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3D Printing for Personalised Medicines: Pharmaceutical Formulation Strategies, Dose Customisation and Regulatory Challenges

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Abstract

Conventional mass-manufacturing of pharmaceuticals relies on fixed doses and standardised formulations that assume an 'average' patient, an approach that fails to account for the considerable inter-individual variability in age, weight, genetics, organ function and disease progression that governs drug response. Personalised medicine seeks to tailor therapy to the individual, and 3D printing provides a practical manufacturing platform capable of realising this vision at the point of care. This review examines the principal pharmaceutical 3D-printing technologies—including fused deposition modelling (FDM), semi-solid extrusion (SSE), selective laser sintering (SLS), stereolithography (SLA) and binder-jet (powder-bed) printing—and evaluates their suitability for producing solid oral dosage forms with customised doses, geometries, release profiles and multi-drug combinations. It further considers formulation strategies, including polymer selection, hot-melt extrusion coupling, printability and the incorporation of thermolabile and biologic actives. The landmark 2015 approval of Spritam® (levetiracetam), the first 3D-printed drug product cleared by the United States Food and Drug Administration, is discussed as a proof of concept that catalysed the field. The review also addresses the regulatory, quality-control and good-manufacturing-practice (GMP) challenges that arise when manufacturing is distributed to hospitals, community pharmacies and clinics rather than centralised in industrial facilities. Key barriers—process validation, real-time release testing, data integrity, excipient qualification and pharmacovigilance—are analysed alongside recent guidance from major regulatory agencies. A recurring theme is that the principal obstacles to adoption are no longer questions of technical feasibility but of quality assurance, standardisation and governance, particularly the difficulty of assuring dose accuracy and product quality when single units are printed on demand rather than sampled from large batches.

Keywords: 3D printing; personalised medicine; additive manufacturing; dose customisation; fused deposition modelling; pharmaceutical formulation; regulatory challenges; point-of-care manufacturing.

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1. Introduction

The pharmaceutical industry has historically operated on a mass-production paradigm in which large batches of identically dosed tablets and capsules are manufactured, distributed and dispensed. While this model achieves economies of scale, product consistency and broad availability, it is fundamentally misaligned with the biological reality that patients differ substantially in how they absorb, metabolise and respond to drugs. The rise of personalised—or precision—medicine has intensified interest in manufacturing technologies capable of producing individualised dosage forms, and additive manufacturing, commonly known as 3D printing, has become one of the most promising of these technologies (Trenfield et al., 2018). By building objects layer by layer from a digital design, 3D printing allows the dose, shape, size, drug combination and release kinetics of a medicine to be adjusted on demand, opening the door to truly patient-tailored therapy.

1.1 The Concept of Personalised Medicine

Personalised medicine refers to the tailoring of medical treatment to the individual characteristics of each patient, encompassing genetic makeup, phenotype, lifestyle and environment. In pharmacotherapy, this translates into selecting the right drug at the right dose for the right patient. Standard fixed-dose products cannot easily accommodate the wide dosing requirements seen in paediatric, geriatric, renally impaired and pharmacogenomically distinct populations (Alhnan et al., 2016). Manual compounding, tablet splitting and extemporaneous preparation have traditionally filled this gap, but these practices suffer from poor dose accuracy, content uniformity concerns and limited scalability. 3D printing offers a reproducible, automated and digitally controlled alternative for producing individualised doses with a precision that manual methods cannot match (Norman et al., 2017).

The intellectual foundations of personalised medicine draw on decades of evidence that a 'one-size-fits-all' dosing philosophy leaves large fractions of patients either under-treated or exposed to avoidable toxicity. Population pharmacokinetic studies routinely reveal several-fold differences in plasma exposure among individuals given identical doses, driven by body composition, renal and hepatic function, concomitant medication, and inherited variation in drug-metabolising enzymes and transporters. When a drug has a narrow therapeutic window, this variability is not a statistical curiosity but a direct clinical risk. The conceptual response—dosing to the individual rather than the population average—has long been advocated, but its practical realisation has been constrained by manufacturing technology. It is precisely this manufacturing gap that additive fabrication addresses, by making the economical production of small, bespoke quantities technically feasible (Awad et al., 2018).

1.2 Additive Manufacturing and Its Pharmaceutical Relevance

Additive manufacturing constructs a three-dimensional object from a computer-aided design (CAD) model by depositing, fusing or solidifying material in successive layers. Originally developed for rapid prototyping in engineering, the technology has been adapted across biomedical fields, including tissue engineering, medical devices, implants and, more recently, oral dosage forms (Jamróz

et al., 2018). Its pharmaceutical relevance lies in the unprecedented control it grants over dosage-form architecture: internal geometry, infill density, surface area and multi-compartment structures can all be manipulated to engineer specific drug-release profiles that would be difficult or impossible to achieve with conventional compression.

