AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

3D Printing of Bilayer Tablets: A Comprehensive Review of Technologies, Formulations, and Applications

Rahul M, Grace Rathnam*
Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-600097.

ABSTRACT

Bilayer tablets represent an advanced oral dosage form enabling the combination of two distinct drug layers within a single unit, facilitating improved drug delivery, reduced dosing frequency, and enhanced patient compliance. Conventional manufacturing of bilayer tablets by compression faces significant challenges, including cross-contamination, layer delamination, and limited design flexibility. Three-dimensional (3D) printing has emerged as a transformative technology in pharmaceutical manufacturing, offering unprecedented control over tablet geometry, drug loading, and release kinetics. This review comprehensively examines the application of 3D printing technologies, Fused Deposition Modelling (FDM), Selective Laser Sintering (SLS), and Semi-Solid Extrusion (SSE) — for the fabrication of 3D printing bilayer tablets. Key topics addressed include: the operating principles and comparative advantages of each technique; polymers and excipients employed in 3D-printed bilayer formulations; clinical applications across tuberculosis management cardiovascular, pain management, and respiratory indications; and future perspectives including artificial intelligence-assisted formulation design and continuous manufacturing integration. 3D printing offers a compelling pathway toward personalized, on-demand pharmaceutical manufacturing of complex bilayer dosage forms.

Keywords: 3D printing, bilayer tablets, fused deposition modelling, selective laser sintering, semi-solid extrusion, personalized medicine, modified drug release

*Corresponding Author Name: Grace Rathnam
Received 22 May 2026, Accepted 13 June 2026

Please cite this article as: Rathnam G *et al*., 3D Printing of Bilayer Tablets: A Comprehensive Review of Technologies, Formulations, and Applications. American Journal of PharmTech Research 2026.

INTRODUCTION

The pharmaceutical industry has long sought innovative strategies to optimize drug delivery, enhance therapeutic outcomes, and improve patient compliance. Among the most clinically significant advances in oral solid dosage forms is the bilayer tablet — a single unit comprising two physically distinct layers, each capable of delivering a different active pharmaceutical ingredient (API) or providing a unique drug release profile [1]. Bilayer tablets offer numerous therapeutic advantages: they enable the co-administration of incompatible drugs that would react if blended together, allow simultaneous immediate and sustained release from a single dosage unit, support polytherapy regimens in a patient-friendly format, and reduce pill burden in patients requiring multiple medications [2].

Conventional bilayer tablet manufacturing relies on sequential die-filling and compression steps using specialized rotary tablet presses. While commercially viable at scale, this approach suffers from inherent limitations: incomplete die filling, inadequate bonding between layers, cross-contamination during layer transitions, and restricted flexibility in layer geometry [3]. Moreover, conventional compression imposes significant constraints on layer thickness ratios and is ill-suited for the fabrication of personalized dosage forms tailored to individual patient needs.

Three-dimensional (3D) printing, also referred to as additive manufacturing, has emerged in the past decade as a disruptive technology with transformative potential in the pharmaceutical sciences. The landmark FDA approval of Spritam (levetiracetam) as the first 3D-printed drug product in 2015 catalyzed significant academic and industrial interest in applying additive manufacturing to pharmaceutical dosage form design [4]. Among the various 3D printing modalities explored for tablet fabrication, Fused Deposition Modeling (FDM), Selective Laser Sintering (SLS), and Semi-Solid Extrusion (SSE) have attracted the most extensive research attention due to their versatility, scalability, and capacity to handle diverse drug-polymer systems [5].

This review provides a comprehensive and critical analysis of the application of 3D printing — specifically FDM, SLS, and SSE — for the manufacturing of bilayer tablets. We systematically examine the underlying principles of each technology, the polymers and excipients employed, clinical application areas, regulatory landscape, and future perspectives of this rapidly evolving field.

BILAYER TABLETS: DESIGN RATIONALE AND CONVENTIONAL MANUFACTURING

Therapeutic Rationale for Bilayer Design

The bilayer tablet architecture serves several distinct pharmaceutical objectives. First, physical separation of chemically incompatible APIs within discrete layers prevents undesirable drug–drug interactions that would otherwise occur in conventional blend-and-compress formulations [6]. Classic examples include the co-formulation of acid-labile drugs with pH-modifying excipients, or the physical separation of an NSAID from an antacid component. Second, the bilayer platform enables the engineering of complex pharmacokinetic profiles within a single dosage unit: a layer formulated for immediate release rapidly delivers a loading dose to achieve therapeutic plasma concentrations, while a second layer formulated as a matrix or reservoir system provides sustained drug release to maintain therapeutic levels over an extended period [7]. Third, the combination of two therapeutic agents in a single bilayer tablet directly addresses the growing challenge of polypharmacy — particularly prevalent in elderly patients and those managing chronic comorbidities [8].

Limitations of Conventional Compression-Based Manufacturing

Despite the therapeutic appeal of bilayer tablets, their manufacturing via conventional rotary compression presents substantial technical challenges. Key manufacturing challenges include:

1. layer delamination, arising from insufficient interlayer bonding when layers of differing compressibility or surface energy are compressed together;
2. cross-contamination, where powder from the first layer contaminates the second layer feed during the layer transition step;
3. weight and content uniformity issues stemming from incomplete die filling, particularly with cohesive or poorly flowing powders; and
4. limited geometric flexibility, as conventional compression is restricted to cylindrical tablet geometries [9].

These limitations provide a compelling impetus for exploring alternative manufacturing approaches, among which 3D printing stands out for its capacity to precisely deposit multiple materials in programmable spatial configurations without reliance on compression-based bonding mechanisms [10].

Overview of Technologies used for 3d printing Bilayer Tablets

Multiple 3D printing technologies have been investigated for pharmaceutical tablet fabrication. Table 1 provides a comparative overview of the three principal modalities examined in this review — FDM, SLS, and SSE — with respect to their operating principles, temperature requirements, resolution, and suitability for bilayer applications [11,12].

