CHAPTER

2

Opportunities and challenges of 3D-printed pharmaceutical dosage forms

Adam Procopio[1], *Divya Tewari*[2]

[1]Merck & Co., Inc., Kenilworth, NJ, United States; [2]Noramco Inc., Wilmington, DE, United States

1. Introduction

Drug product development can be a long and complex process. On average, it is estimated that it takes about 10 years and costs US$2.5−5 billion for a new drug product to get to the market [1,1a]. Given this significant investment, and the knowledge that any delay in getting the drug product to the market reduces exclusivity, there is a desire to reduce this development timeline providing an overall benefit to patients and the industry. 3D printing (3DP) can allow for a robust, flexible, and cost-effective approach to drug development in which drug release profiles may be tailored to a particular outcome using a single manufacturing method. Moreover, 3DP allows for custom designs and dosing amounts such that the dosage forms may be tailored to a specific patient population. Due to longer and complex formulation processes, development of delayed or extended release formulations is typically even more prolonged as well as requiring expensive and propriety drug release technology. To date there is only one approved product (Spritam) that uses a 3DP technology based on powder layering launched by Aprecia Pharmaceuticals. There are existing examples of implementing 3DP technology to rapidly prototype release rates using different strategies, largely focused on maintaining a similar material feedstock and using creative printing parameters to generate various releases. With these examples, at least one solid filament material is preprocessed to contain active pharmaceutical ingredients (APIs). Modifications to what is called the "infill" parameters of the printed tablet can manipulate release rates [1b−3]. During a fused deposition modeling (FDM) printing process, the print head will print an outer shell in the shape of the part, and the inside of the shell is largely hollow. The material that is printed on the inside of the shell is called the infill and can be controlled through software by taking into account what percentage of the shell is hollow and the geometric design of the infill (honeycomb, rectilinear, etc.). Other published work involves the changing of the active dosage form's overall shape, size, and surface area, which has

https://doi.org/10.1016/B978-0-12-817870-6.00002-X

shown to modify the release rate [4–7]. Manufacturing of drug product dosage forms that combine a shell-based approach to be described in detail in a later section have demonstrated a unique ability to generate distinct release rates. Such core/shell tablets have been manufactured by using a second API-containing material [8] or a placebo material with the intent to mimic enteric-coated tablets [9,10] and have demonstrated the agility of 3DP to change the onset of the release of the core of the dosage form.

While these approaches have demonstrated an ability to use software for tuning drug release rate while maintaining a constant material feedstock, they are reliant on a successful hot melt extrusion (HME) formulation of a printable filament for each API. Developing process conditions to incorporate API into an excipient-based solid filament is not trivial [11–14], and these filament processing developments add to the product development burden, reducing the rapid prototyping advantage 3DP brings to the table for early drug screenings. A major hurdle the pharmaceutical 3DP field has yet to overcome is providing a wide, distinct range of dosage forms using a universal set of starting print-ready materials to accommodate any API without filament formulation burden, and has even a greater hurdle on aligning manufacturing partners to generate good manufacturing-processed pharmaceutical materials that are printer ready.

2. Materials

Pharmaceutical dosage form design begins with material selection. Because the materials are altered during the 3DP process, it is imperative to understand the source, purity and associated material chemistry changes of the chosen material. Material properties have wide-ranging impact, from influencing the preferred route of manufacturing to the physical properties of the dosage form to its pharmacodynamic fate in the body. A wide range of materials are used as substrates in 3DP; however, because of their origin in industrial prototyping, most 3DP techniques lack availability of suitable developed materials [15].

The successful design and printability of the 3D-printed dosage forms is dictated by the physical, chemical, thermal, and mechanical properties of the chosen material. Additional considerations should be given to ease of availability and the regulatory status of the materials. In the absence of the standard test methods a specifically designed method to characterize the material properties of the additives can be used, and we have compiled current test procedures employed by various researchers and highlighted some of the standard utilized ASTM methods.