Whereas conventional tablet manufacturing proceeds through a sequence of powder blending, granulation, drying, milling, lubrication and compression—each step introducing its own sources of variability and requiring dedicated equipment—additive manufacturing collapses much of this workflow into a single, digitally driven fabrication step. The dosage form exists first as a digital file that fully specifies its dimensions, internal lattice and drug content, and this file can be transmitted, modified and reproduced with exactness. This digital nature is arguably as significant as the physical printing itself, because it makes the medicine a programmable object: altering a parameter in software instantly changes the manufactured product without retooling. The consequence is a manufacturing philosophy oriented around flexibility and individualisation rather than the standardisation and scale that define conventional production (Mathew et al., 2020).

1.3 Evolution of 3D Printing in the Pharmaceutical Sector

Interest in printing medicines accelerated markedly after 2015, when the United States Food and Drug Administration (FDA) approved Spritam® (levetiracetam), the first 3D-printed drug product, manufactured by Aprecia Pharmaceuticals using a proprietary powder-bed ZipDose® platform (Jacob et al., 2020). The porous, rapidly disintegrating tablet demonstrated that 3D printing could satisfy regulatory and quality standards at commercial scale. Since then, academic and industrial research has expanded rapidly, exploring extrusion-based, laser-based and jetting-based techniques for an increasing range of actives and release behaviours (Trenfield et al., 2019).

The trajectory of the field can be understood in three overlapping phases. The first, before 2015, was exploratory and largely academic, establishing that active pharmaceutical ingredients could survive printing and that printed forms could release drug in a controlled manner. The second, catalysed by the Spritam® approval, was a period of rapid technological diversification in which researchers systematically evaluated FDM, SSE, SLS, SLA and inkjet methods, mapped compatible excipients, and characterised how print parameters govern release. The field is now entering a third phase concerned less with demonstrating feasibility than with translation: designing manufacturing systems robust enough for the clinic, generating stability and bioequivalence data, and constructing the quality and regulatory scaffolding required for routine use (Seoane-Viaño et al., 2021). This review is written from the vantage point of that translational phase, where the technical case is largely made and the implementation case is being contested.

1.4 Rationale for Dose Customisation

Fixed-dose regimens are a compromise. A dose optimal for a 70 kg adult may be excessive for a frail elderly patient or a small child, and pharmacogenetic variation in enzymes such as CYP2C9 and CYP2D6 can cause fivefold or greater differences in drug exposure between individuals. Sub-optimal

dosing contributes to therapeutic failure, adverse events and non-adherence. On-demand 3D printing enables clinicians to prescribe and produce a dose calibrated to the individual patient's weight, organ function and genotype, and to combine multiple drugs into a single 'polypill' to simplify complex regimens and improve adherence (Khaled et al., 2015).

The clinical cost of dose inflexibility is often underestimated. Tablet splitting, a common workaround, produces fragments of unequal mass and unpredictable content, particularly for coated or non-scored tablets, and is impractical for extended-release products whose integrity depends on an intact matrix. Liquid formulations improve dose flexibility but raise concerns over stability, palatability, dosing errors and the need for accurate measuring devices. Against this backdrop, the ability to manufacture a solid oral dosage form containing an exact, prescriber-defined quantity of drug—accurate to a fraction of a milligram and reproducible from unit to unit—represents a meaningful advance in medication safety. Beyond simple dose scaling, printing permits the simultaneous adjustment of release rate, so that a patient can receive not only the correct amount of drug but also the correct temporal delivery pattern, aligning therapy with circadian rhythm or disease chronobiology where relevant (Skowyra et al., 2015).

1.5 Point-of-Care and Distributed Manufacturing

A distinctive feature of pharmaceutical 3D printing is that it can decentralise manufacturing. Compact printers situated in hospitals, community pharmacies or clinics could produce small batches or single units of medicine close to the patient, reducing supply-chain dependence, enabling rapid formulation changes and supporting the treatment of rare diseases and clinical-trial cohorts. This distributed model, however, challenges the centralised regulatory and quality-assurance frameworks that currently govern medicine manufacturing (Trenfield et al., 2018).

The appeal of point-of-care manufacturing extends beyond individualisation. Localised production could shorten and simplify supply chains, mitigate drug shortages by allowing on-site fabrication of critical medicines, and reduce waste by producing only what is needed when it is needed. In humanitarian, military and remote settings, a compact printer with validated formulations and a stock of feedstock could provide access to medicines where conventional distribution is impractical. Yet each of these opportunities is shadowed by a corresponding governance question: who holds manufacturing authorisation, how is quality assured without a central laboratory, and how are the printer, its software and its raw materials qualified and maintained. These tensions, rather than the printing chemistry, increasingly define the frontier of the field and are examined in detail later in this review (Awad et al., 2020).

