

Personalized medicine via additive manufacturing

Abstract

Additive manufacturing or three-dimensional printing offers an alternative to conventional manufacturing methods that typically produce uniform products for a broad population rather than tailoring to individual patient needs. As such, it is a growing field of exploration with the promise and opportunities it can bring for personalized medicine. This review paper specifically discusses the various methods of additive manufacturing techniques, including extrusion-based methods, vat photopolymerization, powder bed fusion, inkjet printing, and binder jetting. An overview of the interaction between how process-parameters influence final performance is then explored, followed by personalized medicine applications, such as nanoparticle integration. Finally, limitations (regulatory, education, scalability, and cost) and future directions with the implementation of artificial intelligence are examined. Comprehensively, this review encompasses the possibilities and gaps that come along with the intersection of additive manufacturing and personalized medicine.

Keywords: additive manufacturing, 3D printing, personalized medicine, drug delivery, nanoparticles, patient compliance, artificial intelligence.

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Nomenclature

2D	two-dimensional	ML	machine learning
3D	three-dimensional	PAM	pressure-assisted microsyringe
3DP	three-dimensional printing	PEG	polyethylene glycol
AI	artificial intelligence	PEGDA	polyethylene glycol diacrylate
AM	additive manufacturing	PEO	polyethylene oxide
AMF	additive manufacturing file	PLA	polylactic acid
API(s)	active pharmaceutical ingredient(s)	PLGA	poly(lactic-co-glycolic acid)
BBB	blood-brain barrier	PM	precision medicine/personalized medicine
CAD	computer-aided design	PPP	process-property-performance
CIJ	continuous inkjet	PVA	polyvinyl alcohol
DLP	digital light processing	QbD	quality by design
DoD	drop-on-demand	SLA	stereolithography
DPE	direct powder extrusion	SLS	selective laser sintering
EMA	european medicines agency	SSE	semi-solid extrusion
FDA	food and drug administration	STL	standard tessellation language
FDM	fused deposition modeling	UV	ultraviolet
GMP	good manufacturing practice		
HME	hot-melt extrusion		
HPC	hydroxypropyl cellulose		
HPMC	hydroxypropyl methylcellulose		
HPMC-AS	hydroxypropyl methylcellulose acetate succinate		
IONP(s)	iron oxide nanoparticle(s)		
LDL	low-density lipoprotein		

Introduction

Personalized or precision medicine (PM) refers to the practice of tailoring diagnoses and treatment to the individual patient. This approach matters because each patient has different needs for medicine and care based on factors such as age and biological makeup, including metabolism and genetics. Patients also differ in their medical history, so diagnosing and treating them effectively requires accounting for disease state and comorbidities among other factors.¹

PM has become a growing priority in healthcare, and certain changes in manufacturing can further increase the level of personalization and customization available to patients. Traditional large scale manufacturing processes for medications have largely

maintained a one-size-fits-all approach to therapeutics,² and a standard pill can work well for adult patients with typical metabolism and a straightforward diagnosis. However, this approach quickly becomes inefficient in several situations. Pediatric populations often need different dosage forms with different organoleptic properties to improve patient compliance;³ geriatric populations may struggle with deglutition for certain medications;⁴ and patients with complex or progressive diagnoses and comorbidities may require staggered pill regimens with specific dosage amounts that are not available in commercial formulations.

The development of three-dimensional printing (3DP) and additive manufacturing (AM) in recent years has opened a path to address this gap. While 3DP cannot yet be translated directly into clinical practice, it holds promise to reshape the field. This is largely due to its ability to control release rates, APIs (Active Pharmaceutical Ingredients), dosage amounts, shape, color, and properties of a dosage form through printer settings and process-property-performance (PPP) relationships. The incorporation of AI (Artificial Intelligence) can further improve optimization during the prototyping of 3DP medications and support their implementation in real world settings (Figure 1).

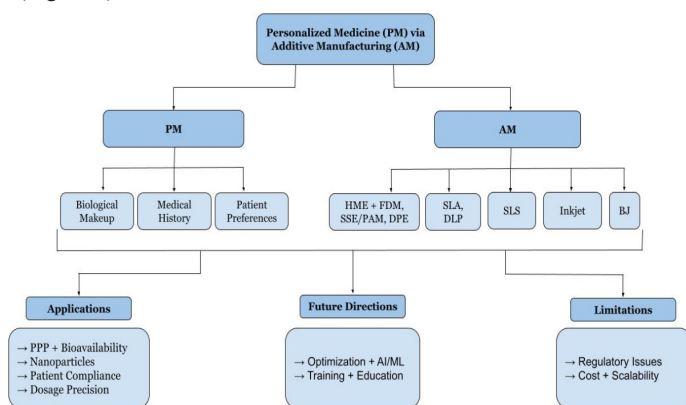


Figure 1 Flowchart of thematic sections discussed in the review paper.

Additive manufacturing

While subtractive manufacturing methods include cutting and removal of material to create finalized products such as drilling² and formative manufacturing involves re-organizing and shaping the same material into an end product,⁵ additive manufacturing, as the name suggests, creates an end product by adding material and building it layer by layer.⁶ There are many variances between the types of 3DP methods. But a general outline of how additive manufacturing works for making drug delivery vehicles in a pharmaceutical context starts by understanding what the end product should achieve and pinpointing the API or material to be used, a stage referred to as lead discovery.⁷ This idea is then built into a digital three-dimensional (3D) model using computer-aided design (CAD) software and saved as a file, typically in standard tessellation language (STL) format or additive manufacturing file (AMF) format. That file is divided into thin 2D horizontal cross-sections, which enables the layer-by-layer construction characteristic of 3D printing. The chosen material is loaded into the printer, which forms the object one layer at a time by following these cross-sectional instructions. Once the build is finished, the product goes through additional post-processing steps, such as drying or dusting, to reach its final usable form (Figure 2).

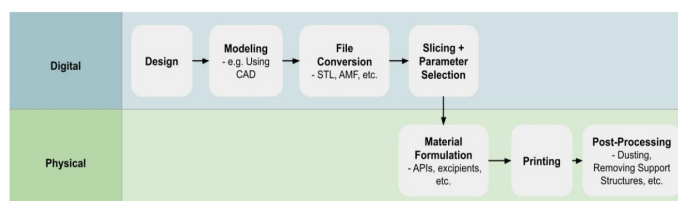


Figure 2 General Digital and Physical Workflow of 3DP methods.

