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A new chapter in pharmaceutical manufacturing: 3D-printed drug products☆,☆☆

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ABSTRACT

FDA recently approved a 3D-printed drug product in August 2015, which is indicative of a new chapter for pharmaceutical manufacturing. This review article summarizes progress with 3D printed drug products and discusses process development for solid oral dosage forms.

3D printing is a layer-by-layer process capable of producing 3D drug products from digital designs. Traditional pharmaceutical processes, such as tablet compression, have been used for decades with established regulatory pathways. These processes are well understood, but antiquated in terms of process capability and manufacturing flexibility. 3D printing, as a platform technology, has competitive advantages for complex products, personalized products, and products made on-demand. These advantages create opportunities for improving the safety, efficacy, and accessibility of medicines.

Although 3D printing differs from traditional manufacturing processes for solid oral dosage forms, risk-based process development is feasible. This review highlights how product and process understanding can facilitate the development of a control strategy for different 3D printing methods.

Overall, the authors believe that the recent approval of a 3D printed drug product will stimulate continual innovation in pharmaceutical manufacturing technology. FDA encourages the development of advanced manufacturing technologies, including 3D-printing, using science- and risk-based approaches.

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1. Introduction

3D printing is layer-by-layer production of 3D objects from digital designs. This technology developed at the confluence of chemistry, optics, and robotics research more than 30 years ago to facilitate the creation of prototypes from UV-cured resins [1]. It quickly became a standard tool in the automotive, aerospace, and consumer goods industries. More recently, 3D printing has gained traction in pharmaceutical manufacturing, illustrated by FDA's approval of a 3D-printed drug product in August 2015 [2]. In the midst of that approval, research interest in 3D printed drug products has been growing [1,3–10]. We prepared this article to compare and contrast 3D printing and traditional pharmaceutical processes, to discuss the potential impact on drug delivery, and to outline considerations for mitigating the unique risks tied to 3D printing. (See Box 1.)

The review article begins with an overview of 3D printing technology. We describe the most common 3D printing methods applied to drug product manufacturing and discuss recent advances in 3D printing technology that affect drug product development.

The next section summarizes the potential benefits of 3D printing for drug delivery. Literature references for 3D printed drug products are organized in three topical areas — increased drug product complexity, personalization, or on-demand manufacturing. For each topic area, we speculate on how 3D printed drug products might improve on the existing standard of care.

The final section investigates how the uniqueness of 3D printing technology impacts process development. Because 3D printing is unlike any other pharmaceutical process, special consideration must be given to the control strategies for raw materials, process parameters, and manufacturing defects.

2. 3D printing technology

2.1. Terminology

2.1.1. Drug product

A drug product means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients [11]. 3D printing of drug products, therefore, refers to printing finished products from active pharmaceutical ingredients and excipients rather than synthesizing drug substances in a step-wise, computer-controlled manner. 3D printing can produce other regulated products which do not contain drugs such as tissue cultures and medical devices. These products, which have distinct quality and regulatory considerations, are outside the scope of this review.

2.1.2. 3D printing

According to the United States Government Accountability Office (GAO), 3D printing produces 3D objects from digital models using a layer-by-layer process [12]. With a change in the underlying digital model, the same 3D printing equipment can print a limitless variety of products.

3D printing is synonymous with “rapid prototyping”, “solid free form fabrication”, and “additive manufacturing”. In response to calls for standard terminology [13], the American Society of Mechanical Engineers is adopting “additive manufacturing” as a preferred term instead of “3D printing” [14]. For pharmaceutical manufacturing, this could create confusion with additive processes such as coating, capsule filling, or film lamination. Whether it is called “additive manufacturing” or “3D printing”, the critical distinction is that the final structure emerges from the serial addition of raw materials, largely independent of the equipment or raw material geometries.

2.2. Commonalities among 3D printing methods and comparison to traditional manufacturing

Several different 3D printing methods exist with different input materials and operating principles [10]. There is a common denominator, though. Most 3D printing processes follow the same basic procedure for manufacturing solid products from digital designs [15]:

1. Design: The intended product design is digitally rendered. Designs can be rendered in 3D with computer-aided design (CAD) software or in 2D as a series of images corresponding to the to-be-printed layers.
2. Conversion of the design to a machine-readable format: 3D designs are typically converted to the STL file format, which describes the external surface of a 3D model. 3D printing programs “slice” these surfaces into distinct printable layers and transfers layer-by-layer instructions digitally to the printer. For 3D printing methods that produce free-standing objects, software can automatically suggest where to print support material to provide scaffolding for the in-process print.
3. Raw material processing: Raw materials may be processed into granules, filaments, or binder solutions to facilitate the printing process.
4. Printing: Raw materials are added and solidified in an automatic, layer-by-layer manner to produce the desired product.
5. Removal and post-processing: After printing, products may require drying, sintering, polishing or other post-processing steps [16]. At this stage, unprinted material may be harvested and recycled for continued use in the printing process.

In comparison to other pharmaceutical processes, 3D printing is unique in terms of product complexity, flexibility and throughput (see Table 1). As a layer-by-layer process, 3D printing trades throughput for product complexity. As a digital free-form process, 3D printing can trade manufacturing tolerance for personalization. And, as an automated process with minimal operating cost, 3D printing can trade scale for on-demand production. The stark differences between 3D printing and traditional pharmaceutical processes create opportunities for advancing drug delivery.

In the next few sections, we will examine different 3D printing methods used for drug product manufacturing in terms of raw materials, equipment, and solidification. These characteristics, summarized in Table 2, affect the utility of each method for drug delivery applications. Closing this section is a discussion of recent trends in 3D printing that may affect drug delivery research.