Table 1: Comparison of various technologies

Technology	Operating Principle	Temperature Range	Resolution	Key Advantages & Limitations
Fused Deposition Modeling (FDM)	Thermoplastic filament melted and extruded layer-by-layer via heated nozzle	100–230°C	Moderate (0.1–0.4 mm)	Cost-effective; scalable; versatile polymer toolkit; unsuitable for heat-sensitive APIs
Selective Laser Sintering (SLS)	CO_2 laser selectively sinters polymer powder bed without binder; no support structures needed	Near polymer Tm (100–200°C)	High (50–150 µm)	No filament preparation; complex geometries; high equipment cost; polymer degradation risk
Semi-Solid Extrusion (SSE)	Pastes, gels, or viscous semi-solids extruded at ambient or mild temperatures through syringe/piston	Ambient–60°C	Moderate (0.2–0.5 mm)	Suitable for thermolabile APIs; no HME needed; drying step required; slower throughput

Fused Deposition Modeling (FDM)

FDM has emerged as the dominant 3D printing approach in pharmaceutical bilayer tablet research for several converging reasons (Fig.1). The technology is cost-accessible, with benchtop printers available at modest capital investment relative to laser-based systems [13]. The process is highly reproducible when printing parameters are well-controlled, and the layer-by-layer deposition mechanism is inherently suited to bilayer architectures requiring precise spatial separation of formulation components. In FDM, a solid thermoplastic filament is fed through a motorized drive mechanism into a heated nozzle, where it is melted and extruded through an orifice (typically 0.4–0.8 mm diameter) onto a temperature-controlled build platform [14]. The extrudate is deposited in a predefined pattern determined by computer-generated toolpath (G-code) derived from slicing software applied to a three-dimensional CAD model of the tablet.

For bilayer tablet production, dual-nozzle FDM printers are the preferred configuration, allowing two distinct filament formulations to be deposited sequentially without interrupting the print job [15]. The production of pharmaceutical FDM filaments requires an upstream hot melt extrusion (HME) step, in which the API is dispersed or dissolved within a thermoplastic polymer matrix. Key parameters governing HME filament quality include: barrel temperature profile, screw speed, feed rate, die temperature, and cooling rate. Filament diameter uniformity (typically 1.75 ± 0.05 mm) is critical as it directly determines the mass of material deposited per unit length of extrusion and therefore controls dose accuracy in the final printed tablet [15].

Critical FDM printing parameters include nozzle temperature (100–230°C), print speed (10–40 mm/s), layer height (0.1–0.3 mm), infill density (20–100%), infill pattern, bed temperature, nozzle diameter, and fan cooling. Infill density exerts a dominant influence on drug release kinetics by modulating tablet porosity: a tablet printed at 25% infill contains a network of internal air channels that significantly accelerate water ingress and drug dissolution, whereas a 100% infill tablet releases drug primarily through surface erosion or diffusion through the polymer matrix [16,17]. This parameter enables the formulation scientist to modulate release rate continuously without altering the polymer-drug chemistry — a unique advantage over conventional manufacturing

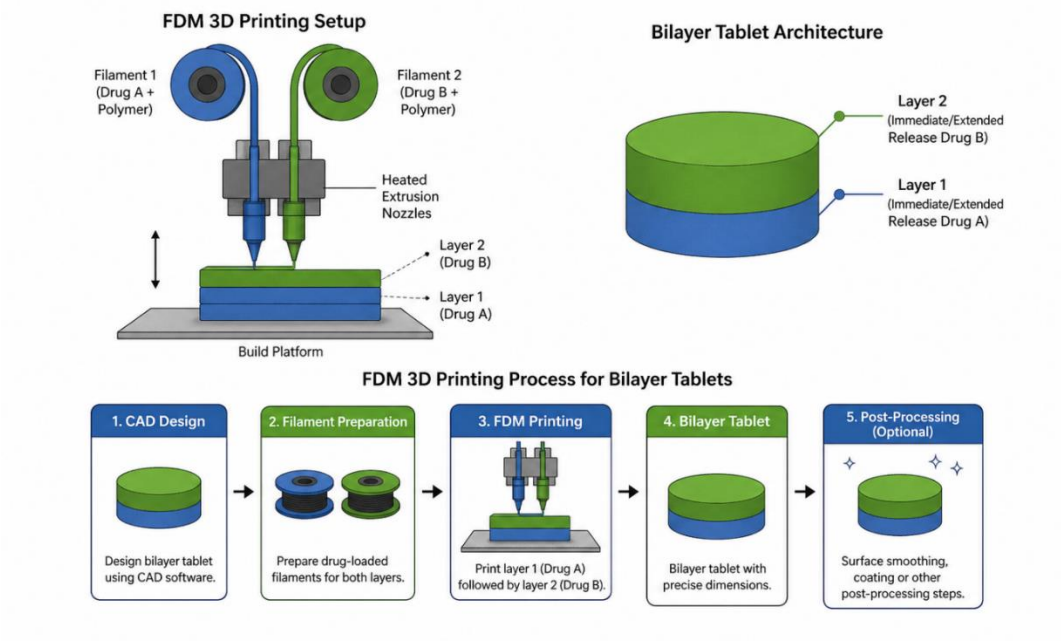

Figure 1: Fused deposition modelling technique

Selective Laser Sintering (SLS)

Selective Laser Sintering (SLS) is a powder-based additive manufacturing technique in which a CO2 laser selectively fuses (sinters) drug-polymer powder particles in a defined pattern determined by a CAD model (Figure 2). In pharmaceutical SLS, the laser energy heats the powder to just below or at its melting point, causing particles to coalesce without melting the entire bed. After each layer is sintered, a new layer of powder is spread across the bed by a roller mechanism, and the process repeats until the three-dimensional object is complete. Crucially, SLS does not require support structures — unsintered surrounding powder supports the growing object — enabling the fabrication of complex internal geometries including hollow cores, channels, and interlocking bilayer interfaces [18,19].