The range of polymers used in 3DP include thermoplastics, thermosets, elastomers, hydrogels, functional polymers, polymer blends, composites, and biomaterials [16]. Polymeric materials—polymers—constitute the majority of materials used in 3DP due to several advantages such as low cost, biocompatibility, availability, ease of processing, and physicochemical properties. Material selection is dictated by the choice of the 3DP technology, e.g., polymeric filaments used by FDM must have a constant diameter of 1.75 mm, an ideal melt viscosity to facilitate viscous melt formation preextrusion and solidification postextrusion, and a sufficient elastic modulus-to-melt viscosity ratio to prevent filament buckling and shear thinning tendencies in liquid form [17]. Commonly used polymers include aliphatic polyesters (poly(lactide) [PLA], poly(glycolide), poly(caprolactone) [PCL]), cellulosic derivatives

(hydroxypropylcellulose [HPC], hypromellose [HPMC], HPMC acetate succinate [HPMCAS], cellulose acetate, and cellulose acetate phthalate), vinyl polymers (polyvinylpyrrolidone [PVP] and copovidone), polyethylene oxide, polyethylene glycol (PEG), and acrylic polymers (Eudragit).

Table 2.1 provides an overview of 3DP technologies and desired material properties required for successful development of 3D-printed dosage forms.

2.1 Aliphatic polyesters

Aliphatic polyesters are synthetic homopolymers or copolymers of lactic acid, glycolic acid, lactide, glycolide, and 6-hydroxycaproic acid. Typically, the molecular weights of homopolymers and copolymers range from 2000 to >100,000 Da. The representative chemical structures are provided in Fig. 2.1 and a brief summary of their physical, chemical, and mechanical properties is outlined in Tables 2.1 and 2.2.

TABLE 2.1 Summary of material properties and test methods commonly employed.

Material properties	Key properties	Testing methods commonly employed
Powder physical properties	Particle shape, particle size distribution, bulk and tap densities, crystallinity, moisture content	Laser light diffraction, densitometry, powder X-ray diffraction, differential scanning calorimetry, Karl Fischer, flow index
Mechanical properties	Yield strength, elasticity, modulus, elongation at break	ASTM D638, D3039, D882, ISO 527-2, three-point bend test
Thermal properties	Melting point, glass transition temperature, degradation temperature	Thermogravimetric analysis
Optical properties	Ultraviolet absorption, laser power	
Rheological properties	Viscosity of the solution, binder–powder interaction, melt viscosity, melt index, surface tension	AERS-G2 rheometers, viscometers (USP 911), ASTM D1238

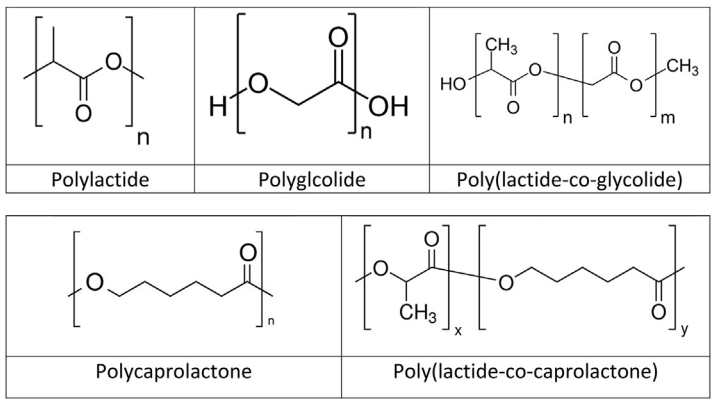


FIGURE 2.1 Representative chemical structures of the aliphatic polyesters.

TABLE 2.2 Typical chemical names and trade names of the representative aliphatic polyesters.