2.3. Binder deposition

The primary 3D printing technology used for pharmaceutical production is inkjet deposition on powder beds. Fig. 1 shows an illustration of a typical 3D printing configuration, based upon several literature sources [15,17–19]. In this schematic, inkjet printers spray formulations of drugs or binders in small droplets at precise speeds, motions, and sizes onto a powder bed. Unbound powder serves as the support material for free-standing or porous structures. The liquid formulation inside the printer may contain a binder only, and the powder bed may contain the active ingredient (API) with additional excipients. Alternatively APIs can be jetted onto powder beds as solutions or nanoparticulate suspensions [20]. A recent review article from Université libre de Bruxelles documents what combinations of powder beds and binders have been used to 3D print drug products [10].

The solidification mechanisms for binder deposition are identical to the mechanisms for wet granulation [21]: formation of binder-based bridges between particles or joining of particles by dissolution and re-crystallization. In inkjet printing as in granulation, solvent choice and powder properties can impact the API polymorphic form after drying. Because of its commonalities with granulation, a ubiquitous process in pharmaceutical manufacturing, inkjet deposition on powder beds has a wide scope of processable raw materials and potential drug delivery applications.

2.4. Material jetting

A powder bed is not necessary for 3D printing with inkjets. Inkjets can also print freeform structures that solidify drop-by-drop, similar to stalagmites. Commonly jetted materials include molten polymers and waxes [22], UV-curable resins [23], solutions [24], suspensions [25], and complex multi-component fluids [26]. Material jetting, shown in Fig. 2, differs substantially from binder deposition [10], and it can be more challenging to implement. The entire formulation needs to be formulated for jetting and rapid solidification, and product geometry becomes highly dependent on droplet flight path, droplet impact, and surface wetting [15,27]. One advantage material jetting has over binder jetting and other methods is resolution; inkjet droplets are about 100 μm in diameter and layer thicknesses for material jetting are smaller than the droplet diameter (due to surface wetting, solvent evaporation, or shrinkage). Recognizing this, researchers have printed microparticles for drug delivery using material jetting techniques [28].

2.5. Extrusion

Globally, extrusion is the most widely used 3D printing technology [15] and interest in this versatile method is growing in pharmaceutical manufacturing.

In an extrusion process, material is extruded from robotically-actuated nozzles. Unlike binder deposition, which requires a powder bed, extrusion methods can print on any substrate [29]. However, due to the lack of a powder bed, extruded objects often require excess support material: “rafts” to planarize the build surface or scaffolding to hold up in-process products. A variety of materials can be extruded for 3D printing, including molten polymers [30,31], pastes [32] and colloidal suspensions [33–34], silicones [35], and other semisolids (including food [19]).

A particularly common type of extrusion printing is fused filament fabrication (FFF) [36], also known by the trademarked name: fused deposition modeling™ (FDM®) [15]. Whereas other extrusion systems use liquid or semisolid formulations for printing, FFF systems use solid, polymeric filaments. A gear system drives the filament into a heated nozzle assembly for extrusion (Fig. 3). Aided by inexpensive equipment [37] and use of a relatively [38–40] non-volatile and non-aerosolizing raw materials, FFF systems are, by far, the most popular 3D printing systems for home use. Several of the articles cited in this review relied on low-cost, consumer FFF systems with poly(lactic acid) [41,42], poly(vinyl alcohol) [43–46], and ethylene vinyl acetate [30] as base polymers for the filaments.

Relative to inkjet systems, FFF and other extrusion systems have simpler equipment and greater diversity in input materials — especially complex pharmaceutically-relevant materials such as polymers, suspensions, and silicones. Potential disadvantages include (1) a requirement for heat, solvents, or cross-linking chemistries for processing and solidification, (2) difficult-to-reprocess support materials, and (3) slow printing speed. Extruded material is typically more viscous than jetted material, which can increase the time required to start and stop fluid flow during printing. Also, the entire product and support structure has to be printed. In binder deposition, only the binder solution is printed. Although extrusion technology has limitations, it is simple and versatile, and it has been widely used for 3D printing of drug products [32,41,44–45].

2.6. Powder bed fusion

Powder bed fusion [15,47] involves sintering (partial surface melting and congealing) or binding of high-melting-point particles with a low-melting-point binder. Both cases require heat, which is typically supplied by a laser. A more recent alternative for heating powders is high-speed sintering: inkjet deposition of a dye followed by targeted infrared radiation absorption [48,49]. Powder bed fusion is a more rapid, but also more complex, alternative to extrusion for heat-processable materials such as poly(lactic acid) [50].

2.7. Photopolymerization

Photopolymerization (also known as stereolithography) [15,51] involves exposing liquid resins to ultraviolet or other high-energy light source to induce polymerization reactions. The primary limitation of this technique is the need for photopolymerizable raw materials, which are relatively uncommon in pharmaceutical manufacturing. Also, residual resin can represent a toxicology risk because the uncured material is chemically distinct from the printed product and may contain functional groups that are plausible structural alerts for genotoxicity. In terms of potential advantages, photopolymerization systems tend to be among the fastest and highest resolution 3D printers available [52,53]. An example drug delivery application is 3D printing of photopolymerizable hydrogels [54].

2.8. Pen-based 3D printing

Pen-based 3D printing is an extension of the extrusion 3D printing process where the layer-by-layer assembly is manually-controlled with a hand held device. Researchers are considering this approach for deposition of 3D-structured materials during surgery [55].

2.9. Use of 3D-printed molds

Every 3D printing method has restrictions on what can and cannot be printed in a reasonable amount of time. Creating molds from a 3D printed object may enable drug product manufacturers to fabricate complex objects with non-printable materials [56]. Molding may also speed the process of creating replica dosage units from a single 3D print. 3D printed products can also be shrunken and molded to create micro-scale products from mm-scale 3D prints [57].