Extrusion based printing methods

Extrusion based printing methods are one of the most commonly used categories of 3DP, and their popularity has risen in recent years.⁸ They facilitate printing through the usage of a nozzle, and use a mixture of materials (e.g. APIs, polymers, etc.), to build the final product layer-by-layer. The three main methods that will be discussed are Fused Deposition Modeling (FDM), Semi-Solid Extrusion (SSE) or Pressure-Assisted Microsyringe (PAM), and Direct Powder Extrusion (DPE). Extrusion based printing methods are commonly used for personalized, complex dosage forms,³ creating solid dosage forms, parenteral implants, and tissue engineering.⁴

Fused deposition modeling (FDM): Fused Deposition Modeling (FDM) works by feeding a filament, composed of polymers, APIs, and excipients such as plasticizers and binders, into the machine (Figure 3), where it is heated until the filament melts.⁴ This melted material must reach a semi-liquid state precise enough to extrude smoothly through the nozzle, without cooling so quickly that it clogs, yet remain firm enough to hold its shape once deposited layer-by-layer onto the build platform.^{9,10} Most commercial filaments used in FDM fall within a diameter range of 1.75 to 2.85 μm , and common polymers include cellulose derivatives such as hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC),³ as well as polyvinyl alcohol (PVA), polylactic acid (PLA), and poly(lactic-co-glycolic acid) (PLGA).⁸ FDM is frequently paired with hot-melt extrusion (HME), the process used to manufacture the filament itself, and successful printing depends on maintaining the correct parameters throughout, including nozzle and filament diameter, temperature, infill, extrusion speed, printing time, layer height, and filament composition.^{4,8} Compared to other AM methods, FDM is considered the most cost-effective.¹¹ However, it is not suitable for handling high drug loading.⁸ Additionally, because FDM relies on high processing temperatures, it is not well suited for thermolabile drugs, since API degradation becomes a significant limitation. Goyanes et al.¹² demonstrated this using a commercial water-soluble PVA filament with an operating temperature of 210°C: drug heat tolerance testing (via differential scanning calorimetry and thermogravimetric analysis) showed that 4-aminosalicylate began degrading at 130°C, and subsequent analysis confirmed that half of the drug was lost during printing, whereas 5-aminosalicylate, with a melting point of 278°C, showed no drug loss under the same conditions. Despite this challenge, one way to help offset this limitation is by incorporating excipients with low glass transition temperatures, such as polyethylene glycol (PEG), which can lower the required melting temperature of the filament.⁴

Semi-solid extrusion (SSE): Pressure Assisted Microsyringe (PAM) printing is a type of Semi-Solid Extrusion (SSE) printing that relies on a syringe that extrudes a semi-liquid material using a pressurized air piston⁹ (Figure 4). Because it does not require the high temperatures associated with FDM, PAM is commonly applied in tissue engineering⁴ and can operate at room temperature, making it well-suited to thermolabile drugs.¹¹ However, the paste mixture of drugs, polymers, solvents, and other excipients¹¹ (Figure 5), needs to be heated at 30

°C above the glass transition so that the mixture is evenly heated and has good resolution.⁴ Along with tissue engineering, the method has been applied to a range of personalized medicine formats, including tablets,¹³ medical devices such as patches,¹⁴ parenteral implants, oral films,¹⁵ and chewable printlets.^{16,17} Successful printing depends heavily on key rheological parameters, namely viscosity, viscoelasticity, and apparent elastic limit.⁹ This is because these properties directly influence both the extrusion process itself and the structural integrity of the final product.¹¹ One notable challenge of this method is that the solvents involved can introduce toxicity concerns and drug instability issues affecting the API. Additionally, the resolution achievable through SSE/PAM tends to be lower than other methods, sometimes due to nozzle-related constraints.¹¹

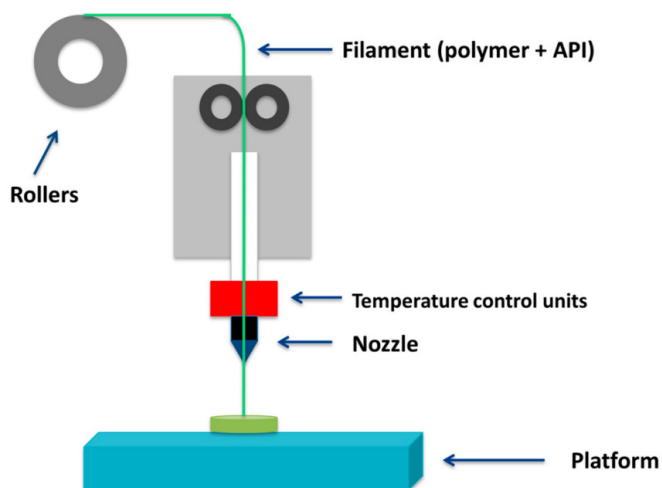


Figure 3 Fused deposition modelling (FDM) printing system. Extracted from author Konta et al.⁹ Copyright © 2018 Konta, García-Piña and Serrano. Licensed under CC BY 4.0.

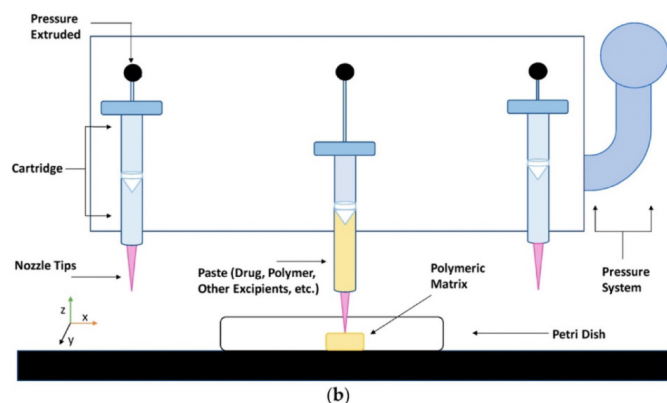


Figure 4 (b) Pressure-assisted microsyringe (PAM). Adapted from author Azad et al.¹¹ Copyright © 2020 Azad, Olawuni, Kimbell, Badruddoza, Hossain and Sultana. Licensed under CC BY 4.0.

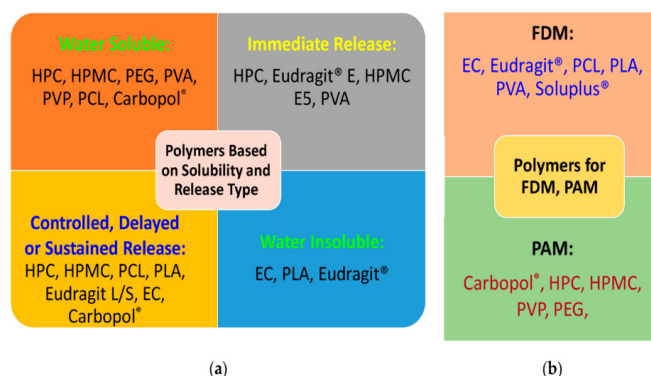


Figure 5 Summary of polymers based on (a) water solubility and drug release type, (b) their selection for either FDM or PAM 3D printing method. Extracted from author Azad et al.¹¹ Copyright © 2020 Azad, Olawuni, Kimbell, Badruddoza, Hossain and Sultana. Licensed under CC BY 4.0.