Generic name	Composition			Trade name	Manufacturer
	Lactide	Glycolide	Caprolactone		
Poly(**L**-lactide)	100	0	0	Lactel L-PLA 100L Resomer L206 S, 207S, 209 S, 210 and 201 S	Durect Lakeshore Boehringer Ingelheim
Poly(**DL**-lactide)	100	0	0	Lactel DL-PLA Purasorb PDL 02A, 02, 04, 05 Resomer R 202 S, 202 H, 203 S, 203 H	Durect Purac Boehringer Ingelheim
Poly(**L**-lactide-*co*-glycolide)	85	15	0	Resomer LG 855 S, 857 S	Lakeshore Boehringer Ingelheim
Poly-ε-caprolactone	0	0	100	Lactel PCL 100 PCL	Durect Lakeshore
Poly-(DL-lactide-*co*-ε-caprolactone)	85	0	15	8515 L/PCL	Lakeshore

Adapted from Handbook of Pharmaceutical Excipients.

Aliphatic polyesters are United States Food and Drug Administration (FDA) and European Medicine Agency approved, versatile thermoplastic polymers that are used in a number of 3DP technologies such as FDM, selective laser sintering (SLS), pressure-assisted microsyringes (PAMs), etc. due to their biocompatibility, biodegradability, high mechanical strength and modulus, and processability [18]. Ease of availability and cost effectiveness make aliphatic polyesters highly desirable polymers for 3DP, whereas the main disadvantages are the appearance of rough surfaces and low resolution.

PLA is by far the most widely used material for FDM printing. PLA and its derivatives are poorly water soluble but have good solubility in dioxane, acetonitrile, chloroform, methylene chloride, 1,1,2-trichloroethane, and dichloroacetic acid. The thermal and mechanical properties of PLA are influenced by small amounts of enantiomeric impurities. Amorphous grades were reported to have better processability and a wider processability window but lower mechanical properties [19] (Table 2.2).

PCL is a hydrophobic polymer with excellent blend compatibility with many other polymers such as polyvinyl(acetate), poly(vinylchloride), poly(styrene-acrylonitrile), and poly(acrylonitrile butadiene styrene). Its blend compatibility, biodegradability, low melting point, and solubility make this polymer suitable for precise extrusion deposition and FDM techniques. The only disadvantage of PCL is its hydrophobicity, which might adversely impact drug dissolution characteristics.

2.2 Cellulose ethers and esters

Cellulose is the most abundant naturally occurring polysaccharide. Each polysaccharide unit is linked by β-1,4-glycosidic bonds. Each glucose unit has three hydroxyl groups that can be derivatized and the average substitution grade cannot exceed three. Alkalization of

cellulose, followed by etherification reaction at elevated temperatures and pressures, is used to convert cellulose molecules into their corresponding ether, such as HPC, HPMC, and many other semisynthetic cellulosics. Esterification of the cellulose ethers could be used to derive molecules such as HPMCAS. At the basic level, cellulose derivatives are characterized by their average molecular weight distribution and average composition. Compositionally, these polymers are defined by the percent weight of the functional group attached to the backbone, the degree of substitution per anhydroglucose, or the total molar substitution per anhydroglucose residue [20]. The representative chemical structures are provided in Fig. 2.2 and a summary of their physical, chemical, and mechanical properties is provided in Table 2.3.

Thermoplastic polymers are typically materials of choice in 3DP coupled with extrusion because they can be processed at suitable temperatures without affecting the stability of the APIs [21]. Cellulose esters and ethers have been tested as carriers or matrices for drugs in FDM technology with HME [22]. HPMC in either solution, dispersion, or paste forms has also been used in PAMs printing technology [23].