2.10. Example 3D printing methods not yet applied to drug product manufacturing

- Directed energy deposition [15] is a process where raw materials are melted by a focused energy source (ex: laser or electron beam) as

they are being deposited. The concept of printing with molten materials is similar to extrusion, but this method allows the use of powders or other raw materials that cannot be extruded.
- Laminated object manufacturing [15] is automated laser-cutting and sheet-by-sheet assembly of products. This process is quick and inexpensive but also low-resolution and more wasteful than most printing methods.
- Electrospinning: electrospun fibers and random woven mats are common in drug delivery research [58,59]. Researchers at Chongqing University in China recently developed a method for controlled, 3D printing with electrospun fibers [60]. Another group at the University of Sheffield developed a combination of extrusion, electrospinning, and sacrificial molding to prepare 3D electrospun structures for tissue engineering [61]. 3D printing with electrospun fibers may be useful for drug product development.
- Voxel printing or rapid assembly [19,62] is a hybrid of 3D printing and assembly where the raw materials include ordered, microstructured parts such as electronic circuits, microfluidic channels, or interlocking subunits. This is a departure from other 3D printing methods which use relatively simple raw materials like powders, liquids, filaments, and semisolids.

2.11. Trends in 3D printing

As manufacturers in different fields gain experience with 3D printing, they are discovering ways to increase speed and resolution, print new materials, and employ process analytical technology and process modeling.

A typical volumetric flow rate for extrusion printing of a mm-scale product is ~2.8 μL/s (90 mm/s for a 200-μm-diameter extrudate [31]). At this rate, a tablet with a total mass of 500 mg and a specific gravity of 1.0 would require at least 3 min of production time per nozzle. In comparison, a tablet press operating at 30 rpm compresses one tablet per punch-and-die-set every 2 s, independent of tablet size. Across all industries using 3D printing, there is interest in increasing printing speed relative to traditional processes. Example advances in this area include:

- Continuous liquid interface production [52], a photopolymerization technique that eliminates the need to make micrometer-level changes in fluid height during processing
- Racetrack printing [63], which eliminates all print head movement and enables the print bed to move at a constant speed. This saves significant time compared to simple extrusion systems, for instance, which have to accelerate and decelerate as they track across a 2-dimensional printing area.
- Contour crafting [64], where a product's exterior surface is smoothed with a blade during printing. This enables printing with much thicker build layers (and higher volumetric flow rates) while maintaining similar surface finish.
- Printing relatively flat products that can be folded and assembled (like origami) into three-dimensional structures [65]. This reduces printing time by reducing the number of printing layers and eliminating the need for support material.
- Printing products on rotating platforms [66], which eliminates the need for support material by printing at various angles such that the in-progress product is self-supporting at all times during printing.

Other researchers are investigating ways to print 3D structures slowly, but with better spatial resolution [67]. One method, two-photon stereolithography [53,68], can achieve sub-100-nm resolution at build speeds of approximately 5000 $\mu m^3/s$ (5 ng/s at a specific gravity of 1.0) [69]. Another method is 3D printing with electrospun fibers less than 200 nm in diameter [70]. High resolution printing methods with slow build speeds may not be practical for manufacturing tablets. But, there are nanostructured drug products under development [71,72] that could utilize nanoscale 3D printing.

Another trend in 3D printing is printing with novel materials and creating material gradients during printing. Advances in the past few years include 3D printing of silicones [35] and stimuli-responsive polymers [73], which have potentially applicability in drug delivery. Researchers are also polymerizing and blending materials during printing in such a way that the final product has a spatial gradient of material properties [74]. A similar concept was recently used to manufacture modified release tablets with a gradient of ethyl cellulose as a rate-controlling excipient [75].

Lastly, researchers are developing models and process analytical technology (PAT) for 3D printing to improve process understanding and characterization. Models for 3D printing can be useful for identifying critical process parameters [76], simulating heat transfer [77], and predicting the state of a powder bed during printing [78]. Another potential use, currently unexplored is using modeling to generate quality-by-design design spaces [79] for pharmaceutical manufacturing.

Process analytical technology (PAT) is defined as a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality [80]. Thermal imaging [81], spectroscopy [82,83], interferometry [84], and ultrasonic inspection [85] have been applied as PAT for 3D printing. Such technologies could enable real-time control of 3D printing processes [81].

In summary, 3D printing technology refers to several disparate processes that share a common link in layer-by-layer, emergent manufacturing. After years of research, there are still improvements being made in printing speed, printing resolution, material selection, and process characterization. The next section discusses how the different methods and recent advances in 3D printing can be applied to drug product manufacturing to benefit the public health.

3. Motivation for developing 3D-printed drug products

In Table 1, we identified three attributes where 3D Printing distinguishes itself from traditional manufacturing processes: product complexity, personalization, and on-demand manufacturing. Not surprisingly, these three attributes drive the development of 3D-printed drug products.

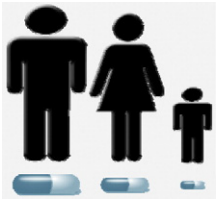
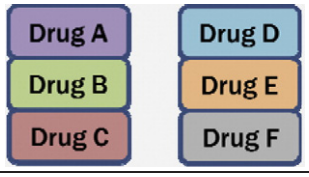
3.1. Increased product complexity

Pharmaceutical dosage forms have evolved in complexity over millennia from harvested botanicals to ointments, powders, and lotions prepared by the Greeks and Romans [86], to compressed tablets, first prepared in 1878 by Dr. Robert Fuller [87]. Dosage form evolution in the 20th century was largely fueled by polymer science, which underpins extended and delayed release tablets, transdermal systems, and long-acting implants. 3D printing of pharmaceuticals, first reported around 1996 [88], introduces a new element into dosage form evolution — digital control over the arrangement of matter. For medicines manufactured with 20th century technology, the distribution of drugs and excipients within a product is controlled almost entirely by blending or film coating. Digital control over the arrangement of matter is a step-change in dosage form evolution that may produce striking changes in immediate release, modified release, and combination drug products.