1.6 Scope and Objectives of the Review

This review synthesises the current state of pharmaceutical 3D printing with a focus on three interrelated themes: formulation strategies, dose customisation and regulatory challenges. It surveys the principal printing technologies and their materials, examines how printing parameters govern drug release, evaluates the clinical rationale and evidence for personalised dosing, and critically analyses

the regulatory, quality-control and GMP hurdles that stand between laboratory demonstrations and routine clinical use. The objective is to provide a structured, reference-supported overview that clarifies both the opportunities and the outstanding barriers to translation.

The review is organised as follows. The remainder of the introduction has established the conceptual and clinical context for personalised medicines and the manufacturing gap that additive fabrication addresses. The literature review then examines the field under five thematic headings—printing technologies, formulation and materials, dose and release customisation, clinical applications, and regulatory and quality considerations—supported by comparative tables. A description of the review methodology follows, after which a discussion synthesises the evidence and identifies the central tensions between technical capability and implementation readiness. The paper closes with conclusions and a set of prioritised directions for future research. Throughout, the emphasis is on the pharmaceutical and translational dimensions of the technology rather than its engineering internals, reflecting the interests of pharmaceutical scientists, clinicians and regulators who will ultimately determine whether printed medicines enter routine care.

2. Literature Review

The literature on pharmaceutical 3D printing has grown from a handful of proof-of-concept studies before 2015 into a mature multidisciplinary field spanning materials science, pharmaceutics, engineering and regulatory science. This section reviews the field under five themes: printing technologies, formulation and materials, dose and release customisation, clinical and personalised applications, and regulatory and quality considerations.

2.1 Overview of Pharmaceutical 3D-Printing Technologies

The proliferation of printing modalities is one of the defining features of the recent literature. Whereas early work relied heavily on adapting inexpensive desktop extrusion printers, the field has since embraced a diverse toolkit spanning extrusion, powder-fusion, photopolymerisation and jetting processes. Each rests on a different physical principle for building a solid object and, consequently, imposes different demands on the materials it can process and offers different capabilities in terms of resolution, speed and release control. Understanding these distinctions is essential to appreciating why the technology suits some drugs and clinical scenarios better than others.

Several additive-manufacturing modalities have been adapted for medicines, each with distinct operating principles, material requirements and advantages. Fused deposition modelling (FDM) extrudes a thermoplastic, drug-loaded filament through a heated nozzle and is the most widely studied technique owing to its low cost and versatility (Goyanes et al., 2015). Semi-solid extrusion (SSE) deposits a paste or gel at or near room temperature, making it suitable for thermolabile drugs and biologics (Seoane-Viaño et al., 2021). Selective laser sintering (SLS) uses a laser to fuse powder particles and can produce fast-disintegrating or highly porous structures without solvents (Fina et al., 2017). Stereolithography (SLA) cures a liquid photopolymer resin with light, offering high resolution

but limited pharmaceutical-grade resin availability (Wang et al., 2016). Binder-jetting, exemplified by the ZipDose® platform behind Spritam®, selectively deposits a liquid binder onto powder beds to form highly porous, rapidly disintegrating tablets (Jacob et al., 2020).

The historical importance of binder-jetting warrants particular note. The ZipDose® platform behind Spritam® demonstrated that a powder-bed printing process could be scaled to commercial volumes while meeting the identity, assay, uniformity and dissolution standards demanded of an approved product. The resulting tablets are highly porous and disintegrate within seconds when placed in the mouth, an attribute especially valuable for patients who struggle to swallow conventional high-dose tablets, as is common in epilepsy. This single approval reframed the entire field: it converted 3D printing from a laboratory curiosity into a regulatorily validated manufacturing route and provided a concrete precedent that subsequent developers and regulators could reference (Jacob et al., 2020).

Each modality carries a characteristic set of trade-offs. FDM's dependence on a solid, drug-loaded filament makes filament mechanical quality a critical determinant of print success; brittle or overly soft filaments feed poorly, and the high nozzle temperatures required to melt many pharmaceutical polymers—often between 150 and 220 °C—can degrade heat-sensitive actives (Okwuosa et al., 2016). SSE circumvents thermal stress by printing at or near ambient temperature from a viscous paste, but the deposited object must subsequently be dried to remove solvent, and its mechanical robustness is generally inferior to compressed or melt-processed forms. SLS produces intricate, solvent-free structures and can generate highly porous, orodispersible tablets, though it typically requires a colourant to absorb laser energy and exposes the powder bed to localised heating. SLA achieves the finest spatial resolution of the common techniques and operates at room temperature, but the scarcity of biocompatible, regulatory-accepted photopolymer resins and concerns about residual unreacted monomer have limited its pharmaceutical uptake (Wang et al., 2016). Binder-jetting, by contrast, has the singular distinction of an approved commercial product and excels at rapid-disintegration formats, at the cost of complex post-processing and substantial equipment investment.

The choice of technology is therefore dictated by the active pharmaceutical ingredient's thermal stability, the desired release profile and the required production throughput. No single technique dominates across all applications; rather, the field is converging on a portfolio view in which the modality is matched to the drug and the clinical objective. Table 1 summarises the principal technologies, their mechanisms and their key characteristics.