Direct powder extrusion (DPE): Direct Powder Extrusion (DPE) is a single screw extrusion based technique that serves as an alternative to FDM. Rather than requiring a pre-fabricated filament as an intermediate feedstock, DPE feeds pellets or powder blends directly through the extruder die to the nozzle, with material transport usually governed by screw rotation, however there are also other internal mechanisms¹⁸ (Figure 6). By eliminating the filament fabrication step, this approach reduces the overall process complexity relative to FDM. It also removes the need for an ink phase as required in pressure assisted microsyringe (PAM) printing while still producing parts with high mechanical strength.⁴ From a formulation standpoint, DPE offers several practical advantages. Because feedstock is fed as loose powder rather than as filament, it requires substantially smaller material quantities (on the order of 3.5 to 10 g for single screw systems) which is particularly advantageous in pre-clinical settings where drug supply is limited.¹⁸ DPE also accommodates higher drug loadings with fewer excipients than FDM since FDM formulations must incorporate additional excipients purely to render the filament mechanically printable during the upstream hot melt extrusion (HME) step.¹⁸ Despite these benefits, DPE still presents processing challenges. Achieving compositional homogeneity within the powder blend can be difficult and the technique often demands elevated processing temperatures to reach an extrudable viscosity.⁴ The heat is still comparatively less than FDM.¹⁸ This tradeoff between thermal stability and rheological processability is illustrated in a study by Rosch et al.¹⁹ in which tablets containing Levodopa or Carbidopa were printed via DPE. The resulting tablets exhibited favorable mechanical properties such as high crushing strength but Carbidopa degraded at the temperatures required for extrusion. Lowering the temperature to avoid degradation increased material viscosity more than what could be extruded so no processing window existed that satisfied both thermal stability and rheological requirements simultaneously. Key process parameters for DPE include the rheological behavior of the feedstock (particularly viscosity) and the quantity of feeding material used.¹⁸

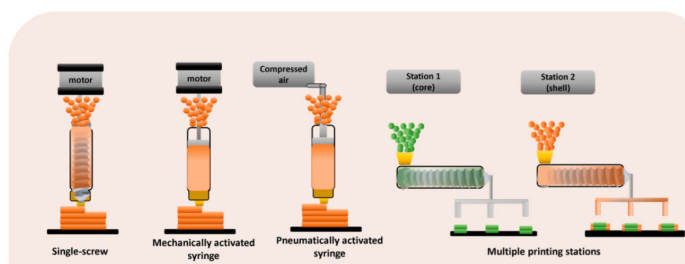


Figure 6 3D printers based on DPE technology. Extracted from author Aguilar-de-Leyva et al.¹⁸ Copyright © 2024 Aguilar-de-Leyva, Casas, Ferrero, Linares and Caraballo. Licensed under CC BY 4.0.

Vat photopolymerization

Vat photopolymerization, sometimes termed Laser-Writing Systems,⁴ belongs to the AM category in which a vat of liquid photopolymer resin undergoes selective solidification layer by layer through exposure to a light source, typically an ultraviolet (UV) laser or a projected UV image.^{2,20} The versatility of the resin's polymer chemistry means this method can produce parts with a wide range of tunable optical, chemical, and mechanical characteristics.²¹

Stereolithography (SLA): Stereolithography (SLA) is one of the main techniques that falls under vat photopolymerization (Figure 7). It has been used in a range of applications including microneedles and transdermal patches,^{22,23} hydrogels,²⁴ and implants such as tissue engineering scaffolds.²⁵ One strength of SLA is its potential for very high resolution.²⁶ While commercially available SLA machines typically achieve resolutions around 200 μm , specialized micro and submicron scale SLA systems can achieve much finer resolution. For example, Maruo and Ikuta used two photon initiation of the polymerization reaction to achieve a resolution of 0.43 μm , demonstrating that SLA can potentially be applied down to the micron and submicron scale. Important processing parameters for SLA include the speed of laser curing,⁸ and common materials used include polyethylene glycol diacrylate (PEGDA) and polyethylene glycol (PEG).⁸ Some disadvantages of SLA include potential toxicity, relatively high cost, and the need for post processing after printing.⁸ However, one benefit includes the lower processing temperatures. In a study reported by Wang et al.,²⁷ no drug loss occurred with 4-aminosalicylate, whereas Goyanes et al.¹² found drug loss occurred with 4-aminosalicylate using FDM. This suggests SLA to be an alternative printing method for some thermolabile drugs. However, APIs used in SLA should still be light-stable, as the printing process relies on light-induced curing.²⁸

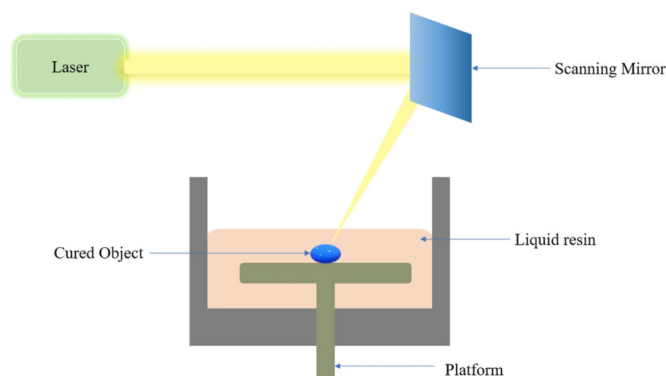


Figure 7 Schematic diagram of working of SLA. Extracted from author Prabhu et al.²¹ Copyright © 2025 Prabhu, Baliga, Shenoy, Dessai and Nayak. Licensed under CC BY 4.0.

Digital light processing (DLP): Digital Light Processing (DLP) is another vat photopolymerization technique. Instead of tracing each layer with a single laser point like SLA, DLP uses an array of millions of digital micromirrors that tilt on and off to project an entire two-dimensional (2D) image onto a cross section of the resin at once (Figure 8).²⁰ The projected UV light triggers the photopolymerization reaction that hardens the resin and forms each new layer.²¹ Because DLP cures a whole cross section at once, its print time depends mainly on the parameters of layer thickness and the light exposure time rather than on the size of the object in the horizontal plane or number of objects being printed.²⁰ This gives DLP a speed advantage over SLA.^{20,21} DLP has also been applied to microneedle fabrication.²⁹

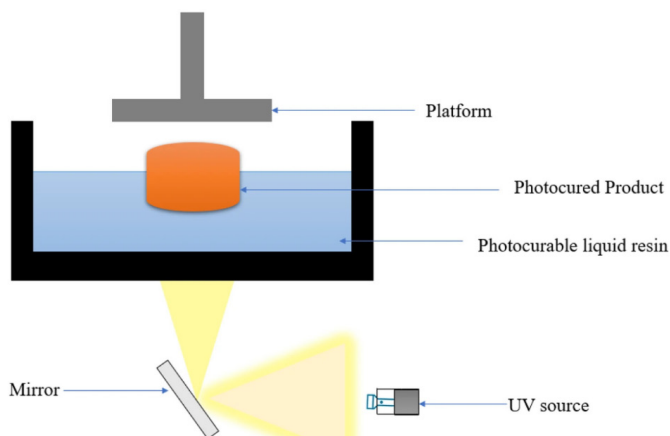


Figure 8 Schematic diagram of working of DLP. Extracted from author Prabhu et al.²¹ Copyright © 2025 Prabhu, Baliga, Shenoy, Dessai and Nayak. Licensed under CC BY 4.0.