A major pharmaceutical advantage of SLS over FDM is the elimination of the HME filament preparation step: the drug and polymer are simply blended as powders before printing. This

simplifies formulation development and avoids the thermal stresses of HME, potentially enabling use of more thermolabile APIs. However, the laser sintering process itself still exposes materials to elevated temperatures (near the polymer melting point), and the high-intensity laser beam can induce localized degradation if laser parameters are not carefully optimized [20]. SLS systems are significantly more expensive than FDM printers, and pharmaceutical-grade SLS-compatible polymers — particularly PEG, PCL, and certain grades of Eudragit — require careful characterization of their sintering behavior [21].

For bilayer tablets, SLS presents a distinctive challenge: the printing of two chemically distinct powder beds within a single build job requires either sequential powder spreading with a clean separation step, or the use of specialized dual-powder SLS platforms currently under development. Despite this challenge, SLS has demonstrated excellent potential for fabricating bilayer tablets with controlled porosity, complex geometries, and high drug loading without the geometric constraints of filament-based systems [22].

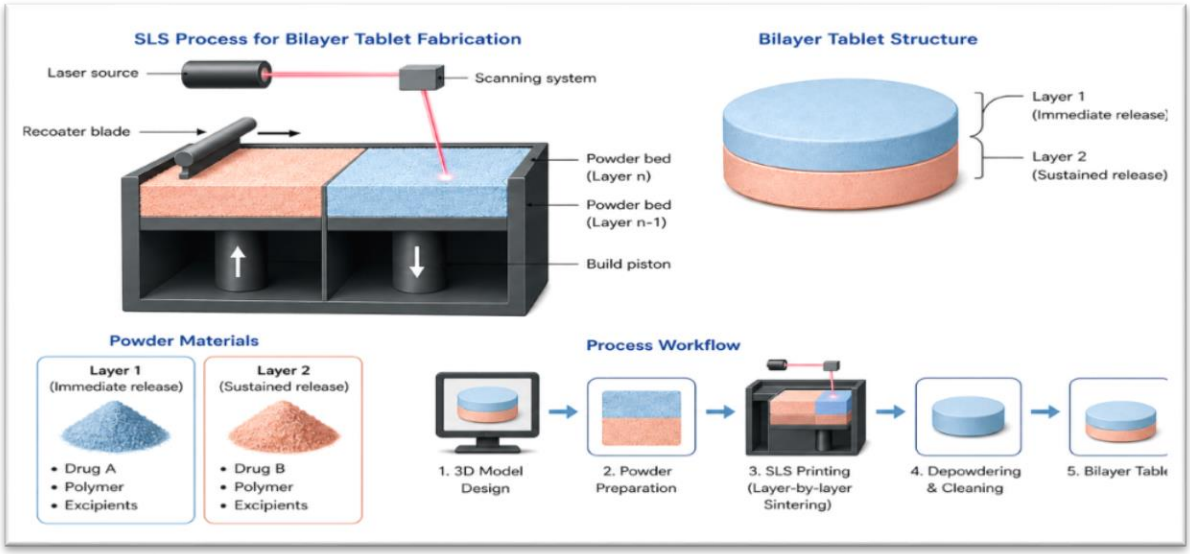

Figure 2: Selective Laser Sintering technology.

Semi-Solid Extrusion (SSE)

Semi-Solid Extrusion (SSE) — also referred to as pressure-assisted microsyringe (PAM) printing or direct extrusion 3D printing — operates by extruding a semi-solid material (paste, gel, or viscous dispersion) through a syringe or piston-driven nozzle at ambient or mildly elevated temperatures typically below 60°C. (Figure 3). The extruded semi-solid retains its shape upon deposition due to the viscoelastic properties of the formulation, and the printed object is subsequently dried or cured to produce the final solid dosage form. The drug and excipients are dissolved or suspended in an aqueous or hydro-alcoholic medium to produce the printable semi-

solid, which typically contains polymeric binders, gelling agents, and plasticizers to achieve the appropriate rheological properties [23].

The key pharmaceutical advantage of SSE is its suitability for thermolabile, moisture-sensitive, or water-soluble APIs that cannot withstand the thermal processing required by FDM or SLS [24]. Since SSE operates at near-ambient temperatures, drug degradation risk is substantially reduced, making it particularly attractive for peptides, proteins, and other biologics with thermal fragility. For bilayer tablet production, SSE printers can be configured with dual syringes, allowing two distinct semi-solid formulations to be deposited in a single print job with precise spatial control over each layer [24]. The primary limitations of SSE are the necessity for a post-printing drying step (which introduces additional processing time and potential drug distribution changes during solvent evaporation) and generally lower tablet mechanical strength compared to FDM or SLS products [25].