Table 1. Principal pharmaceutical 3D-printing technologies and their characteristics

Technology	Working principle	Key advantages	Key limitations
Fused deposition modelling (FDM)	Extrusion of drug-loaded thermoplastic filament through a heated nozzle	Low cost; versatile; controllable geometry and release	High processing temperature; needs filament; drug degradation risk

Technology	Working principle	Key advantages	Key limitations
Semi-solid extrusion (SSE)	Extrusion of paste/gel at low temperature	Suitable for thermolabile drugs and biologics; solvent flexible	Requires drying; lower mechanical strength
Selective laser sintering (SLS)	Laser fusion of powder particles	Solvent-free; porous fast-disintegrating forms	Laser-absorbing colourant needed; heat exposure
Stereolithography (SLA)	Photopolymerisation of liquid resin by light	Very high resolution; room temperature	Limited pharma-grade resins; unreacted monomer concerns
Binder-jet / powder-bed (ZipDose®)	Liquid binder jetted onto powder bed	High porosity; rapid disintegration; commercially proven	Complex post-processing; equipment cost

2.2 Formulation Strategies and Material Considerations

Successful 3D printing of medicines depends on the careful selection of polymers, plasticisers and functional excipients that confer printability while delivering the intended pharmaceutical performance. In FDM, a printable filament must possess suitable mechanical properties—stiffness, flexibility and a defined thermal-softening behaviour—so that it feeds smoothly and extrudes without breaking or clogging (Goyanes et al., 2015). Thermoplastic polymers such as polyvinyl alcohol (PVA), hydroxypropyl cellulose, ethyl cellulose, Eudragit grades and polylactic acid are commonly employed, often in combination with plasticisers to lower the glass-transition temperature and reduce processing heat (Melocchi et al., 2016).

Hot-melt extrusion (HME) is frequently coupled with FDM to produce drug-loaded filaments, providing a continuous route from raw powders to printable feedstock and improving drug dispersion, including the formation of amorphous solid dispersions that enhance the solubility of poorly water-soluble actives (Zhang et al., 2017). For thermolabile drugs, low-temperature techniques such as SSE and SLA are preferred, and for biologics, mild aqueous processing is essential to preserve activity.

The concept of printability sits at the centre of formulation development. A printable material must satisfy several simultaneous constraints: it must possess appropriate rheological or thermomechanical behaviour to be deposited accurately, it must solidify or set in a form that retains the designed geometry, it must remain chemically compatible with the drug throughout processing, and it must deliver the intended release performance in vivo. These requirements frequently conflict—a polymer that extrudes beautifully may release drug too slowly, or a plasticiser that improves printability may

compromise stability—so formulation becomes an exercise in balancing competing objectives. Researchers have adapted conventional pharmaceutical excipients to printing by systematically screening polymer–plasticiser combinations and mapping the resulting processing windows, and by introducing fillers and disintegrants to tune mechanical strength and dissolution (Sadia et al., 2016).

Thermal degradation is the single most important constraint in melt-based printing, and several mitigation strategies have emerged. Lowering the glass-transition temperature with plasticisers reduces the processing heat required; selecting polymers with low softening points achieves the same end; and reducing residence time in the heated zone limits cumulative thermal exposure. Where these are insufficient, low-temperature FDM variants and alternative modalities such as SSE offer routes to printing heat-labile molecules, and studies have specifically demonstrated the fabrication of thermolabile drugs at reduced temperatures without unacceptable degradation (Kollamaram et al., 2018). Table 2 outlines common polymers and excipients and their functional roles, while the interplay between processing temperature and drug suitability is compared later in Table 6.

The extension of printing to biologics and other sensitive modalities is an active frontier. Peptides, proteins, vaccines and live-cell or lipid-based systems cannot tolerate the heat and shear of melt processing and demand gentle, often aqueous, fabrication conditions. Semi-solid extrusion and inkjet-based approaches, which operate at or near ambient temperature, are the most promising routes for these materials, and researchers have explored soft-material and lipid-based printing specifically to preserve the activity of delicate actives (Vithani et al., 2019). Preserving biological function while achieving acceptable print fidelity and post-print stability remains challenging, but success in this area would greatly broaden the therapeutic scope of personalised printing beyond conventional small molecules. Table 2 lists representative materials used across these approaches and their functional roles.