Powder bed fusion

Powder bed fusion is an AM category in which a layer of powder is spread across a build platform and selectively fused together, typically using a laser, to build an object layer by layer. Selective laser sintering (SLS) is considered the main example of powder bed fusion.² In SLS, a laser, which can be a CO₂ laser, is directed onto the surface of the powder bed following a predetermined 2D pattern for each layer (Figure 9).^{30,4} The laser heats the powder below its melting point, allowing the particles to fuse and solidify without fully liquefying.⁴ After each layer is completed, a roller spreads a new, even layer of powder over the build area and the process repeats until the object is fully formed.³¹ This method does not require a liquid binder or solvent, distinguishing it from techniques that rely on a spray solution to bind material.^{8,31} Several parameters influence the SLS process. These include the speed and temperature of laser sintering,⁸ along with additional factors such as particle spacing, laser power, refresh rate, and layer thickness.³⁰ Particle size is also a critical parameter. Powders ranging from about 45 to 90 μm are generally considered ideal for SLS printing.³⁰ If particles are too small, static forces between particles begin to interfere with the printing process, and if particles are too large, the powder does not pack as densely and requires more energy to melt.³⁰ However, in pharmaceutical applications, larger particle sizes, around 150 to 300 μm , can also be used intentionally, since they increase the porosity of the final structure, which in turn affects the dissolution behavior. This relationship between particle size, porosity, and drug release will be discussed further in later sections. SLS offers several advantages. Because the unfused powder surrounding each printed layer acts as a natural support structure, SLS does not require the separate support materials needed in techniques such as FDM or SLA.⁴ The precision of the laser also allows SLS to produce objects with high resolution.³¹ SLS is widely used in tissue

engineering applications.³² A significant disadvantage of SLS includes the generation of excess powder, containing unused excipients and active pharmaceutical ingredients (APIs), which must be removed through post processing steps such as shaking and sieving, and this excess material can be costly.^{30,31} In addition, the high energy input from the laser beam can potentially cause degradation of APIs and excipients.³³

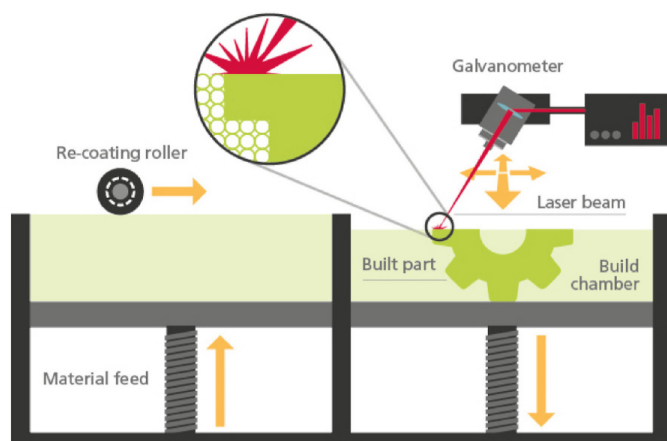


Figure 9 Diagram of SLS process. Extracted from author Ghanizadeh Tabriz et al.³⁰ Copyright © 2023 Ghanizadeh Tabriz, Kuofie, Scoble, Boulton and Douroumis. Licensed under CC BY 4.0.

Inkjet printing

Material jetting is an AM category in which droplets of the actual build material are deposited layer-by-layer to form an object, with inkjet based printheads serving as the underlying deposition technology. Inkjet printing itself can be divided into two main modes, continuous inkjet (CIJ) and drop-on-demand (DoD) (Figure 10), which differ primarily in how droplets are generated.³⁵ Both are considered non-contact techniques since droplets are deposited onto a substrate without the printhead physically touching it.²

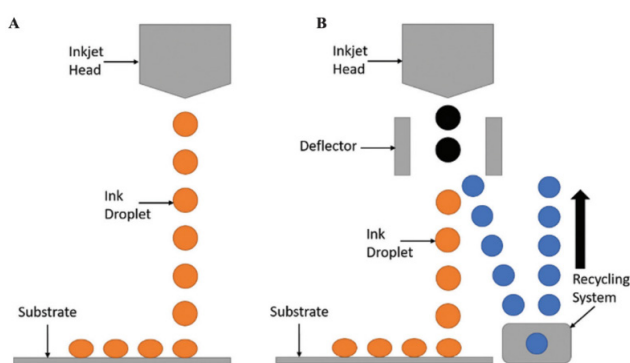


Figure 10 (A) Drop on demand (DoD); (B) continuous inkjet (CIJ). Extracted from author Mancilla-De-la-Cruz et al.³⁴ Copyright © 2022 Mancilla-De-la-Cruz, Rodriguez-Salvador, An and Chua. Licensed under CC BY 4.0.

In continuous inkjet printing, a steady stream of liquid is forced out of a nozzle, often with a piezoelectric transducer positioned behind it, and surface tension naturally breaks this stream into a series of uniformly sized droplets. These droplets are guided to their intended location by passing through an electrostatic field that deflects them as needed. Droplets that are not needed for printing

are captured by a collection channel, sometimes called a gutter, and recycled back into the system for reuse.³⁶ In drop-on-demand printing, a droplet is only produced when triggered by a control signal, rather than continuously. A typical DoD printhead contains more than one hundred nozzles, although some specialized printheads use only a single nozzle. Droplet size in DoD printing is closely tied to the diameter of the nozzle itself, with typical droplet diameters falling between about 10 to 50 μm . Because resolution scales with droplet size, nozzle diameter is an important parameter for controlling print precision.³⁶ DoD systems can generate droplets using either thermal or piezoelectric mechanisms. Thermal printheads rely on rapidly vaporizing a small portion of the liquid to create a pressure pulse that ejects a droplet, which means they only work well with liquids capable of vaporizing appropriately under these conditions. Piezoelectric printheads instead generate the ejection force through a nearby mechanical energy source rather than vaporization, which makes them more broadly applicable across different liquid formulations and represents an advantage over thermal systems in this respect.³⁶ Although not yet widely implemented, several potential drug delivery applications have been proposed for inkjet based printing. These include producing particulate formulations for injectable, inhalable, or liquid based dosing, printing rapid dissolving oral dosage forms directly, and more. Some parameters in this printing process include the viscosity of the printing solution and the nozzle diameter used.³⁶ There are still multiple challenges that need to be addressed: ensuring the mechanical durability of printed dosage forms during packaging and storage, understanding how drugs interact with different substrate materials, determining how ink formulation and printing parameters affect overall print quality, and improving the sensitivity of analytical methods used to characterize printed dosage forms.³⁷ In addition, the usefulness of inkjet printing for drug delivery is limited by the requirement that drugs be formulated as soluble and stable solutions in order to be printable.²