Because a drug product's structure can affect drug release, complex 3D structures create new opportunities for drug delivery. For instance, the 3D printed drug product recently approved by the FDA, SPRITAM®, has a unitary porous structure produced by a 3D printing process that binds powders without compression. This structure allows tablets

Box 1
Potential benefits of 3D-printed drug products.

Traditional drug products like tablets are simple, uniform, and made for a shelf-life of 2 + years. With 3D printing, pharmaceutical developers are breaking these boundaries. 3D printing can create complex products, personalized products, and products made for immediate consumption. Complex products modify how drugs interact with the patient, which in turn can improve adherence and effectiveness. Personalized products can reduce side effects and simplify treatments for pediatric and elderly populations. On demand products expand the capabilities of emergency medicine and create marketing opportunities for new drugs with limited stability. Overall, 3D printing has great potential to create new therapies and improve adherence, safety, and efficacy for existing therapies. FDA encourages continued development of 3D printed products to realize these benefits.

Benefit category	3D printing capabilities		Example uses for drug delivery	Potential medical and economic benefits
Increased product complexity	Printing un-moldable or difficult-to-make shapes		• Highly porous products that orally disintegrate • Toroidal products with approximately zero-order release	• Improved adherence to medicine • Improved drug effectiveness • Reduced side effects • New therapies based on combination products
	Digitally controlling the arrangement of matter		• Excipient gradients that modify drug release • Control over API polymorphic form during printing • Complex drug-device combination products	
Personalization	Printing an infinite variety of shapes with the same equipment		• Personalized dosing for potent drugs • Personalized dosing for growing children • Drug-loaded implants that match the anatomy of individual patients • Custom SODF shapes for children	• Reduced side effects • Appropriate doses for children • Reduced complications after implantation • Improved pediatric adherence
	Varying composition within simple, modular designs		• "Polypills" that combine different drugs and release mechanisms into single doses • Hollow products with variable in-fill to control drug release rate	• Reduced medical burden for the elderly • Appropriate drug release based on a patient's anatomy and drug metabolism
On-demand manufacturing	Rapid printing from digital designs – no intermediate machining		• Printing in emergency settings • Printing directly onto patients • Reducing barriers to experimentation during drug product development	• Expanded capabilities for surgery and emergency medicine • Reduced time to market for new drugs
	Printing at the point-of-care		• Drugs with limited shelf lives	• New drugs brought to market

with up to 1000 mg of levetiracetam to disintegrate within seconds when taken with a sip of water [2].

Disintegration is only one quality attribute affected by structure. Complex 3D-printed shapes can have speedier dissolution than traditional immediate-release products. Strategies for increasing dissolution rates include printing high-surface-area shapes [44] and printing amorphous dispersions by hot melt extrusion [7,30]. 3D printing may also create new manufacturing options for potent APIs. To solve problems associated with occupational exposure to potent APIs, researchers developed powder-free printing processes that encapsulate API in multiple layers of excipients [7,89]. Others have printed extremely low-dose products containing as little as 3 ng of API with 10% RSD [9]. It is unknown if conventional processes would have better or worse content uniformity at the nanogram level. Fluid bed granulation can

Table 1
Comparison of a common 3D printing process (binder jetting) to other pharmaceutical processes.

Manufacturing method	Example product	Throughput	Dimensional tolerance	Mechanical integrity	Product complexity	Potential for personalization	On demand capability
Compression	Tablet	High	Medium	Medium	Low	Low	Low
Encapsulation	Capsule	High	High	Medium	Low	Low	Medium
Molding	Suppository	High	High	High	Medium	Low	Low
Extrusion	Ocular implant	High	Medium	High	Low	Low	Low
Laser machining	Absorbable stent	Medium	High	Medium	Low	Medium	Low
Coating	Coated stent	Medium	Medium	Low	Low	Low	Low
Lyophilization	ODT*	Medium	Medium	Low	Low	Low	Low
Typical 3D printed drug product made by binder jetting		Low	Low	Low	High	High	High

*Orally disintegrating tablet.
Comparisons for this table were derived in part from opinion and in part from Ref. [137].

produce 1 μg tablets with <5% RSD [90]. But, we are unaware of any studies that compare conventional processes and 3D printing using the same analytical method.

Although 3D printing can be utilized for immediate-release products, the majority of 3D printing research focuses on modified-release (MR) products. For developers seeking greater control over release kinetics and drug targeting, the increased complexity of 3D printing is a powerful tool.

Much of the initial work demonstrated that 3D printing could replicate existing MR solid oral dosage forms (SODFs) such as matrix tablets [31,45], reservoirs with insoluble [91] or enteric [92] coatings, bilayer [93] and coated [46,92] tablets for pulsatile release, and osmotic pumps [32]. More recently, researchers are exploring novel product designs and processes to achieve new release profiles for MR SODFs. Examples in this area include:

- Creating radial gradients of diffusion-controlling excipients such as ethyl cellulose to achieve near-zero-order release [75],
- Conjoining osmotic pumps (composed of cellulose acetate, D-mannitol, and PEG) and hypromellose-based MR structures to create a single product with multiple release modalities [32],
- Varying the in-fill of poly(vinyl alcohol) products as a means of accelerating or decelerating drug release, [45]
- Implementing structured break-away components to deposit different parts of a SODF in different parts of the lumen [92],
- Printing SODFs with all but one side covered by an impermeable membrane so that the dissolvable portion maintains a constant-surface area during drug release [94],
- Stacking six or more distinct layers in a single product for multi-phasic release [46,95], and
- Printing toroidal SODFs that achieve near-zero-order release [44].