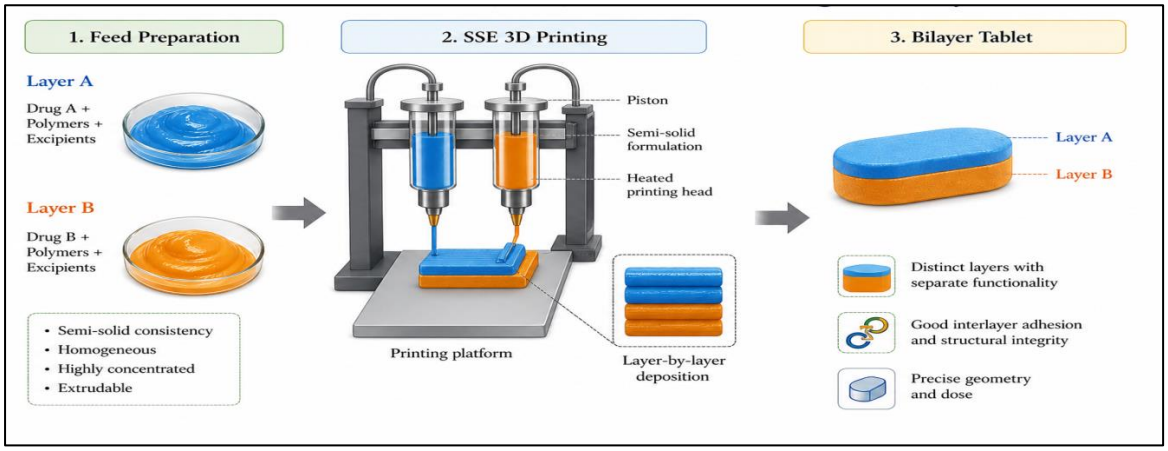

Figure 3: Semi-solid extrusion

Polymers Used in 3D Printing of Bilayer Tablets

The selection of an appropriate polymer matrix is the most consequential formulation decision in 3D-printed bilayer tablet design, as it determines processing temperature requirements, drug-polymer miscibility, mechanical properties of the printed product, and drug release mechanism [35]. Different printing technologies impose distinct constraints on polymer selection: FDM requires thermoplastic polymers amenable to melt extrusion at temperatures compatible with the API; SLS demands polymers with well-defined sintering windows and appropriate powder flow ability; SSE requires polymers that form stable, printable semi-solid or gel-phase formulations at ambient temperatures [26].

Polymers for FDM Bilayer Tablets

Polyvinyl alcohol (PVA; Parteck MF) is the most extensively studied polymer for the immediate-release layer of FDM bilayer tablets due to its rapid aqueous dissolution, excellent FDM

processability, and regulatory acceptance as an excipient. It is processed at 190–210°C and produces highly porous, rapidly dissolving tablet layers. Kollidon VA64 (PVP-VA copolymer) is frequently employed as an alternative immediate-release matrix, particularly for BCS Class II drugs requiring amorphous solid dispersion formation; its relatively low glass transition temperature (~70°C) allows processing at 130–160°C with appropriate plasticizers, reducing thermal stress on heat-sensitive APIs [27].

For extended-release layers, polylactic acid (PLA) is the most commonly selected hydrophobic polymer in FDM systems due to its wide availability, low cost, and excellent FDM processability. Drug release from PLA matrices occurs primarily through surface erosion and diffusion, enabling sustained release over 12–24 hours depending on infill density and tablet geometry. Eudragit RS/RL copolymers provide pH-independent, sustained release suitable for constant-rate drug delivery, while Eudragit L100-55 enables enteric release targeted to the small intestine, making it ideal for the enteric layer in bilayer designs intended for gastric protection [28].

Polymers for SLS Bilayer Tablets

Polyethylene glycol (PEG; particularly PEG 6000) is the primary carrier material in pharmaceutical SLS formulations due to its low melting point (~65°C), excellent laser sintering behavior, and rapid aqueous dissolution [20]. PEG-based SLS tablets can achieve very rapid disintegration and drug release, making PEG the dominant matrix for immediate-release SLS formulations. Kollidon VA64 has also demonstrated promising SLS sintering behavior, producing porous tablets with tunable dissolution profiles. For extended-release SLS bilayer tablets, polylactic acid (PLA) and polycaprolactone (PCL) have been investigated; PCL's very low melting point (~58–65°C) is particularly advantageous for SLS of thermolabile APIs, enabling laser processing at temperatures lower than those required for most FDM polymers.

Ethyl cellulose (EC) grades have shown potential as hydrophobic matrix-forming polymers in SLS extended-release systems, providing diffusion-controlled drug release through the insoluble polymer network. Eudragit RS PO has been evaluated in SLS printing, where the laser energy is sufficient to sinter the polymer particles into a coherent tablet structure with sustained drug release characteristics. The challenge with SLS polymer selection is ensuring that the polymer powder has appropriate particle size (typically 10–100 µm), flowability, and a sintering window sufficiently wide to enable uniform laser fusion without complete melting or thermal degradation [29].

Polymers for SSE Bilayer Tablets

Hydroxypropyl methylcellulose (HPMC; Methocel K4M, K15M) is the most frequently employed polymer in SSE pharmaceutical formulations due to its ability to form stable, printable gels or

pastes at ambient temperature when dissolved in aqueous or hydro-alcoholic solvents. HPMC concentration controls gel viscosity and therefore the printability and shape retention of the extruded semi-solid. After printing and drying, HPMC matrices produce sustained-release tablets through hydrophilic swelling and erosion mechanisms. Hydroxypropyl cellulose (HPC; Klucel GF) is an alternative thermoplastic cellulosic polymer that can be formulated into SSE pastes at lower concentrations while providing excellent layer adhesion.

Carbomer (polyacrylic acid; Carbomer 974P) and xanthan gum are employed as gelling agents in SSE formulations requiring high viscosity at low polymer concentrations, particularly for APIs that require aqueous dispersion to achieve adequate drug loading. Sodium alginate and gelatin provide biocompatible, rapidly gelling matrices suitable for SSE formulations; gelatin-based SSE tablets have demonstrated particularly good interlayer bonding due to the thermoreversible gel properties of gelatin, which allows mild heat application at the bilayer interface to promote adhesion. HPMC acetate succinate (HPMC-AS) is increasingly being explored in SSE formulations for enteric bilayer tablets, as it dissolves in aqueous media at physiological intestinal pH while remaining solid during SSE processing and drying [30].

Excipients in 3D Printed Bilayer Tablets

Beyond the polymer matrix, numerous excipient categories play critical roles in the processability, mechanical properties, and drug release performance of 3D-printed bilayer tablets. Table 2 summarizes the principal excipient categories employed across FDM, SLS, and SSE bilayer tablet formulations. [31,32].