Binder jetting

Binder jetting is the AM technique behind Spritam, the first Food and Drug Administration (FDA) approved 3D printed medication, which uses Aprelia's ZipDose technology to produce fast-dissolving Levetiracetam tablets for treating epilepsy. In this process, a liquid binder is selectively applied onto a bed of powder, and this deposition happens one layer at a time, gradually building up a complete 3D object as each successive layer of powder is bound in the desired pattern³¹ (Figure 11). The powder bed itself typically consists of powdered excipients or a blend containing the active drug.² Because the binder is applied as a liquid rather than as a heat based method, this process avoids the high processing temperatures required by techniques such as FDM or SLS. However, a challenge is that it still relies on a solvent to function.² This makes binder jetting comparatively gentler on heat sensitive, or thermolabile, drug compounds. Printability in binder jetting depends mainly on two properties of the powder and binder solution being used. The first is bindability, or how well the binder is able to hold the powder particles together, and the second is wettability, or how effectively the liquid binder spreads into and interacts with the powder.³⁹ These two parameters largely determine whether a given powder and binder combination will produce a structurally sound printed part. Binder jetting has been applied to a range of pharmaceutical uses, including oral dosage forms, tablets with complex internal geometries, and fast dissolving granules. It is also flexible enough to accommodate both low dose and high dose tablet formulations.⁴⁰

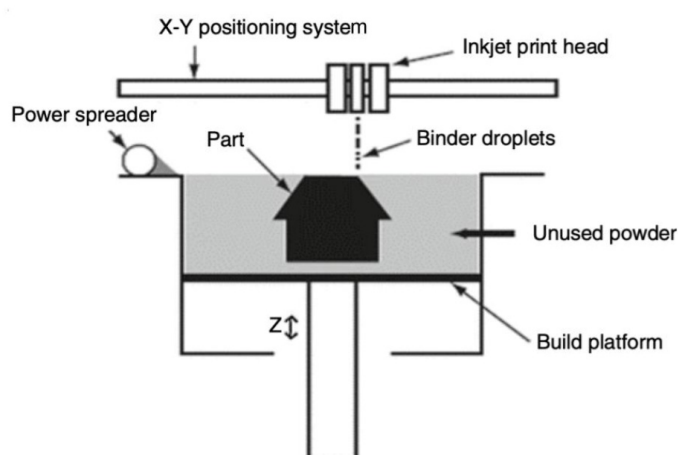


Figure 11 Schematic of the binder jetting process. Adapted from author Chiririwa.³⁸ Copyright © 2021 Chiririwa. Licensed under CC BY 4.0.

Table 1 provides examples of current research-stage applications of 3DP.

Table 1 Examples of research-stage 3DP applications

Active ingredient(s)	Dosage form	3DP method	Reference
Pravastatin, atenolol, ramipril, aspirin, and hydrochlorothiazide	Polypill	SSE	Khaled et al., ⁴¹
Catechin	Orodispersible film	SSE	Tagami et al., ¹⁵
n/a	Dental Implant	SLS	Tunchel et al., ⁴²
Insulin	Transdermal Patch	SLA	Economidou et al., ²²
Lamotrigine	Chewable tablet	SSE	Tagami et al., ⁴³
Ibuprofen	Hydrogel	SLA	Martinez et al., ²⁴
Lidocaine	Tissue Scaffold	PAM	Shao et al., ⁴⁴
Timolol maleate	Contact Lenses	HME + FDM	Mohamdeen et al., ⁴⁵

Note: Spritam® (levetiracetam) is the only FDA-approved 3D-printed drug. It is an oral dissolving tablet manufactured by Aprelia Pharmaceuticals, LLC using ZipDose® technology, a binder jetting 3DP process.

Process-properties-performance (PPP)

The process-property-performance (PPP) relationship describes how deliberate adjustments made at the level of printing parameters (process) affect the measurable physical characteristics of the printed dosage form (properties), which in turn determine how that dosage form behaves once administered (performance).⁴⁶ Essentially, a process variable, such as infill density, layer height, print speed, or laser power, is a mechanism through which specific properties, such as porosity, tensile strength, or crystallinity, can be intentionally engineered into the final product. These resulting properties then control performance outcomes relevant to drug delivery, including dissolution rate, release timing, and mechanical durability.

This PPP relationship is what distinguishes AM from conventional pharmaceutical manufacturing methods, since it allows for a level of granular, patient-specific control that traditional mass-production techniques do not accommodate. Rather than treating a dosage form's behavior as fixed once a drug and polymer combination is selected,

the PPP relationship treats performance as a characteristic that can be changed by adjusting process parameters. Later sections will examine the PPP relationship across several distinct personalization goals, such as nanoparticle applications, and patient adherence and compliance.

However, before considering specific personalization goals, it is useful to establish that this controllability is not limited to a single printing method, but holds across the various AM techniques previously discussed. Yang et al.,⁴⁷ using DLP, found that a thinner layer height (0.02 µm) produced greater external detail accuracy, whereas a thicker layer height (0.05 µm) was better suited to preserving internal channel patency, since fewer total light exposures meant less stray light hardening resin where it was not intended to cure. This shows how process parameters like layer height can be adjusted to achieve different properties in the dosage form (in this case external detail accuracy and inner channel patency).

Speed-related parameters produce a comparable effect. Bom et al.⁴⁸ found that reducing SSE print speed from 30 mm/s to 20 mm/s improved dimensional accuracy on tall, cylindrical geometries by

preventing adjacent layers from fusing together before fully setting. In SLS printing, laser speed exerts an even more direct influence on the resulting tablet's internal structure: Trenfield et al.⁴⁹ found that a slower laser speed (100 mm/s) produced only 19.02% void space compared to 28.87% at a faster speed (180 mm/s), with the denser tablet correspondingly exhibiting greater strength. Pešić et al.⁵⁰ found this same relationship held even with temperature introduced as an additional variable, as slower laser speeds combined with higher surface and chamber temperatures increased tablet breaking strength to as much as 70.8 N, while faster, cooler conditions instead produced more porous tablets with lower hardness values. Across these examples, printing parameters that might otherwise be treated as minor technical settings are, in practice, direct mechanisms for controlling the physical structure of the final product, which is what makes personalization possible.