We note that, in addition to SODFs, 3D printed implants with complex drug release profiles are also common in the literature [41,96–100].

Arguably, the most complex drug products are drug-device and drug-biologic combination products. Digital control over the arrangement of matter may be particularly useful for manufacturing combination products due to this inherent complexity. On the drug-device side, researchers have printed wirelessly-triggered capsules [101] and magnetically-controlled microtransporters several times smaller than a grain of rice [102] for device-controlled oral delivery. Others propose printing passive, drug-loaded devices such as antibiotic-loaded catheters [42,98] and intrauterine devices composed primarily of ethylene vinyl acetate [30]. For drug-biologic combination products, a common application for 3D printing is drug-eluting scaffolds for pharmacologically-controlled tissue engineering [54,103,104]. With the ongoing, growing interest in combination products [105], we anticipate that researchers will continue innovating with 3D printing in this area.

Table 2
Characteristics of the 3D printing methods used in drug delivery.

		Inkjet printing		Extrusion		Electromagnetic radiation		
		Binder deposition	Material jetting	Fused filament fabrication	Other extrusion systems	Photopolymerization	Powder bed fusion	Use of 3D-printed molds
Printing substrates	Layering mechanisms							
Powder bed	Addition of unbound powder	✓					✓	✓
Freeform	Continual buildup of printed material		✓	✓	✓			✓
Vat of resin	Addition of uncured resin between product and light source					✓		✓
Materials that can be printed	Solidification mechanisms							
Binder solution	Wet granulation	✓						✓
Molten polymers and waxes	Freezing		✓	✓	✓			✓
Photo-curable resin	Photopolymerization		✓		✓	✓		✓
Drug solutions	Solvent evaporation				✓			✓
Drug suspensions	Solvent evaporation				✓			✓
Semisolids	Solvent evaporation				✓			✓
	Polymerization				✓			✓
Fine powder	Sintering						✓	✓
	Freezing of a low-melting binder							

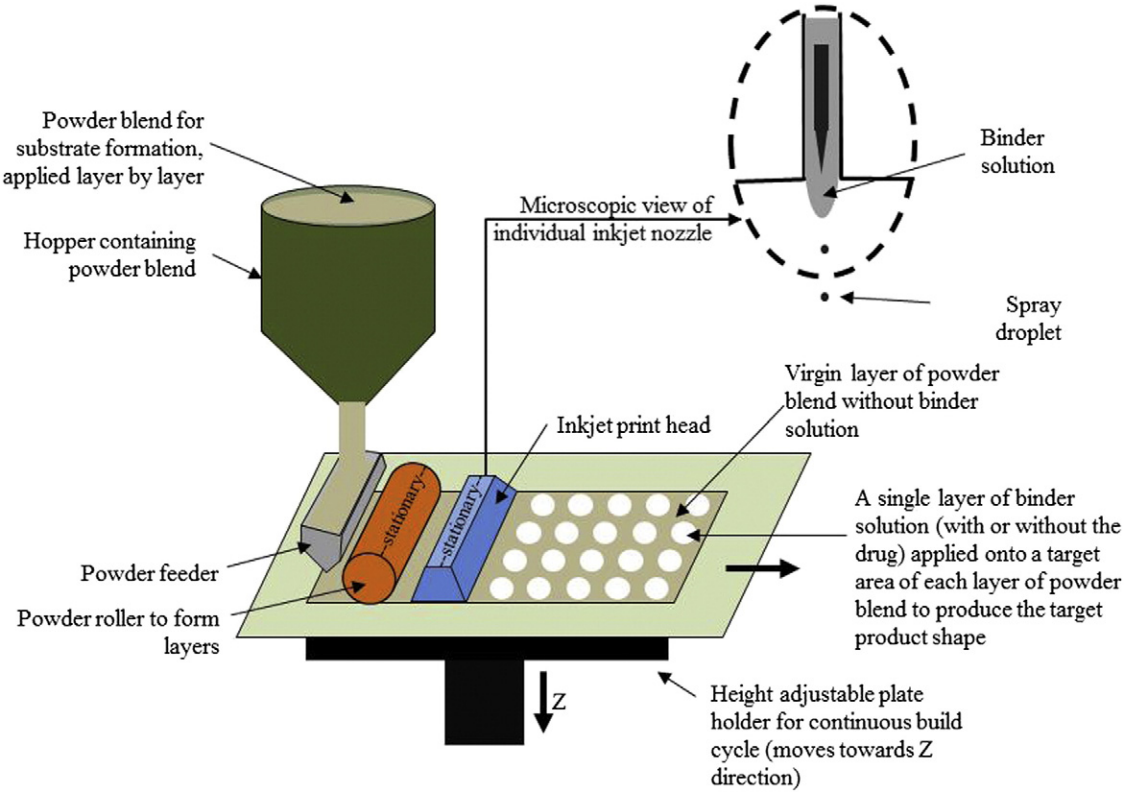


Fig. 1. Schematic of a binder deposition 3D printing process.