Table 2. Types of excipients required

Excipient	Category	Compatible technology	Role in 3D printing of bilayer tablets
Plasticizers	PEG 400, TEC, DBS, Glycerol, Propylene glycol	FDM, SLS, SSE	Reduce polymer Tg; improve filament flexibility; lower HME/printing temperatures by 20–40°C
Surfactants / Wetting Agents	SLS, Polysorbate 80, Vitamin E TPGS, Cremophor EL	FDM, SSE	Enhance API dissolution; improve drug-polymer miscibility; stabilize amorphous solid dispersions
Antioxidants	BHA, BHT, Ascorbic acid, Na metabisulfite, α-Tocopherol	FDM, SSE	Protect thermolabile APIs from oxidative degradation during thermal processing (HME, FDM printing)
Pore Formers	Mannitol, Lactose, PEG 1500, Sorbitol	FDM, SLS, SSE	Dissolve rapidly in aqueous media creating pore channels; modulate drug release rate in extended-release layers
Glidants / Flow Agents	Aerosil 200 (colloidal SiO_2), Talc, Magnesium stearate	SLS	Improve powder flowability in SLS powder bed; critical for uniform powder spreading and sintering

Flow Enhancers (filament)	Silicon dioxide, Magnesium stearate (low %)	FDM	Reduce die swell; improve extrudate consistency during HME filament production
Colorants / Opacifiers	Iron oxides (red, yellow), Titanium dioxide	FDM, SSE	Layer identification in bilayer tablets; aid in visual quality control during printing
pH Modifiers	Citric acid, Na bicarbonate, Fumaric acid	FDM, SSE	Create microenvironmental pH to protect acid-sensitive APIs; modulate enteric polymer dissolution
Binders (SSE pastes)	Gelatin, Carbomer 974P, Xanthan gum, Na alginate	SSE	Provide gel viscosity and structural integrity for semi-solid paste extrusion; maintain shape post-printing before drying
Absorption Enhancers	Poloxamer 407, Sodium caprate	FDM, SSE	Improve bioavailability of poorly permeable APIs incorporated in bilayer tablet formulations

CHARACTERIZATION OF 3D-PRINTED BILAYER TABLETS

Physicochemical Characterization

Comprehensive characterization of 3D-printed bilayer tablets requires a multi-technique approach spanning solid-state analysis, mechanical testing, and drug release assessment. Table 3 summarizes the principal characterization methods and their respective analytical objectives. [33,34]

Table 3. Characterization techniques

Technique	Parameter assessed	Key information
Differential Scanning Calorimetry (DSC)	Thermal transitions, drug-polymer miscibility	API crystallinity in matrix; Tg of formulation; drug-polymer interaction
X-ray Powder Diffraction (XRPD)	Solid-state form, crystallinity	Amorphous vs. crystalline API; polymorph identification; recrystallization detection
Scanning Electron Microscopy (SEM)	Surface/cross-section morphology	Layer interface quality; porosity architecture; drug distribution
Fourier Transform Infrared (FTIR)	Molecular interactions	Drug-polymer hydrogen bonding; chemical degradation detection
Hot Stage Microscopy	Thermal behavior, miscibility	Visual observation of drug melting/dissolution in polymer
USP Dissolution (Type II)	Drug release profile	In vitro release kinetics from each layer; biphasic profile confirmation
HPLC / UV-Vis	Drug content, purity	Content uniformity; degradation product identification
Hardness / Friability	Mechanical integrity	Resistance to breakage; suitability for packaging and handling
Delamination Force Test	Interlayer adhesion strength	Layer separation force; bilayer mechanical robustness
Micro-CT Imaging	Internal architecture	3D visualization of infill structure; porosity quantification

Clinical Applications of 3D Printed Bilayer Tablets

The clinical potential of 3D-printed bilayer tablets spans a broad range of therapeutic areas where fixed-dose combinations, complex pharmacokinetic profiles, or personalized dosing represent unmet clinical needs. The following indicates a summary of the clinical application areas, drug combinations, and therapeutic rationales that have been investigated or proposed for 3D-printed bilayer tablet formulations.

Tuberculosis (TB) Management

- The combination of Isoniazid (INZ) and Rifampicin (RFC) is standard first-line therapy for tuberculosis.
- A major clinical challenge is the poor bioavailability of RFC, which degrades in acidic gastric media, a reaction accelerated by the presence of INZ.
- To overcome this, researchers utilized Fused Deposition Modeling (FDM) 3D printing combined with hot-melt extrusion (HME) to fabricate a bilayer tablet.
- INZ was formulated with a hydroxypropyl cellulose (HPC) matrix to allow for rapid drug release in the stomach's acidic environment.
- RFC was formulated with a hypromellose acetate succinate (HPMCAS) matrix, an ionic polymer that remains insoluble in acid but dissolves rapidly above pH 5.5.
- Dissolution studies showed that over 80% of INZ was released within 45 minutes at pH 1.2, while RFC release was successfully delayed until the medium was adjusted to pH 7.4, at which point approximately 76% was released within 45 minutes. [35]

Cardiovascular Disease and Hypertension

- **Dual Therapy for Heart Conditions:** Selective Laser Sintering (SLS) was used to produce bilayer tablets containing Rosuvastatin (RSV) and Acetylsalicylic acid (AAS).
- AAS was designed for immediate release using a Kollidon VA 64 matrix, while RSV was formulated for delayed release using an HPMCAS-LMP matrix to protect it from gastric acid.
- To meet pharmacopeial dissolution specifications, researchers utilized a customized 3D-printed mesh design to increase the surface-area-to-volume ratio, significantly enhancing the dissolution rate of both drugs.
- **Dynamic Dosing for Hypertension:** Enalapril maleate (EM) and Hydrochlorothiazide (HCT) were formulated into a single FDM 3D-printed bilayer tablet to move away from rigid fixed-dose combinations (FDCs).