Additionally, one of the clearest illustrations of the PPP relationship is the conversion of a drug from a crystalline to an amorphous state. Since crystalline drugs are poorly soluble, converting them to an amorphous state allows for faster dissolution.

While changes in settings were not drastic, Pešić et al.⁵⁰ found that altering temperature and laser speed parameters in SLS allowed for more amorphization of the drug carvedilol. Specifically, higher temperatures and lower laser speeds allowed for more bioavailability of the poorly water-soluble drug.

Hamed et al.⁵¹ applied the same strategy to lopinavir, an antiretroviral used to treat HIV that is otherwise slow to dissolve in its crystalline form. Using SLS, Hamed et al.⁵¹ found that as laser scanning speed increased from 75 to 100 mm/s, crystalline fraction also increased. This means slower laser scanning speeds resulted in the amorphous formulation because of greater laser exposure time and powder interaction, which improved dissolution. Another example of improved dissolution is shown in Goyanes et al.'s^{16,17} study where they utilized DPE to produce sustained-release itraconazole (a drug with low solubility) tablets as an amorphous solid dispersion because of the lower molecular weight and viscosity of the ultra-low HPC excipient.

A drug's release timing can also be controlled without modifying the drug itself, simply by adjusting how densely the tablet is constructed. Zhang et al.⁵² found that a thinner shell and lower infill (0.4 μm shell, 25% infill) released drug more quickly than a thicker, denser tablet (1.6 μm shell, 75% infill). Thakkar et al.⁵³ found an even sharper contrast using HPMC-AS: tablets printed at 20% infill released over 85% of their drug within two hours, while identical tablets printed at 80% infill released only about 30% over four hours. Bhingoli et al.⁵⁴ observed the same pattern with *Bacopa monnieri*, where 10% infill released 99% of the drug within four hours compared to a much slower twelve-hour release at 100% infill. Across these studies, infill percentage consistently emerges as a process parameter that can increase density (property) and therefore release speed (performance).

This same controllability has also been applied to a more specific formulation challenge: keeping a tablet buoyant in the stomach long enough to extend drug absorption. Li et al.⁵⁵ used infill percentage, without any chemical gas-generating agents, to control how long a tablet remained afloat: tablets printed at 30% and 50% infill floated for more than twelve hours, those at 70% infill floated for roughly eight hours, and a fully solid tablet sank immediately. The 50% infill formulation proved the most effective balance of floatation and sustained release for the drug dipyrindamole.

However, when noticing this pattern, it is important to consider a meaningful finding from Goyanes et al.¹² Goyanes et al.¹² found that for 4-aminosalicylate, lower infill (10%) released the drug fully

within four hours while higher infill (50%, 90%) released more slowly, consistent with the pattern observed above. On the other hand, when the same infill levels were tested with 5-aminosalicylate, a closely related compound, all three infill levels reached full release within four hours regardless. This suggests that infill's influence on release is filtered through the individual drug's own solubility and its interaction with the polymer matrix, meaning infill must still be calibrated to the specific drug involved.

Personalized medicine applications

This section discusses how AM can be integrated to advance PM, starting with the incorporation of nanoparticles.

Nanoparticles

Nanoparticles are an emerging area with significant potential for future applications. For example, the small scale of iron oxide nanoparticles (IONPs) allows them to cross the blood-brain barrier (BBB), positioning them as a promising candidate for targeting brain tumors such as glioblastoma.⁵⁶ This is further advanced through the fact that IONPs exhibit superparamagnetic properties that allow them to generate a hyperthermic effect. In a study done by Álvarez-Olcina et al.,⁵⁷ they found that when IONPs were embedded into FDM PLA/hydroxyapatite scaffolds, an external alternating magnetic field can heat the scaffold to therapeutic temperature ranges, 42–50°C to induce tumor cell apoptosis, or 50–55°C for antibacterial effect, without inducing cytotoxicity.

Another application includes nutrient supplementation. Santos et al.⁵⁸ successfully integrated nanoparticles in 3DP. They mixed IONPs with the polymer PVA and using HME paired with FDM, they printed tablets (printlets) for oral iron supplementation.

Fang et al.⁵⁹ extended this application range even further, embedding minoxidil-loaded iron oxide nanoparticles into dissolvable DLP printed microneedle patches for treating androgenetic alopecia. Because the nanoparticles were paramagnetic, an external magnetic field could trigger localized heating and accelerate drug release on command, more than doubling release compared to conditions without magnetic stimulation.

With a type of nanoparticle other than IONPs, Doadrio et al.⁶⁰ demonstrated using mesoporous silica nanoparticles as a carrier to give each drug within a four-drug polypill (which is a solid dosage form with more than one API) its own distinct release behavior. Hydrochlorothiazide, intended for rapid action during a hypertensive emergency, released over 80% of its dose within five minutes, while the remaining three drugs released gradually to support long-term blood pressure and LDL cholesterol management. The nanoparticle carrier also extended each drug's chemical stability more than the body's typical metabolism window, illustrating that nanoparticle integration can be used to engineer both when a drug acts and how long it remains chemically stable within a single dosage form.

Ultimately, combining nanoparticles and additive manufacturing can lead to progress in both personalized medicine and healthcare, and it is a valuable intersection to explore further.

Patient adherence and compliance

Patient adherence and compliance is important. For example, Kim et al.,⁶¹ tracking over 33,728 adults in South Korea who were newly diagnosed with hypertension over several years, found that patients with intermediate medication adherence faced a 39% higher risk of all-cause mortality than those with good adherence, while patients with poor adherence faced a 75% higher risk. Additive manufacturing

supports adherence and personalization by consolidating multiple medications into a single solid dosage form, a polypill. This can help reduce the burden of managing a complex regimen. For example, polypills can increase patient compliance for progressive conditions such as Alzheimer's disease and other complex neurological disorders like Epilepsy that require multiple medications (Figure 12).⁶²

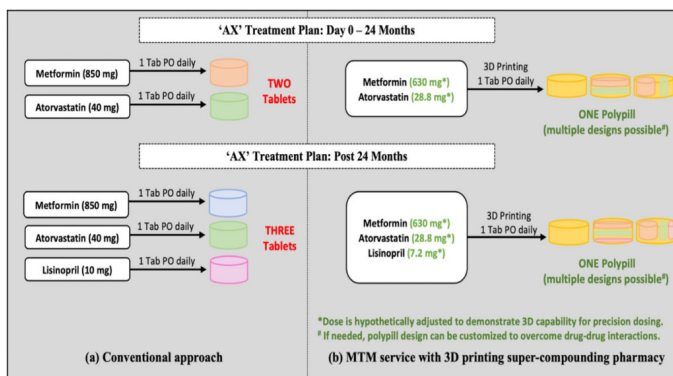


Figure 12 Multiple chronic diseases management plan for patient AX by (a) conventional approach, (b) MTM service using 3D printing super-compounding pharmacy approach. Extracted from author Desai et al.⁶³ Copyright © 2026 Desai, Bang, Wang, Chan, Hsu, Hata and Prabhu. Licensed under CC BY 4.0.