3.2. Personalization

Personalized medicine commonly refers to stratification of patient populations based on biomarkers to aid therapeutic decisions (ex: use of Herceptin to treat *HER2*-overexpressing breast cancer [106]), but the term can also apply to personalized dosage form design [107]. Compared to traditional processes, 3D printing facilitates personalization. Modifying digital designs is easier than modifying physical equipment. Also, automated, small-scale 3D printing may have negligible operating costs. In short, 3D printing could make multiple small, individualized

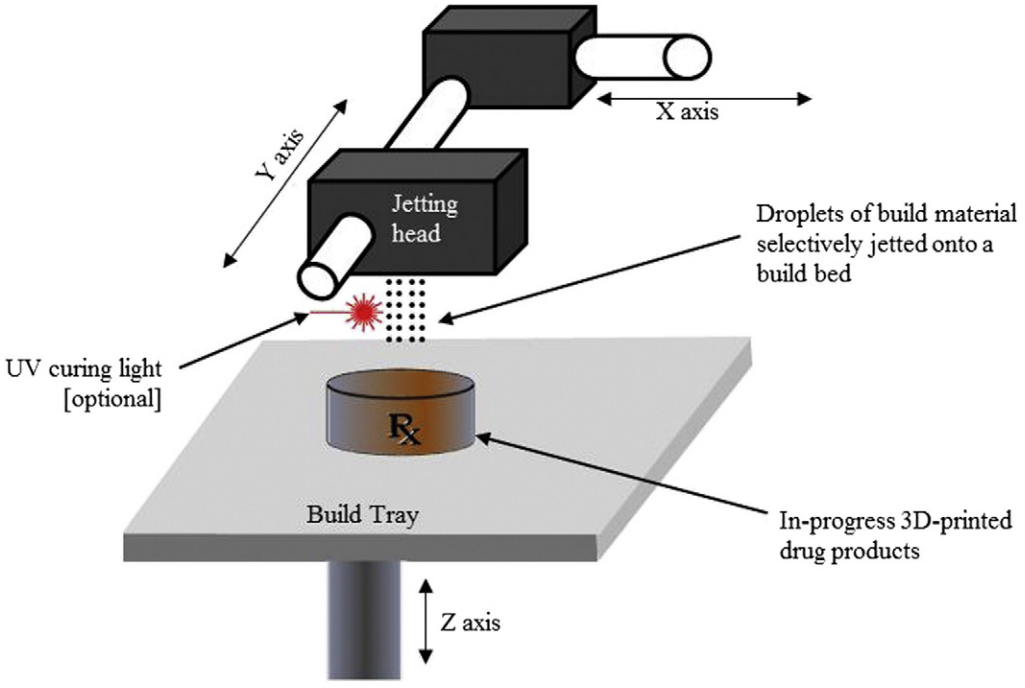
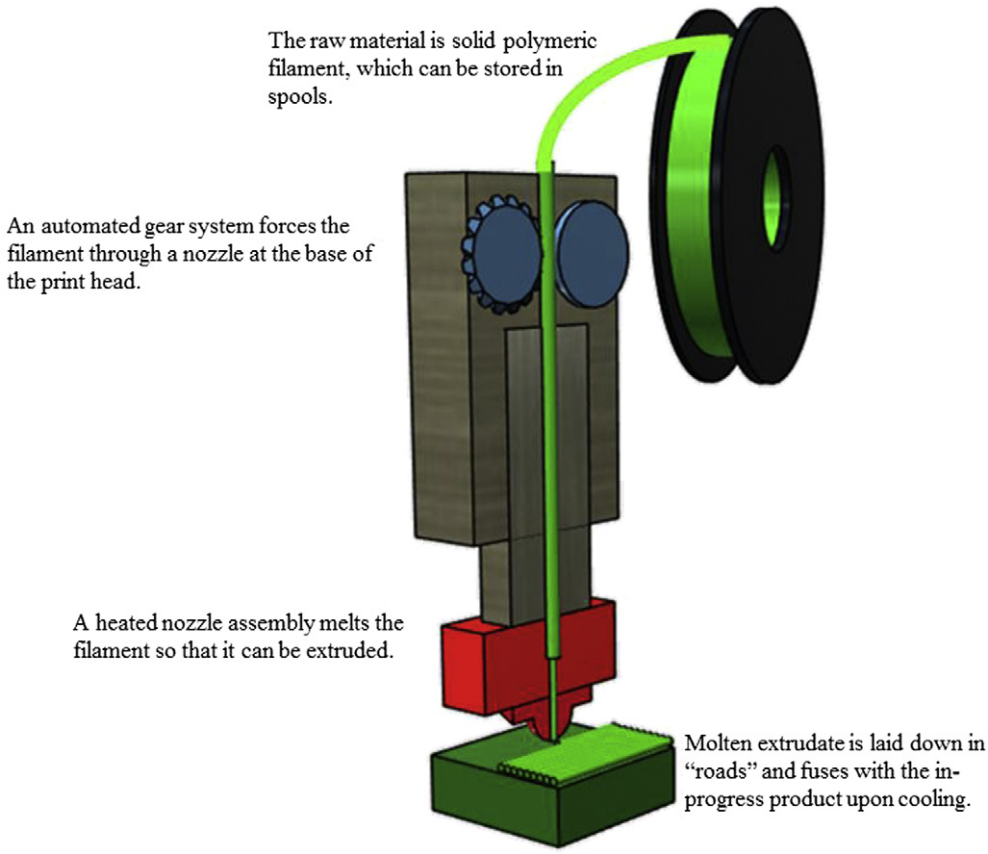


Fig. 2. Schematic of a material jetting 3D printing process.



This figure was adapted from an image available online from the RepRap project (http://reprap.org/wiki/Fused_filament_fabrication).

Fig. 3. Schematic of a fused filament fabrication (FFF) 3D printing process.

batches economically feasible. This mode of production may enable personalized doses, personalized implants, and personalized products designed to improve adherence.