- This "dynamic dose combiner" allows the specific dosage of each antihypertensive drug to be titrated to individual patient needs simply by modifying the thickness (and thus the volume) of the corresponding printed layer.
- By utilizing a methacrylate polymeric matrix, both EM and HCT exhibited similar, predictable *in vitro* release profiles regardless of layer thickness or the vastly different aqueous solubilities of the two drugs. [36,37]

Pain Management and Anti-Inflammatory Therapy

Analgesic Combinations:

- Acetaminophen (APAP) and Caffeine Citrate (CC) were fabricated into bilayer tablets using HME paired with dual-nozzle FDM 3D printing.

  This combination is clinically relevant because caffeine acts as an adjuvant that accelerates the absorption of APAP and enhances its analgesic effect.
- Both drugs were extruded with different grades of hydroxypropyl methylcellulose (HPMC), resulting in sustained release kinetics largely driven by Fickian and non-Fickian diffusion mechanisms.

Single-Drug Dual-Release:

- A bilayer tablet of Diclofenac Sodium was developed using FDM 3D printing to provide both a rapid onset of action and prolonged pain relief.
- The immediate-release layer was printed with a honeycomb structure to maximize the surface area and formulated with a high drug loading (50% w/w) to ensure fast dissolution.
- The sustained-release layer was printed with a 100% infill (completely solid) structure to minimize porosity and was formulated with a polyvinyl alcohol (PVA) and Kollidon SR matrix to prolong drug release over a 24-hour timeframe.

Respiratory and Bacterial Infections

Antibiotic Combinations:

- Clarithromycin (CAM) and Levofloxacin (LVX), often combined for community-acquired pneumonia and *H. pylori* infections, were printed via FDM into differential-release bilayer tablets.
- LVX was formulated into an immediate-release layer using a cationic Eudragit EPO polymer, achieving nearly 100% drug release within the first hour.
- CAM was formulated into a sustained-release layer using Eudragit RS100 and RL100 polymers, effectively retarding the release of the drug for up to 24 hours to reduce gastrointestinal side effects and dosing frequency.

Expectorants:

- Guaifenesin bilayer tablets were successfully produced using a room-temperature extrusion 3D printer (Fab@Home) feeding viscous pastes.
- The immediate-release layer utilized HPMC 2910 as a binder alongside superdisintegrants (microcrystalline cellulose and sodium starch glycolate) to provide a burst release for rapid symptom alleviation.
- The sustained-release layer utilized HPMC 2208 and poly (acrylic acid) to form a hydrating gel barrier, controlling the drug release via Fickian diffusion over a 12-hour period. [38]

Regulatory Challenges and Quality Assurance:

Pharmaceutical 3D printing presents previously unheard-of regulatory challenges as it moves from a novelty in prototyping to a practical clinical manufacturing method. Large-scale, centralized batch production is the foundation upon which international regulatory organizations like the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have built their frameworks. This paradigm is shifted toward unit level, decentralized production by 3D printing, which fundamentally challenges current methods of regulatory compliance and quality assurance [39].

Lack of Standardized Guidelines

Good Manufacturing Practice (GMP) rules and current pharmacopeial monographs are specifically made for mass-produced, compressed batch tablets. For example, a consistent, solid compression matrix is assumed in conventional pharmacopeial tests for tablet hardness, friability, and disintegration. Because internal porosity and varying infill densities are frequently deliberate features designed to control drug release, these guidelines do not exactly translate to layer-by-layer 3D-printed tablets. A 3D-printed drug delivery system may, depending on the jurisdiction, blur the regulatory boundaries between a standard drug, a medical device, or a complex combination product, which frequently results in unclear approval pathways and delayed clinical implementation [39]. Regulatory bodies also face difficulties with basic product classification.

Quality by Design (QbD) in Additive Manufacturing:

In conventional manufacturing, the entire batch is statistically validated by end-product destructive testing, such as dissolving 10 tablets out of a batch of 10,000. On the other hand, one highly tailored bilayer tablet may make up a batch in personalized 3D printing. The industry must strictly implement Quality by Design (QbD) principles since destructive testing of a "batch of one" is not feasible [48]. A QbD framework integrates quality directly into the digital workflow rather than testing it in the finished result. Formulators must rigorously regulate the Critical Process

Parameters (CPPs), such as extruder temperature, nozzle speed, and polymer rheology, and methodically determine Critical Quality Attributes (CQAs), such as layer volume and drug load.[40]

Process Analytical Technology (PAT) and Real-Time Monitoring:

Decentralized printing has very little post-production testing, therefore Process Analytical Technology (PAT) is required to enforce Quality by Design. PAT incorporates continuous, real-time quality monitoring right into the 3D printer [41]. Closed-loop sensor systems are becoming more and more integrated into contemporary pharmaceutical printers. For instance, laser micrometres confirm that the immediate-release and sustained-release layers adhere to precise millimetre thickness requirements during deposition, while high-resolution thermal imaging cameras continually monitor the extrusion temperature to prevent API deterioration. Additionally, printheads are now directly equipped with sophisticated inline Near-Infrared (NIR) or Raman spectroscopy probes to measure the precise drug load and chemical distribution of each layer during printing. In order to prevent a faulty tablet from ever reaching the patient, the PAT system has the ability to automatically stop the process if it finds a layer error or dose anomaly halfway through the print [42].

Liability in Decentralized Manufacturing (Point-of-Care):

The disintegration of the conventional pharmaceutical supply chain is arguably the most complicated regulatory issue associated with 3D printing. The "Pharmacy on Demand" model involves point-of-care manufacturing, where hospital pharmacies or clinical centres adopt in house 3D printing capabilities to produce patient-specific tablets. This decentralized method seriously obfuscates the legal distinction between "manufacturer" and "healthcare provider." It is very difficult to determine who is legally responsible if a patient is harmed by a 3D-printed bilayer pill that does not provide the proper dose. Whether the pharmaceutical business that produced the raw drug-loaded filament, the software provider who licensed the digital CAD plan, the 3D printer hardware manufacturer, or the hospital pharmacist who physically started the print is still unclear from a legal standpoint. This legal ambiguity continues to be a major obstacle to wider clinical adoption until international regulatory bodies provide standardized liability frameworks and point-of-care GMP requirements.[42].