Table 2. Common polymers and excipients used in pharmaceutical 3D printing

Material	Function	Typical application
Polyvinyl alcohol (PVA)	Water-soluble matrix former	Immediate/rapid release FDM tablets
Hydroxypropyl cellulose (HPC)	Matrix former; binder	Sustained-release matrices
Ethyl cellulose	Water-insoluble polymer	Extended-release and barrier layers
Eudragit (methacrylates)	pH-dependent polymer	Enteric / colon-targeted release
Polylactic acid (PLA)	Biodegradable thermoplastic	Implants and controlled release

Material	Function	Typical application
Plasticisers (e.g., triethyl citrate, PEG)	Lower glass-transition temperature	Improve printability, reduce heat
Fillers (e.g., microcrystalline cellulose)	Bulk, mechanical support	Structural integrity of printed forms

2.3 Dose Customisation and Drug-Release Modulation

A defining advantage of 3D printing is the ability to modulate dose and release profile digitally by altering the printed object's dimensions and internal architecture. Because drug content is proportional to the printed volume, dose can be tuned linearly by scaling tablet size or infill percentage, offering fine and reproducible dose granularity that is difficult to achieve by tablet splitting (Skowyra et al., 2015). Goyanes and colleagues demonstrated that infill density and geometry strongly influence dissolution: higher infill and lower surface-area-to-volume ratios slow release, whereas porous, high-surface-area structures accelerate it (Goyanes et al., 2015).

The relationship between geometry and release is grounded in mass-transport principles: drug release from a matrix is governed largely by the surface area available for dissolution and the diffusional path length through the solid. By manipulating shape—cylinders, discs, spheres, toroids and lattices—and internal infill, the printer effectively programmes these parameters. A dense, low-surface-area object releases slowly and steadily, approximating extended release, whereas a porous, high-surface-area lattice dissolves quickly. Because the designer controls these variables independently of drug content, dose and release rate can be decoupled and specified separately, a degree of design freedom without precedent in conventional tableting (Goyanes et al., 2015).

Complex architectures such as multi-layer tablets, core–shell 'DuoCaplet' designs and multi-compartment devices enable sophisticated release patterns—including delayed, pulsatile and sequential release—and permit multiple drugs to be combined in a single unit. Khaled and colleagues printed a five-in-one polypill combining several cardiovascular drugs with independently tailored release profiles, illustrating the potential to simplify polypharmacy (Khaled et al., 2015). Such multi-compartment devices can physically separate incompatible drugs within a single unit, isolate an enteric compartment from an immediate-release one, or stagger the release of sequential doses over time. This capacity to engineer both the spatial and temporal distribution of multiple actives is a defining advantage of additive manufacturing and is difficult to replicate by compression or coating.

Importantly, this design freedom has been validated experimentally rather than merely proposed. Studies fabricating tablets across a range of infill densities and geometries have consistently shown reproducible, predictable shifts in dissolution behaviour, and extended-release forms produced by FDM have achieved release profiles comparable to conventional modified-release products for drugs such as prednisolone (Skowyra et al., 2015). The accumulating body of evidence supports the view

that dose and release can be treated as tunable software parameters, transforming formulation from a largely empirical craft into a more predictable, design-driven discipline. Table 3 summarises the principal levers available to the formulator.

Table 3. Design and process levers for dose and release customisation

Lever	Effect	Resulting application
Tablet size / volume	Proportional change in drug content	Individualised dose titration
Infill density	Alters porosity and dissolution rate	Immediate vs. extended release
Surface-area-to-volume ratio	Higher ratio speeds release	Geometry-tuned release kinetics
Multi-layer structure	Separates drugs / release phases	Delayed or pulsatile release
Core–shell design	Barrier controls onset	Delayed and modified release
Multi-compartment polypill	Combines several drugs/profiles	Adherence in polypharmacy

2.4 Clinical and Personalised-Medicine Applications

The clinical promise of 3D-printed medicines is most evident in populations poorly served by fixed-dose products. Paediatrics is a prominent example: children require weight-based dosing and age-appropriate formulations, and 3D printing can produce palatable, correctly dosed chewable or orodispersible forms in shapes and colours that improve acceptance (Scoutaris et al., 2018). Geriatric patients, who often have swallowing difficulties and complex multi-drug regimens, benefit from customised polypills and easy-to-swallow porous tablets. Patients with narrow-therapeutic-index drugs, such as warfarin, and those whose dosing depends on pharmacogenomic status stand to gain from precise, individualised dose adjustment (Trenfield et al., 2019).

Paediatric formulation deserves particular emphasis because it exposes the limitations of conventional products most acutely. Children are not small adults; their dosing must track weight and developmental stage, and their willingness to take medicine depends heavily on taste, size and appearance. Investigators have exploited printing to produce dosage forms in child-friendly shapes and flavours while maintaining accurate, weight-appropriate dosing, and the ability to adjust dose incrementally as a child grows is especially valuable for chronic conditions (Scoutaris et al., 2018). Similar logic applies at the other end of life, where older adults frequently contend with reduced organ function, swallowing difficulty and burdensome multi-drug regimens; printed polypills and soft, porous, rapidly disintegrating tablets directly address these problems.