Personalized dosing allows for tailoring the amount of drug delivered based on a patient's mass and metabolism. For oral dosage forms, this is often achieved with simple devices such as powder scoops or mini-tablet counters [108]. However, there are certain indications that could potentially benefit more precise, personalized dosing. 3D printed dosage forms could ensure accurate dosing in growing children [109] and permit personalized dosing of highly potent drugs like theophylline [83,110] and prednisolone [43]. Another personalized dosing concept is printing multi-drug "polypills" to combine all of a patient's medications into a single daily dose [93]. Researchers have also stated the potential importance of personalizing drug release based on patient anatomy and population-level variability in drug metabolism [94,111–112].

Personalization of implants allows for printing implants that match patients' anatomical features. This technique has gained traction for medical devices such as tracheal splints [113] and bone grafts [1]. Drug-loaded, 3D-printed implants are reported in the literature [99, 114], and *personalized* drug-loaded implants are alluded to [115]. Researchers at MIT recently reported on another type of personalized implant: multi-drug implants to screen drugs for chemotherapeutic effectiveness in patient tumors [116]. These types of implants could conceivably be 3D printed since 3D printing excels at creating complex structures with local composition control.

Finally, personalization could improve patients' adherence to medication. To demonstrate this concept, researchers at University College London printed custom, animal-shaped drug products for children [31,117]. The researchers hypothesized that printed figurines "could potentially increase compliance for pediatric patients." With the cost of poor adherence in the United States topping $100 billion per year [118], printing custom drug products to improve adherence has merit.

3.3. On-demand manufacturing

Like a home inkjet printer, a 3D printer can make a variety of quality products within minutes [119]. We found three instances where this on-demand capability could be beneficial for public health — printing directly onto patients, printing in time- or other resource-constrained settings, and printing low-stability drugs for immediate consumption.

Although printing on patients sounds fanciful, extrusion and jetting techniques have been applied to create tissue engineering scaffolds [55] and wound-healing gels [120] on-demand.

On-demand printing could prove useful in time- or resource-constrained settings such as disaster areas, emergency rooms, operating rooms, ambulances, intensive care units, and military operations. Another time-constrained setting is product development. Drug product formulators could potentially adopt a technique from automotive manufacturing where 3D printing is used to generate and test several product iterations within minimal effort [121]. A team from the University of Milan recently used this concept to print and test variations of an injection-molded, delayed-release capsule [122]. This use of 3D printing may enable faster formulation optimization during drug product development.

Printing low-stability drugs with on-demand inkjet printing began as early as 2011 [110,123]. Researchers then applied this concept to

Table 3
Risks and potential control strategies for 3D-printing processes.

3D printing method	Some unique risks associated with 3D printing		Potential controls
General, applicable to most 3D printing methods	Inability to print a given design with a given printer		Software controls
	Variability in layer thickness		Real-time layer thickness monitoring
	Variability in the quality of recycled materials		In-process tests for assay, purity, blend uniformity, water content, and particle size distribution Restrictions on how many times a material can be recycled
	Improper layering due to environmental conditions		Temperature and humidity of the printing environment
	Inaccurate positioning during printing		Print head height Print head speed
	Compositional variation, thermal variation, etc.		Various types of PAT
Binder deposition	Raw material risks	Uneven layers	Powder water content Powder particle size distribution
		Print head clogging	Suspension particle size distribution Real time monitoring of inkjet flow
		Inconsistent binding/agglomeration between layers	Binder viscosity Binder surface tension
	Process parameter risks	Uneven layers	Powder deposition rate Roller speed relative to the powder
		Inconsistent binding/agglomeration between layers	Jetting rate Jetting temperature Liquid fill height in the print head Print head speed relative to the powder Drying time between layers
Fused filament fabrication	Raw material risks	Inconsistent extrusion patters due to variability in raw material rheology	Water content Polymer molecular weight distribution, T_g, composition Melt viscosity Filament uniformity
		Friability after printing	Polymer toughness
	Process parameter risks	Inconsistent extrusion during printing	Extrusion pressure/gear speed Extruder temperature Print head speed
Fusion	Raw material risks	Uneven layers	Particle size distribution Particle shape distribution
		Incomplete fusion, Unintentional fusion across layers	Raw material rheological properties at relevant heating rates and temperatures
	Process parameter risks	Uneven layers	Powder deposition rate Roller speed relative to the powder
		Inconsistent fusion, Laser-induced degradation	Laser energy Laser duty cycle Raster pattern and raster speed

3D printing in 2014 [93]. A University of Nottingham team proposed using "1,2,3-trinitroxypropane (nitroglycerin), a drug used to treat angina pectoris, … noted for its tendency to degrade on storage …. If produced for immediate use this issue is reduced in significance" [93]. Others proposed combining 3D printing with small-scale API synthesis to obviate the need for API storage altogether [119,124–126].

4. Process considerations for solid oral 3D-printed drug products

The first parts of this review showed how 3D printing is unlike any other pharmaceutical process. Nevertheless, 3D-printed drug products must be manufactured according to appropriate quality standards [79]. This section describes how the characteristics of 3D printing technology, described earlier, create a need for unique raw material controls, process controls, and control strategies for solid oral 3D-printed drug products. Three of the most common 3D printing methods are focused on: binder deposition, fused filament fabrication (FFF), and fusion. Table 3 summarizes some of the unconventional risks associated with these processes and discusses what attributes and parameters could be controlled to mitigate these risks.

Implantable products fall outside the scope of this discussion, and readers can refer to the medical device literature to see how 3D printing affects sterility and biocompatibility [127].