Future Perspectives

Artificial Intelligence in Bilayer Formulation Design

Machine learning and artificial intelligence approaches are beginning to be applied to FDM pharmaceutical formulation development, offering the potential to dramatically accelerate the

optimization process. Supervised learning models trained on datasets of polymer-drug properties, printing parameters, and dissolution outcomes can potentially predict optimal formulation compositions and printing conditions for target release profiles, reducing the number of experimental runs required.

Reinforcement learning frameworks, in which an algorithm iteratively proposes and evaluates formulation candidates, offer a promising approach for multi-objective optimization — simultaneously targeting drug release profile, mechanical strength, content uniformity, and chemical stability. Integration of high-throughput small-scale HME and printing systems with automated dissolution testing and data pipelines could enable truly autonomous formulation development workflows.

Continuous Manufacturing Integration

opportunity to integrate FDM, SLS, or SSE printing within continuous processing lines, with Process analytical technology (PAT) tools — including near-infrared spectroscopy for real-time drug content monitoring, acoustic emission sensors for filament fracture detection, and in-line dissolution testers — are being developed to enable real-time quality assurance within integrated continuous printing platforms.

CONCLUSION

Three-dimensional (3D) printing has emerged as a promising and innovative approach for the fabrication of bilayer tablets, overcoming many of the limitations associated with conventional compression techniques. Technologies such as Fused Deposition Modeling (FDM), Selective Laser Sintering (SLS), and Semi-Solid Extrusion (SSE) provide enhanced flexibility in tablet geometry, drug loading, and release modulation, enabling the development of personalized and patient-centric dosage forms. The use of suitable polymers and excipients further improves mechanical strength, stability, and controlled drug delivery characteristics. Moreover, 3D-printed bilayer tablets have demonstrated significant therapeutic potential in the management of tuberculosis, cardiovascular diseases, pain, and respiratory disorders. Despite these advantages, challenges related to regulatory approval, quality assurance, process validation, and decentralized manufacturing still remain. Future integration of artificial intelligence, Quality by Design (QbD), Process Analytical Technology (PAT), and continuous manufacturing systems may accelerate the clinical translation and commercialization of 3D-printed bilayer tablets, paving the way for advanced personalized medicine and on-demand pharmaceutical manufacturing.

REFERENCE

1. Agiba AM, Abul-Ella SS, Abd El-Monem RA. Pharmacotechnical development and optimization of multilayered tablets: An updated industrial review with emphasis on bilayer tablets. Int J Appl Pharm.2021; 13:55-64
2. Sadia M, Isreb A, Abbadi I, Isreb M, Aziz D, Selo A, mmins P, Alhnan MA. From ‘fixed dose combinations’ to ‘a dynamic dose combiner’: 3D printed bi-layer antihypertensive tablets. Eur J Pharm Sci. 2018; 123:484-9
3. 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.
4. Aprecia Pharmaceuticals. Spritam (levetiracetam): first FDA-approved 3D-printed drug product [Internet]. Warren (NJ): Aprecia Pharmaceuticals; 2015 [cited 2024 Jan 10]. Available from: https://www.aprecia.com.
5. Hossain KR, Jami MM, Shyeed A, Khatun K, Hasan K, Cobra K, Ahmed F. Application of 3D printing in medicine: Technologies and challenges. Al-bahir J Eng Pure Sci. 2023;3(1):7.
6. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. J Control Release.2015;217:308-14.
7. Pereira BC, Isreb A, Forbes RT, Dores F, Habashy R, Petit JB, et al. 'Temporary Plasticiser': a novel solution to fabricate 3D printed patient-centred cardiovascular 'polypill' architectures. Eur J Pharm Biopharm. 2019; 135:94-103.
8. Curti C, Kirby DJ, Russell CA. Current formulation approaches in design and development of solid oral dosage forms through three-dimensional printing, Prog. Addit Manuf.2020; 5:111-123.
9. Dimitrov M, Georgieva D, Ilieva S, Petkova V. The era of digital pharmacy. 3D printing-realities and perspectives. Pharmacia.70 (4):1083–1092.
10. Jamróz W, Szafraniec J, Kurek M, Jachowicz R. 3D printing in pharmaceutical and medical applications: recent achievements and challenges. Pharm Res. 2018;35(9):176.
11. Chakka LRJ, Chede S. 3D printing of pharmaceuticals for disease treatment. Front Med Technol. 2022;4:1040052.
12. Sharma P, Jain V. An overview of current advances and pharmaceutical uses of 3D and 4D printing. Explor Med. 2023;4(4):560-575.