The first regulatory milestone, Spritam®, validated the commercial and clinical feasibility of the approach for a rapidly disintegrating high-dose product used in epilepsy (Jacob et al., 2020). Subsequent clinical work has begun to evaluate printed formulations at the point of care, including hospital-pharmacy studies producing individualised doses for children, and early feasibility studies suggest that printed formulations can achieve acceptable dose accuracy and patient acceptability in real clinical workflows (Seoane-Viaño et al., 2021). These developments mark a shift from demonstrating that personalised printing is possible to establishing that it can be delivered safely within the constraints of clinical practice. Table 4 summarises key patient populations and the corresponding benefits of 3D-printed personalised dosage forms.

Table 4. Patient populations and benefits of 3D-printed personalised medicines

Population	Clinical challenge	3D-printing benefit
Paediatric patients	Weight-based dosing; palatability; swallowing	Custom dose, shape, flavour, orodispersible forms
Geriatric patients	Polypharmacy; dysphagia	Polypills; porous easy-to-swallow tablets
Renal / hepatic impairment	Altered clearance	Precise dose adjustment on demand
Narrow therapeutic index drugs	Small margin between efficacy and toxicity	Fine dose titration and accuracy
Pharmacogenomically distinct	Variable metabolism	Genotype-guided individualised dosing
Rare-disease / trial cohorts	Small, variable populations	Flexible small-batch manufacturing

2.5 Regulatory and Quality Considerations in the Literature

The regulatory conversation has been shaped in part by the recognition that 3D printing does not fit neatly into any single existing category. It sits at the intersection of pharmaceutical manufacturing, compounding and medical-device regulation, drawing elements from each without being fully captured by any. A printed medicine is a drug product, yet the printer is a device, the print file is software, and the act of producing a single unit for a named patient resembles compounding. This categorical ambiguity complicates the assignment of regulatory oversight and has prompted calls for purpose-built frameworks rather than the forced application of legacy rules (Mohapatra et al., 2020). Resolving how additive manufacturing is classified is a precondition for coherent regulation and remains an area of active deliberation among agencies internationally.

As the technology matured, the literature increasingly focused on the regulatory and quality dimensions of manufacturing medicines by 3D printing, particularly when production shifts to distributed, point-of-care settings. This shift in emphasis is telling: the earliest papers concentrated almost exclusively on whether printing was chemically and mechanically possible, whereas the more recent literature is preoccupied with how printed medicines can be governed, quality-assured and integrated into clinical practice. The centre of gravity of the field has moved from the printer to the system surrounding it. Traditional pharmaceutical regulation assumes centralised, well-characterised, batch-based manufacturing subject to established GMP controls, but printing single units on demand in a pharmacy disrupts these assumptions (Trenfield et al., 2018). Authors have highlighted challenges in process validation, content-uniformity assurance for very small batches, in-line quality control, data integrity for digital designs and printer software, and the qualification of printers and excipients as manufacturing inputs (Awad et al., 2020).

Quality control poses an especially acute problem for distributed production. Conventional pharmaceutical quality assurance relies on statistical sampling from large, homogeneous batches, with destructive testing of representative units to confirm identity, assay, content uniformity and dissolution. This paradigm breaks down when a single, unique unit is printed for one patient: there is no batch to sample, and destroying the product to test it defeats the purpose. The literature therefore emphasises non-destructive, in-line analytical methods—near-infrared and Raman spectroscopy, terahertz imaging and machine-vision inspection—that can verify identity, dose and structure during or immediately after printing, ideally enabling real-time release (Trenfield et al., 2018). Data integrity is a parallel concern, because the medicine's specification lives in digital files and printer firmware that must be protected against error, corruption and tampering, extending pharmaceutical quality requirements into the domain of software validation and cybersecurity.

Regulatory agencies, including the FDA, have begun to engage with additive manufacturing, and researchers have called for adaptable frameworks, process analytical technology (PAT) for real-time release, and clear allocation of responsibility between printer manufacturers, software providers and dispensing pharmacies (Mohapatra et al., 2020). A recurring theme is that existing GMP and regulatory structures were designed for centralised industrial manufacturing and do not map cleanly onto a model in which a hospital pharmacy fabricates medicines on demand. Commentators have proposed treating the printer and its validated formulation as a qualified 'system', analogous to a compounding process, with the manufacturer supplying validated print files and materials and the point-of-care site operating under defined, auditable procedures. Whether such models can be reconciled with statutory manufacturing-authorisation requirements remains an open question that will shape the pace of clinical adoption (Beg et al., 2020). Table 5 summarises the main regulatory and quality challenges identified across the literature.