4.1. Raw material controls

Controlling the printability of raw materials requires process understanding — insight into the physics and chemistry of the printing process. Selection of raw material controls follows logically from there.

Raw materials for binder deposition include binder (typically a polymer), solvent, and powder residing in a printing bed. Printing begins by forming a uniform powder layer on an existing powder layer with the aid of a rolling pin. Particle size distribution can be critical here, since this property affects layer thickness and the risk of segregation during layering. Water content may also be critical, especially for cohesive powders. After layering, the next step in binder deposition is jetting of small binder droplets. Droplet formation greatly depends on the viscoelastic properties and surface tension of the binder solution. Some jetting systems create droplets with heat or deflect droplets with parallel plate capacitors [15,18,128]. Thermal and electrical properties such as heat capacity, thermal conductivity, capacitance,

and electrical conductivity might seem critical. But practically speaking, these properties should co-vary with concentration for a given binder-solvent system. Infiltration of the binder into the powder bed is also an important raw material property that may depend on powder density and surface energetics [8,129]. Lastly, raw material variability such as particle size distribution can impact the risk of clogs for jetted suspensions.

For extrusion printing, each layer of a 3D product is built line-by-line where layer thickness depends on printing speed, extrusion flow rate, and nozzle diameter. Many different types of materials can be extruded. But, the raw material for FFF is a polymer filament that melts easily before extrusion and solidifies rapidly after extrusion. Viscoelastic properties of the filament are significant, and rheological properties may need to be understood at multiple temperatures [130,131]. Since water is a potent plasticizer of many pharmaceutical polymers, water content may also be critical. If a 3D printed product has a non-standard shape susceptible to fracture, understanding of mechanical properties (such as elastic modulus, yield strength, and toughness) may also be necessary.

Fusion systems heat powder with lasers to induce fusion among nearest neighbors. As a powder-based method reliant on heat, fusion has many potential critical attributes in common with binder deposition and extrusion. However, very little material flow occurs during fusion compared to binder deposition and extrusion. Because of this, contact between particles can be essential to understand. Developers may need to consider particle shape in addition to particle size distribution for raw materials in fusion processes.

4.2. Process controls

This section considers controls for higher risk steps in the 3D printing process including printing, solidification, and recycling of printing material. Generally applicable controls are presented first, followed by specific considerations for binder deposition, extrusion, and fusion.

Although 3D printing methods vary, they can use similar in-process and environmental controls. Controls for equipment design, product orientation, layer thickness, printer height, printing speed, and printing pattern apply to all 3D printing processes. Printing pattern refers to the vector pattern used to fill in a two-dimension section of a printed layer (for example, an orthogonal cross-hatch) [15]. Most 3D printing processes also recycle unprinted materials. So, control strategies might include recycling parameters and in-process tests of recycled material. Process analytical technology (PAT) can be used to monitor layer-by-layer quality for any printing process [80–85]. And lastly, printing operations can be sensitive to water content and solidification conditions. Therefore, controls for temperature and humidity might apply universally. We note that printing in a heated chamber is a technique used to improve layer-to-layer bonding for melt-based processes by extending the amount of time that a molten material remains above its T_m or T_g [8].

For a specific printing method, process development might focus on controlling mass and energy transport. Parameters that control mass and energy transport can affect critical quality attributes [79,132] such as identity, appearance, assay, content uniformity, drug release, impurity level, hardness, friability, crystallinity [22], and API polymorphic form [82].

For binder deposition, transport depends on powder handling and layer thickness, jetting rate, jetting temperature, and drying conditions. For extrusion, transport properties include extruder pressure, extruder temperature, and linear extrusion speed. And for fusion, energy input is a function of laser energy, laser angle of incidence, duty cycle, spot size, and scan strategy [15,81]. This list is not exhaustive, of course, and printers can have additional settings to consider. For example, jetting systems may have control over dot-per-inch resolution or liquid fill height within the print head. In general, if a tunable parameter affects mass and energy transport, it has a high probability of being a critical process parameter.

4.3. Defect control

3D-printed drug products might have novel, equipment-related defects unrelated to raw material and process controls. Consider the following defects, defined in Refs. [15,133,134] and online literature on 3D printing:

- Banding: ripples on a product's sides caused by vibration in the x–y plane during printing
- Leaning: off-axis products caused by drift in the x–y plane during printing
- Warping: product distortion caused by thermal expansion or contraction
- Stringing: wisps of filament caused by filament elongation during an extruder's off phase
- Collapse: loss of porosity caused by sagging layers or excessive mass/energy input
- Residuals: unbound powder or uncrosslinked monomer caused by incomplete printing

Defects can also occur after printing due to relaxation of residual stress [81].

These defects typically depend more on equipment drift than raw material attributes or process parameters. Other defects like jetted suspensions causing clogs in jets can depend more on raw material controls such as API or excipient particle size. If defects affect the appearance or performance of a 3D printed product, it is important to monitor and control for defects during manufacturing or packaging [135]. Defects can also carry over and affect downstream operations such as sterilization and fluid bed coating of 3D-printed objects [136].

5. Conclusion

3D printing is a layer-by-layer, automated process capable of producing complex, personalized products on demand. In recent years, researchers proposed dozens of 3D printing innovations to improve the safety, efficacy, and tolerability of medicines. The commercial feasibility of this technology has been shown through the FDA approval of a 3D printed drug product in August 2015.

While experience with 3D printed drug products is limited and 3D printing techniques are varied, risk-based control strategies are feasible. As always, physical and chemical process understanding guide the choice of appropriate raw material and process controls. Overall, FDA encourages development of complex dosage forms and manufacturing processes, such as 3D tablet printing, using science- and risk-based approaches.

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