2.3 Acrylic polymers

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios [24]. Eudragit polymers are copolymers derived from esters of acrylic and methacrylic acid whose

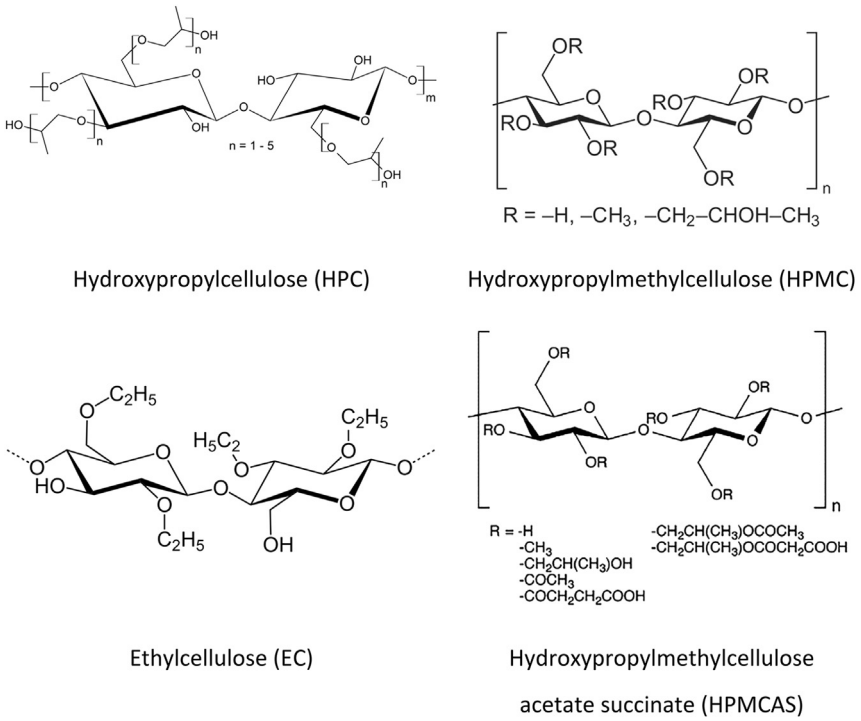


FIGURE 2.2 Representative chemical structures of cellulose ethers and esters.

TABLE 2.3 Typical physical and mechanical properties of the aliphatic polyesters.

Properties	L-PLA[a]	DL-PLA[a]	PGA[a]	PCL[a]	85/15 DL-PLG[a]	8515 L/PCL[b]
Molecular weight (Da)	40,000–100,000	40,000–100,000	>100,000	80,000–150,000	40,000–100,000	
Melting point (°C)	173–178	Amorphous	225–230	58–63	Amorphous	Amorphous
Glass transition temperature (°C)	60–65	50–60	35–40	−65 to −60	50–55	20–25[b]
Color	White	White	Light tan	White	White to light gold	
Tensile strength (psi)	8,000–12,000	4,000–6,000	10,000+	3,000–5,000	6,000–8,000	3,254
Elongation (%)	5–10	3–10	15–20	300–500	3–10	>6.4
Modulus (psi)	$4–6 \times 10^5$	$2–4 \times 10^5$	1×10^6	$3–5 \times 10^4$	$2–4 \times 10^5$	8.4×10^4

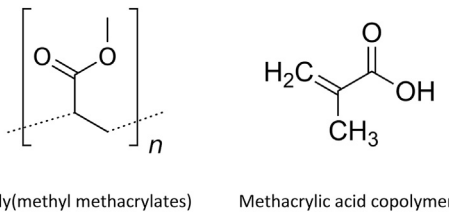
PCL, Polycaprolactone; *PGA*, poly(glycolide); *PLA*, poly(lactide); *PLG*, poly(lactide-co-glycerol).
[a] *Specifications from Durect,* [b] *Specifications from Lakeshore Biomaterials and process temperature range 140–160°C.*
Adapted from Handbook of Pharmaceutical Excipients.

physicochemical properties are determined by functional groups. Several compositional copolymer variants are derived from esters of acrylic and methacrylic acid, whose physical, chemical, mechanical, and thermal properties are determined by the functional groups. The representative chemical structures and summary of typical trade names and suppliers is provided in Fig. 2.3 and Tables 2.4–2.6, respectively.

Acrylic polymers have been used for FDM [11,12], binder jetting additive manufacturing, and SLS printing technologies [25–28].