13. Korte C, Quodbach J. Formulation development and 3D printing of bilayer tablets via fused deposition modeling. Int J Pharm. 2018;548(1):310-319.
14. Zhang J, et al. Investigation of the fused deposition modeling additive manufacturing i: influence of process temperature on the quality and crystallinity of the dosage forms. AAPS PharmSciTech. (2021) 22(8):258.
15. Goyanes A, Kobayashi M, Martinez-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.
16. Crișan AG, Porfire A, Iurian S, Casian T, Muntean DM, Gâvan A, *et al*. Development of a bilayer tablet by fused deposition modeling as a sustained-release drug delivery system. Pharmaceuticals. 2023;16(9):1321.
17. Tan DK, Maniruzzaman M, Nokhodchi A. Advanced pharmaceutical applications of hot-melt extrusion coupled with fused deposition modelling (FDM) 3D printing for personalised drug delivery. Pharmaceutics. 2018;10(4):203.
18. Charoo NA, Barakh Ali SF, Mohamed EM, Kuttolamadom MA, Ozkan T, Khan MA,Rahman Z *et al*. Selective laser sintering 3D printing – an overview of the technology and pharmaceutical applications. Drug Dev. Ind. Pharm. 2020;46 (6):869–877.
19. Fina, F, Goyanes A, Gaisford S, Basit AW. 2017.Selective laser sintering (SLS) 3D printing of medicines. Int J Pharm.2017;529 (1–2):285–293.
20. Junqueira LA, Tabriz GA, Vivek Garg, Kolipaka SS, Ho-Wah Hui, Boersen N, Roberts S, Jones J, Douroumis D. Selective laser sintering for printing bilayer tablets. Int J Pharma. 2025;670:125116.
21. Allahham N, Fina F, Marcuta C, Kraschew L, Mohr W, Gaisford S, et al. Selective laser sintering 3D printing of orally disintegrating printlets containing ondansetron. Pharmaceutics. 2020;12(2):110.
22. Junqueira LA, Tabriz AG, Garg V, Kolipaka SS, Hui HW, Boersen N, Roberts S, Jones J, Douroumis D. Selective laser sintering for printing bilayer tablets. Int J Pharm. 2025;670:125116.
23. Seoane-Viaño I, Januskaite P, Alvarez-Lorenzo C, Basit AW, Goyanes A. Semi-solid extrusion 3D printing in drug delivery and biomedicine: towards printing of 3D cells and tissues. J Control Release. 2021;332:667-684.
24. Vojinovic A, Medarevik D, Stanojevic G, Mircovic D, Mugosa S, Adamov I *et al*. Development and evaluation of 3D-printed losartan potassium tablets using semi-solid

extrusion: The effect of geometry, drug loading and superdisintegrant. Pharmaceuticals. 2025;18(10):1504.

25. Mathiyalagan R, Westerlund M, Mahran A, Altunay R, Suuronen J, Palo M *et al*. 3D printing of tailored veterinary dual-release tablets: a semi-solid extrusion approach. RSC Pharm Med. 2025;4:322.
26. Muehlenfeld C, Duffy P, Yang F, Zermeño Pérez D, El-Saleh F, Durig T. Excipients in Pharmaceutical Additive Manufacturing: A comprehensive exploration of polymeric material selection for enhanced 3D printing. Pharmaceutics. 2024; 16(3):317.
27. Lee S, Song ES, Lee E, Kwon G, Kim DW. Tunable drug release from 3d-printed bilayer tablets: combining hot-melt extrusion and fused deposition modeling. Polymers. 2026; 18(2):210.
28. Prasad E, Islam MT, Goodwin DJ, Megarry AJ, Halbert GW, Florence AJ, et al. Development of a hot-melt extrusion (HME) process to produce drug loaded Affinisol HPMC HME filaments for fused deposition modelling (FDM) 3D printing. Addit Manuf. 2019;29:100776.
29. Sadia M, Sosnicka A, Arafat B, Isreb A, Ahmed W, Kelarakis A, et al. Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets. Int J Pharm. 2016;513(1-2):659-68.
30. 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.
31. Prasad E, Islam MT, Goodwin DJ, Megarry AJ, Halbert GW, Florence AJ, et al. Development of a hot-melt extrusion (HME) process to produce drug loaded Affinisol HPMC HME filaments for fused deposition modelling (FDM) 3D printing. Addit Manuf. 2019;29:100776.
32. Sadia M, Sosnicka A, Arafat B, Isreb A, Ahmed W, Kelarakis A, et al. Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets. Int J Pharm. 2016;513(1-2):659-68.
33. Markl D, Zeitler JA. A review of non-destructive analytical techniques for quality by design-based 3D printed pharmaceuticals. Adv Drug Deliv Rev. 2017;117:112-132.
34. Windolf H, Chamberlain R, Quodbach J. Predicting drug release from 3D printed oral medicines based on solid-state properties and spatial distribution. Int J Pharm. 2021;597:120395.

35. Tabriz AG, Nandi U, Hurt AP, Hui HW, Karki S, Gong Y, et al. 3D printed bilayer tablet with dual controlled drug release for tuberculosis treatment. Int J Pharm. 2021;593:120147.
36. Sadia M, Isreb A, Abbadi I, Isreb M, Aziz D, Selo A, et al. From 'fixed dose combinations' to a 'dynamic dose combiner': 3D printed bi-layer antihypertensive tablets. Eur J Pharm Sci. 2018;123:484-494.
37. Crişan AG, Porfire A, Iurian S, Rus LM, Sadia M, Isreb A, Abbadi I, Isreb M, Aziz D, Selo A, et al. From 'fixed dose combinations' to a 'dynamic dose combiner': 3D printed bi-layer antihypertensive tablets. Eur J Pharm Sci. 2018;123:484-494.
38. Lucăcel Ciceo R, Turza A, et al. Development of a bilayer tablet by fused deposition modeling as a sustained-release drug delivery system. Pharmaceuticals. 2023;16(9):1321.
39. Lalitha KA, Raghava D, Rao NK, Sravani NP. Regulatory hurdles in the commercialization of 3D printed pharmaceuticals and medical devices. J Cardiovasc Dis Res. 2025;16(10):139-145.
40. Joshi D, Shukla P, Choudhary NK. Enhancing pharmaceutical 3D printing through Quality-by-Design (QbD): Challenges, strategies, and regulatory insights. Int J Newgen Res Pharm Health. 2025;3(1):158-168.
41. Cader HK, et al. Non-destructive analytical techniques and Process Analytical Technology (PAT) for 3D printed pharmaceuticals. J Pharm Biomed Anal. 2020;189:113426.
42. Awad A, et al. A case study on decentralized manufacturing of 3D printed medicines: Integration of inline NIR spectroscopy. Int J Pharm. 2023;632:122557.