Table 5. Regulatory and quality challenges for 3D-printed medicines

Challenge area	Description	Implication
Process validation	Validating on-demand, low-volume printing	Need for adaptable GMP frameworks
Content uniformity	Assuring dose accuracy in single units	Requires in-line verification
Real-time quality control	Testing without destroying the unit	Adoption of PAT and non-destructive methods
Data integrity	Digital designs, printer firmware, software	Cybersecurity and audit-trail controls
Excipient / printer qualification	Materials and hardware as GMP inputs	New qualification standards
Responsibility allocation	Distributed manufacturing roles	Clear regulatory accountability

Table 6. Comparison of 3D-printing techniques by processing temperature and release capability

Technique	Processing temperature	Thermolabile-drug suitability	Release profiles achievable
FDM	High (150–220 °C)	Low	Immediate to extended
SSE	Ambient–moderate	High	Immediate to modified
SLS	Moderate–high (laser)	Low–moderate	Fast-disintegrating to sustained
SLA	Ambient	Moderate	Modified and controlled
Binder-jet	Ambient	High	Rapid disintegration

Taken together, the literature indicates that 3D printing is technically capable of delivering personalised dosage forms across a broad range of drugs and release requirements, but that consistent quality assurance and a coherent regulatory pathway remain the principal barriers to routine adoption.

Table 7 consolidates the reported advantages and limitations of pharmaceutical 3D printing as a manufacturing paradigm.

Table 7. Overall advantages and limitations of pharmaceutical 3D printing

Advantages	Limitations
On-demand, individualised dosing	Limited validated GMP frameworks
Flexible geometry and release control	Thermal degradation with some techniques
Multi-drug polypills for adherence	Slow throughput vs. mass production
Point-of-care / distributed production	Regulatory uncertainty for point of care
Reduced waste and rapid reformulation	Need for in-line quality control (PAT)
Suitability for rare-disease and trials	Excipient and printer qualification gaps

3. Research Methodology

This paper is a narrative literature review designed to synthesise current knowledge on 3D printing for personalised medicines, with emphasis on formulation strategies, dose customisation and regulatory challenges. A structured search of peer-reviewed literature was conducted across major scientific databases, including PubMed, ScienceDirect, Scopus and Google Scholar, restricting results to English-language publications appearing between 2015 and 2023 to capture developments following the landmark 2015 approval of the first 3D-printed drug product.

Search terms combined controlled and free-text keywords such as '3D printing', 'additive manufacturing', 'personalised medicine', 'dose customisation', 'fused deposition modelling', 'pharmaceutical formulation', 'point-of-care manufacturing' and 'regulatory challenges', joined using Boolean operators. Titles and abstracts were screened for relevance, and full texts of eligible articles were assessed. Priority was given to original research articles, authoritative reviews and regulatory-oriented publications that directly addressed pharmaceutical applications of 3D printing.

Inclusion criteria comprised: (i) direct relevance to pharmaceutical or biomedical 3D printing of dosage forms; (ii) publication within the 2015–2025 window; and (iii) sufficient methodological or conceptual detail to inform formulation, clinical or regulatory discussion. Studies focusing solely on non-pharmaceutical additive manufacturing, conference abstracts lacking full text, and non-peer-reviewed sources were excluded. Extracted information was organised thematically into printing technologies, formulation and materials, dose and release customisation, clinical applications and

regulatory considerations, and was synthesised qualitatively. As a review of published literature, this work did not involve human participants, animal subjects or primary experimental data, and therefore required no ethical approval.

As with any narrative review, certain limitations should be acknowledged. The selection and interpretation of sources involve a degree of subjectivity, and the qualitative synthesis does not permit the quantitative pooling of results that a systematic review or meta-analysis would allow. The restriction to English-language, peer-reviewed publications may have excluded relevant work published in other languages or in the grey literature, including regulatory guidance documents and industry reports that evolve rapidly. Furthermore, because the field is developing quickly, some findings summarised here may be superseded by more recent evidence. These limitations notwithstanding, the thematic approach adopted is well suited to synthesising a heterogeneous, multidisciplinary literature and to identifying the conceptual and practical issues that recur across studies, which is the primary aim of this review.

4. Discussion

The reviewed evidence converges on a clear conclusion: 3D printing is technically capable of producing personalised medicines with individualised doses, tailored geometries and diverse release profiles, and it has already crossed the threshold of regulatory feasibility through the approval of Spritam®. The versatility of the available technologies means that almost any release requirement—from rapid disintegration to extended or pulsatile delivery—can be engineered, and multi-drug polypills offer a genuine route to improving adherence in complex regimens (Khaled et al., 2015; Trenfield et al., 2019).

Yet a persistent gap remains between laboratory demonstration and routine clinical practice. The central tension is between the decentralised, on-demand nature of 3D printing and the centralised, batch-oriented logic of existing pharmaceutical regulation and GMP. Assuring content uniformity and quality in single-unit production, validating printers and software as manufacturing systems, and providing real-time, non-destructive release testing are the pivotal technical challenges (Awad et al., 2020). Advances in process analytical technology, near-infrared and Raman spectroscopy, and machine-vision quality control are promising but not yet standardised for point-of-care use.

Formulation science also continues to constrain the field. Thermal processing in FDM limits the range of compatible actives, and while low-temperature techniques mitigate this, they introduce drying, resolution and mechanical-strength trade-offs. The availability of pharmaceutical-grade, regulatory-accepted polymers and resins remains limited, and long-term stability data for printed forms are still accumulating. Addressing these issues will require coordinated progress across materials science, engineering, analytical chemistry and regulatory science.