Robles-Martinez et al.⁶⁴ demonstrated this technically by modifying printer software to pause mid-print, swap in a different drug reservoir, and resume without misaligning the tablet, producing a six-drug polypill in under thirty minutes. Lafeber et al.⁶⁵ used a similar approach to combine four cardiovascular and cholesterol medications into precise, individualized doses within a single tablet. Khaled et al.⁴¹ went further structurally, designing a five-drug polypill with separate immediate-release and sustained-release compartments, allowing a single tablet to deliver both fast-acting and long-acting medications on two distinct timelines.⁶⁵

Dosage form and precision

Adherence also depends on whether the dosage form itself is something a patient is willing and able to take consistently. Bhingoli et al.⁵⁴ addressed this by combining the polymers Klucel Fusion™ and Plasdone™ S-630 Ultra with Bacopa monnieri in a way that preserved the drug's activity while masking its bitter taste; in vitro testing showed the drug released below the recognized bitterness threshold within thirty seconds of simulated oral exposure. This taste-masking is particularly relevant for populations, such as children, who might otherwise reject or resist the medication altogether.

Additionally, the format of the dosage form itself can matter just as much as its flavor. Tagami et al.⁴³ demonstrated this by 3D printing chewable gummy medicines in eight distinct shapes, including stars, hearts, diamonds, and donuts, using various food colorings, without compromising the gummies' structural integrity. This visual customization allows a medication to be tailored to the patient's comfort and willingness to take it (Figure 13).

Dosage precision presents a related but distinct challenge. Pediatric and geriatric patients frequently require doses that fall outside standard commercial tablet strengths, and pill-splitting, the common workaround, is often unreliable. Oliveira et al.⁶⁷ addressed this by 3D printing tablets with intentional score marks built into their geometry, designed specifically to guide an even split, and found that these printed tablets held up far better than commercial ones: FDM printed tablets maintained under 1.5% mass variation even when split into eighths, and binder-jet-printed tablets kept mass variation down to

3.8% for the same split, compared to conventionally split commercial tablets, which lost up to 10% or more of their mass. Bedogni et al.⁶⁸ took a different approach to the same underlying problem, finding that commercial tablets for Chagas disease split by hand lost mass above the FDA-permitted limits in 15% of halved tablets and 60% of quartered tablets. Rather than designing a tablet to be split more accurately, they used FDM to print the drug, combined with a PVA polymer and glycerol plasticizer, directly into individualized dosage strengths from the outset, bypassing the need for splitting altogether.

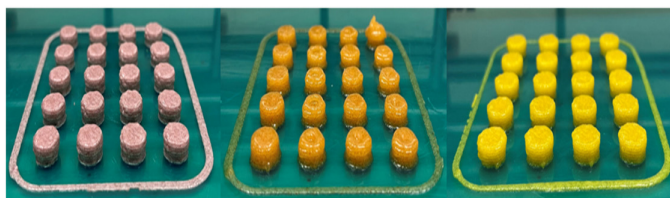


Figure 13 Three-dimensional-printed gummy formulation with the addition of colorants. Extracted from author Veselý et al.⁶⁶ Copyright © 2025 Veselý, Záruba and Elbl. Licensed under CC BY 4.0.

Future directions and limitations

Although 3D printed medicine offers significant promise for personalization, several barriers have so far prevented its widespread translation into clinical practice. Many of these barriers center on regulation, though emerging applications of artificial intelligence (AI) suggest possible paths forward.

Regulatory challenges: destructive testing and batch variability

Much of the difficulty stems from a basic mismatch between how 3D printed medicine is produced and how pharmaceutical regulation was designed to work. Conventional pharmaceutical manufacturing produces large batches of a single, identical product, and regulatory testing reflects this: quality is typically verified through destructive testing, meaning individual sample tablets are physically destroyed during testing to confirm that the batch as a whole meets required standards.⁶⁹ This works reasonably well when thousands of identical tablets are being produced, since a handful of destroyed samples can still represent the batch. But 3D printed medicine is often produced in small batches, sometimes as small as a single patient-specific dose; so destroying a tablet to test it is not a practical model.² Compounding this issue, batch-to-batch variability in the printing process can affect reproducibility, meaning two tablets from the same batch are not guaranteed to be identical, which is a critical concern for regulatory approval.

This is one area where Artificial Intelligence (AI) may offer a path forward, particularly by enabling non-destructive quality control that fits more naturally with a framework called Quality by Design (QbD). QbD is an approach to manufacturing quality that builds quality checks directly into the production process itself, continuously monitoring a product as it is being made. This is a better fit for small-batch, personalized 3DP.

A few early studies illustrate what this kind of AI-assisted monitoring could look like in practice. Wang et al.²⁷ modified an existing computer vision model to detect print defects such as scratches, holes, over-extrusion, and impurities more precisely, by helping the model ignore irrelevant background noise and better localize defects spatially. After training this modified model on thousands of images showing these defect types, it was able to generate a defect report for each layer of an extrusion print as it was being made, correctly identifying problems 91.7% of the time while processing nearly 72

frames per second, fast enough to catch issues in real time rather than only after printing was complete. Lu et al.⁷⁰ demonstrated a related concept, where a camera monitoring a print in progress could detect excessive surface abrasion and automatically adjust the printer's layer thickness by 50 to 100 μm to correct the problem before it worsened. Together, these examples point toward a future in which defects could be caught and corrected mid-print, in real-time, rather than only discovered after the fact, which would support the kind of continuous quality monitoring QbD calls for.

Other analytical tools have also started to emerge as a way to support quality control across different printing methods. Techniques such as micro-computed tomography can verify a tablet's internal geometry, infill pattern, and porosity without damaging it, regardless of whether the tablet was produced via FDM, SLS, or inkjet printing. Spectroscopic methods, including near-infrared, Raman, and terahertz imaging, paired with computational modeling, can rapidly assess how evenly a drug is distributed throughout a tablet, while separate mechanical testing methods can verify the structural integrity of printed devices like microneedles.² Trenfield et al.⁴⁹ demonstrated one such application directly, showing that near-infrared spectroscopy could predict a tablet's density and drug release rate with less than 4.4% error, all without destroying the tablet being tested, a promising sign that these techniques could eventually support the kind of ongoing, non-destructive verification that small-batch 3D printing requires.

Optimization and artificial intelligence

Even before questions of testing and approval come into play, simply identifying the right combination of printing parameters and excipients to address a specific formulation target has traditionally relied on slow, iterative trial and error. Xu et al.'s⁷¹ work on filament "toughness" illustrates this challenge well: toughness, measured through a surface stiffness test, turned out to be the strongest predictor of whether a drug-polymer filament could feed through an FDM printer without snapping or jamming, with a working threshold of about 80 kg/(mm²·%). Filaments falling below this threshold could be brought into a printable range by adding plasticizers such as polyethylene oxide (PEO), HPC, or stearic acid, but arriving at the right plasticizer and concentration to reach that threshold for a given drug-polymer combination still requires extensive experimentation.

