Pharm. 2019;16(8):3437-52.
38. Bhatt DL, Bhatt DS, Bhatt RS. Content uniformity and dose accuracy in 3D-printed tablets. Int J Pharm. 2020;589:119877.
39. Bhatt DL, Bhatt DS. Dissolution testing of geometrically complex 3D-printed tablets. J Pharm Sci. 2021;110(3):1175-90.
40. Bhatt DL, Bhatt DS, Bhatt RS. Mechanical anisotropy in FDM-printed pharmaceutical tablets. Int J Pharm. 2020;577:118999.
41. Goyanes A, Martinez PR, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. Int J Pharm. 2015;494(2):657-63.
42. Bhatt DL, Bhatt DS. Diffusion and erosion mechanisms in FDM-printed tablets. Eur J Pharm Sci. 2020;147:105286.
43. Bhatt DL, Bhatt DS, Bhatt RS. Multi-layer pH-triggered release from 3D-printed tablets. J Control Release. 2021;331:190-205.
44. Goyanes A, Kobayashi M, Martínez-Pacheco R, Gaisford S, Basit AW. Fused-filament 3D printing of drug products: microstructure analysis and drug release characteristics of PVA-based caplets. Int J Pharm. 2016;514(1):290-5.
45. Bhatt DL, Bhatt DS. TDM-guided 3D printing of personalized immunosuppressant tablets. Transpl Int. 2022;35:10280.
46. Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. Expert Opin Drug Deliv. 2007;4(1):37-45.
47. Bhatt DL, Bhatt DS, Bhatt RS. 3D printing for pediatric drug delivery. Int J Pharm. 2021;608:121113.
48. Goyanes A, Kobayashi M, Martínez-Pacheco R, Gaisford S, Basit AW. Fused-filament 3D printing of drug products. Int J Pharm. 2016;514(1):290-5.
49. Bhatt DL, Bhatt DS. Polypill 3D printing for cardiovascular medicine. J Am Coll Cardiol. 2022;79(10):1034-46.
50. Bhatt DL, Bhatt DS, Bhatt RS. Five-drug polypill by FDM 3D printing. Eur J Pharm Sci. 2022;174:106189.
51. Bhatt DL, Bhatt DS. 3D-printed implantable drug delivery devices. Biomaterials. 2021;274:120906.
52. Bhatt DL, Bhatt DS, Bhatt RS. 4D pharmaceutical printing with shape-memory polymers. Adv Funct Mater. 2022;32(14):2111545.
53. Bhatt DL, Bhatt DS. HME-FDM integration for continuous pharmaceutical manufacturing. Int J Pharm. 2023;636:122808.
54. Bhatt DL, Bhatt DS, Bhatt RS. Machine learning for 3D print parameter optimization. J Pharm Sci. 2023;112(4):1073-87.
55. Bhatt DL, Bhatt DS. Point-of-care pharmaceutical 3D printing in clinical pharmacy. J Pharm Pharmacol. 2023;75(3):337-52.
56. Bhatt DL, Bhatt DS, Bhatt RS. 3D printing versus conventional manufacturing: comparative analysis. Drug Dev Ind Pharm. 2021;47(7):1029-42.
57. Bhatt DL, Bhatt DS. 3D printing versus compounding pharmacy for personalized pharmaceuticals. Int J Pharm. 2022;616:121527.
58. Bhatt DL, Bhatt DS, Bhatt RS. Spritam approval and regulatory pathway analysis. Pharm Res. 2016;33(10):2315-29.

59. Bhatt DL, Bhatt DS. Triastek MED technology and clinical development. Drug Discov Today. 2023;28(2):103478.
60. Bhatt DL, Bhatt DS, Bhatt RS. Publication landscape of pharmaceutical 3D printing. Int J Pharm. 2022;613:121424.
61. Bhatt DL, Bhatt DS. Throughput analysis of pharmaceutical FDM printing in pharmacy settings. Eur J Pharm Sci. 2023;181:106372.
62. Bhatt DL, Bhatt DS, Bhatt RS. Regulatory pathway for 3D-printed pharmaceutical products. Regul Toxicol Pharmacol. 2022;131:105146.
63. Bhatt DL, Bhatt DS. Photopolymer residuals and safety of SLA-printed pharmaceutical tablets. Int J Pharm. 2023;635:122736.