A further consideration is the economics and logistics of decentralised production. Distributed manufacturing promises resilience and responsiveness, but it also multiplies the number of sites that

must be qualified, maintained, staffed with trained personnel and subjected to inspection. The cost of equipping and validating printers across many pharmacies, the need for reliable feedstock supply chains, and the training burden for pharmacy staff are practical obstacles that will influence which use cases adopt the technology first. It is plausible that early clinical implementation will concentrate in specialised centres—paediatric hospitals, oncology units and clinical-trial pharmacies—where the value of individualisation is highest and the infrastructure to support quality assurance already exists, before any broader diffusion to community settings occurs (Vithani et al., 2019). Machine-learning approaches that predict printability and optimise formulations may substantially reduce development time and lower the expertise barrier, and such computational tools are likely to be an important enabler of wider adoption (Elbadawi et al., 2020).

5. Conclusion

Three-dimensional printing represents a paradigm shift in pharmaceutical manufacturing, offering an unprecedented capacity to individualise medicines by adjusting dose, geometry, drug combination and release profile on demand. This review has surveyed the principal printing technologies—FDM, SSE, SLS, SLA and binder-jetting—and shown how formulation strategies, particularly polymer selection and coupling with hot-melt extrusion, enable printable feedstocks and tailored performance. The capacity to modulate dose linearly with printed volume and to sculpt release through internal architecture positions 3D printing as a uniquely flexible tool for precision dosing, with clear benefits for paediatric, geriatric, pharmacogenomically distinct and rare-disease populations.

It is worth situating these conclusions within the broader arc of pharmaceutical manufacturing. The industry has periodically undergone shifts in its dominant production philosophy, from extemporaneous compounding to industrial mass production, and more recently towards continuous manufacturing and quality-by-design. Additive manufacturing represents a further inflection, one that reintroduces the individualisation of the compounding era but with the reproducibility, automation and digital control of modern engineering. In this sense, 3D printing does not simply add a new machine to the pharmacy; it invites a reconsideration of what a medicine is—no longer only a physical object mass-produced to a fixed specification, but a digitally defined, patient-specific product fabricated on demand. Realising this vision responsibly requires that the enthusiasm evident throughout the literature be matched by equally rigorous attention to quality, safety and evidence.

The approval of Spritam® confirmed that 3D-printed products can meet commercial regulatory standards, and a decade of subsequent research has broadened the technology's reach. Nonetheless, the transition from centralised proof of concept to distributed, point-of-care personalised manufacturing remains incomplete. The principal barriers are not conceptual but practical: the field must develop validated GMP frameworks suited to low-volume, on-demand production, robust in-line analytical technologies for real-time release, rigorous data-integrity and cybersecurity controls, and clear regulatory pathways that allocate responsibility across printer manufacturers, software developers and

dispensing pharmacies. Only once these quality and regulatory foundations are established will 3D printing fulfil its promise of routine, patient-specific therapy.

6. Future Work

Several priorities should guide the next phase of research and translation. First, validated, GMP-compliant point-of-care manufacturing systems must be developed and tested in real clinical environments such as hospital pharmacies, with standardised procedures for cleaning, calibration and single-unit quality assurance. Second, non-destructive, in-line process analytical technologies—including near-infrared and Raman spectroscopy and machine-vision inspection—should be integrated to enable real-time release testing without sacrificing the printed unit.

Third, artificial intelligence and machine learning offer powerful means to accelerate formulation design, predict printability and optimise print parameters, reducing the empirical burden of developing new products. Predictive models trained on formulation and process data can flag likely failures before printing, narrow the experimental search space and lower the specialist expertise required to develop a new product, making the technology more accessible to non-specialist sites (Elbadawi et al., 2020). Fourth, integration of 3D printing with pharmacogenomic and clinical data would allow genotype- and phenotype-guided dose selection, closing the loop between diagnostics and personalised manufacturing so that a prescriber's decision-support system could translate a patient's genetic and clinical profile directly into a printable dose specification.

Fifth, expanding the library of regulatory-accepted, pharmaceutical-grade printable materials and generating long-term stability data for printed dosage forms will be essential, since the porous and often amorphous structures produced by printing may age differently from conventional tablets and require dedicated stability characterisation. Sixth, robust bioequivalence and clinical-outcome studies are needed to demonstrate that printed personalised forms deliver the intended therapeutic benefit and safety in practice, moving the evidence base beyond in vitro dissolution and small feasibility trials. Finally, close and continuing collaboration between researchers, industry and regulatory agencies is needed to construct adaptable regulatory frameworks, harmonised international standards and pharmacovigilance systems appropriate to distributed manufacturing. Progress across these fronts will determine how rapidly 3D printing moves from a compelling laboratory technology to an established component of routine personalised care.

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