This is precisely the kind of problem AI and Machine Learning are well suited to help address, by predicting optimal settings ahead of time rather than requiring researchers to manually test combination after combination. Kadauw trained a neural network on 54 test pieces printed under varying orientation, lifting speed, lifting distance, and UV exposure time, and found the model could predict resulting mechanical properties, including tensile strength, hardness, and surface roughness, with correlation scores above 0.98, and could identify the ideal parameter combination for maximizing strength and hardness while minimizing roughness.⁷² Likewise, Panico et al.⁷³ found that a Random Forest model outperformed traditional statistical approaches by 40% when predicting tensile strength on data it had not seen before, and pairing this model with a genetic algorithm allowed the researchers to identify optimal settings for strength and stiffness, which they then confirmed through physical testing. Chitnis et al.⁷⁴ similarly trained a model to predict which combinations of speed, temperature, infill density, and flow rate would result in zero surface defects. Additionally, Ong et al.⁷⁵ trained a Random Forest model on both failed (to counter the impact of positive publication bias) and

successful filament formulations and found it could predict, with 84% accuracy, whether a given filament would print successfully, while estimating melting and nozzle temperatures within about 5 to 6 degrees Celsius of actual values; the resulting web application M3DISEEN delivered these predictions in 5.76 milliseconds, compared to the days of manual lab testing this process traditionally requires. Taken together, these examples suggest AI-assisted optimization could substantially shorten the formulation development process, though further work would be needed to validate these approaches specifically for pharmaceutical-grade production.

Regional differences and three-dimensional printing locations

There are also regional disparities in regulation. The FDA and European Medicines Agency (EMA) have taken different regulatory approaches to 3D printed drugs. The FDA approved Spritam, the first 3D printed drug to reach the market, establishing at least one regulatory precedent in the United States. By contrast, the EMA has not yet approved any 3D printed pharmaceutical product, and continues to evaluate these products using traditional drug approval frameworks that were not originally designed with 3D printing in mind. But a related question is where production should be physically located if this technology were to scale. Beer et al.,⁷⁶ drawing on interviews with healthcare experts in the Netherlands, found that hospitals and specialized compounding centers were generally considered the most appropriate locations for medical 3D printers, since hospital pharmacists are already trained in custom medicine preparation and compounding centers see enough patient volume to justify the cost of the equipment. Local pharmacies were considered a reasonable secondary option, though they may not print frequently enough to fully justify the investment. Industrial factories, despite their existing infrastructure, were considered poorly suited to personalized production of medicine given strict regulatory requirements around dose uniformity across mass-produced batches, and at-home printing was considered the least viable option of all, raising additional safety concerns such as the potential for unauthorized or illicit drug production.

Training and education gaps

The prospect of placing 3D printers in hospitals and pharmacies raises a related question: whether healthcare professionals are adequately trained to use them. As additive manufacturing becomes more widely adopted in healthcare settings, the training and educational infrastructure needed to support it has not kept pace. One proposed solution is the integration of AI. Sriwastwa et al.⁷⁷ compared ChatGPT's responses to standard educational references on 3DP topics and found that its accuracy was strongest on foundational, undergraduate-level questions, but declined noticeably as question complexity increased, a limitation made more concerning by the fact that its responses maintained a confident tone regardless of correctness. This suggests that while generative AI may be useful for building initial familiarity with 3DP concepts, it cannot fully substitute for the hands-on mentorship and trial-and-error experience that technical printing skills typically require.

Lastly, Kurien et al.³ point to potential for AI in the clinical management of 3D printed treatment going forward, including forecasting patient adherence, and supporting ongoing treatment monitoring through patient feedback loops (Table 2).^{78,79}

Table 2 Summary of possible future directions with AI implementation

Limitation	Current state	Potential changes with AI
Regulatory gaps	Destructive Testing	Real-time monitoring and altering with computer vision/ML
Training gap	Limited 3DP education	Streamlined foundational education with generative AI
Parameter and material selection	Manual trial-and-error (excipients, temperature, speed, etc.)	AI-driven optimization for improved printability and quality
Personalization over time	Static dosing, adjusted only during clinician visits	AI-driven feedback loops for continuous dose/formulation adjustment

Cost and throughput

Cost adds further complication to all of the regulatory and training challenges discussed above. While basic FDM printers can cost as little as 100 to 200 euros, Serrano et al.⁴ note that printing actual medicines requires a reliable decontamination protocol to prevent cross-contamination between batches of different drugs, a requirement that cheaper FDM printers generally are not equipped to meet. As of their review, only one 3D printer operates under full Good Manufacturing Practice (GMP) standards, and it costs around 80,000 euros. This highlights a substantial gap between what a consumer grade printer costs and what pharmaceutical grade production requires.

The production speed for 3D printing is also substantially slower than conventional manufacturing. A standard high-speed tablet press can produce around 240,000 tablets an hour, while binder-jet 3D printing only manages production in the tens of thousands per hour.¹ Because of this speed gap, 3D printing makes the most sense for small, personalized batches and conventional manufacturing remains the better choice for any drug that does not need to be personalized.

Ultimately, while regulatory gaps, cost, production speed, and training barriers currently limit how widely 3D printed medicine can be adopted, none of these challenges appear insurmountable. AI-assisted optimization and non-destructive quality control, in particular, offer a promising path toward addressing many of these limitations without abandoning the personalization that makes 3DP valuable in the first place. As these tools continue to develop and regulatory frameworks adapt to accommodate small-batch, patient-specific production, additive manufacturing may move from a promising research area to a practical part of personalized clinical care.

Conclusion

In summary, there are many barriers that prevent immediate clinical translation and the application of 3DP techniques, which are largely influenced by regulatory constraints. Despite these challenges, 3DP is valuable as a strategy to move away from the “one-size-fits-all” mindset with traditional manufacturing methods and instead move towards customizing and tailoring medication and treatment for the individual. There is a plethora of additive manufacturing techniques that allow for a wide range of applications and personalization, and understanding how to overcome the limitations associated with 3DP, possibly with the integration of AI, is vital to ultimately improve patient care.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed

as a potential conflict of interest.

Author Contributions

AS: Writing – Original draft, Conceptualization.

NMR: Conceptualization, Writing – review and editing, Supervision.

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Generative AI Statement

During the preparation of this manuscript, the authors used Claude Sonnet 5 (Anthropic) to improve language clarity and readability in select portions of the text. All AI-assisted content was reviewed, edited, and verified by the authors for factual accuracy and originality. The initial draft, core ideas, analysis, and conclusions presented in this manuscript are the work of the authors.

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