2.4 Vinyl polymers

Polyvinyl alcohol (PVA) polymers and PVP polymers and copolymers are important members of this product family. PVA is a water-soluble synthetic polymer represented by the formula $(C_2H_4O)_n$. It is a synthetic, linear, semicrystalline polymer produced via the hydrolysis of polyvinyl acetate in methanol, ethanol, or a mixture of alcohol and methyl acetate, using alkalis or mineral acids as catalysts. Unlike other vinyl polymers, it is not produced via the polymerization of repeating units of vinyl alcohol because it cannot be obtained in the quantities and purities required for polymerization purposes. It is manufactured by hydrolysis of polyvinyl acetate and the removal of acetate groups. It has low solubility in ethanol and is insoluble in many organic solvents. Its physical properties are dictated by the degree of polymerization and the degree of hydrolysis. The pharmaceutical grades are partially hydrolyzed and available in different viscosity types.



Poly(methyl methacrylates) Methacrylic acid copolymers

FIGURE 2.3 Representative chemical structures of acrylic polymers.

PVPs or povidone are water-soluble linear synthetic polymers, manufactured by free radical polymerization of *N*-vinylpyrrolidone. Vinylpyrrolidone-vinylacetate copolymer or copovidone (PVP/VA) are water-soluble copolymers of the two components in the ratio of 6:4. It is also produced by free radical polymerization

TABLE 2.4 Typical chemical names and trade names of the representative cellulosic polymers.

Generic name	Assay	Trade name (grades)	Manufacturer
Hydroxypropylcellulose	% Hydroxypropoxy 53.4–80.5[a]	Klucel HPC (Klucel EL, LF, GF) Nisso HPC (Nisso-L)	Ashland Nippon Soda Nisso (Seppic)
Hydroxypropylmethylcellulose	Type 2910 % Hydroxypropoxy 7.0–12.0 % Methoxyl 28.0–30.0 Type 2208 % Hydroxypropoxy 4.0–12.0 % Methoxyl- 19.0–24.0	Methocel HPMC (Methocel E3, E6, E10, K100LV, K4M) Klucel HPMC (Benecel K100LV PH PRM, Benecel K4M)	DuPont Specialty Solutions (previously Dow Wolff Cellulosics) Ashland ShinEtsu Lotte Fine Chemical
Hydroxypropylmethylcellulose acetate succinate	% Hydroxypropoxy 4.0–23.0 % Methoxyl 12.0–28.0 % Acetate-2.0 16.0 % Succinate 4.0–28.0	Aqoat HPMCAS (LG, MG, HG) Affinisol HPMCAS (LG, MG, HG) Aquasolve HPMCAS (LG, MG, HG)	ShinEtsu DuPont Specialty Solutions Ashland
Ethylcellulose	% Ethoxyl 44.0–51.0	Aqualon ethylcellulose (N types) Ethocel ethylcellulose (N types)	DuPont Specialty Solutions (previously Dow Wolff Cellulosics) Ashland

[a] *Specifications from USP 41-NF 36.*

reaction in an organic solvent such as ethanol or 2-propanol [29].

The representative chemical structures, commercial supplier information, and polymer properties are given in Fig. 2.4 and Tables 2.7 and 2.8, respectively.

PVA is a thermoplastic, water-soluble excipient that is commonly employed as polymeric support material for FDM-based 3DP [5,6,8,30,43,44]. The degree of hydrolysis impacts the physicochemical, thermal, and mechanical properties of the resultant PVA grade. Besides FDM printing, PVA has also been used in inkjet printing [31].

PVP and PVP/VA polymers are known for their application in the solubility enhancement of poorly water-soluble drugs via HME. Due to the complementarity of HME technology with FDM, polymers used in HME are frequently adapted for use in 3DP. Additives, such as plasticizers and fillers, are usually employed to reduce the T_g of PVP polymers and render them suitable for FDM printing coupled with HME. Major et al. examined the material properties of PVP/VA copovidone copolymers in hot melt extrusion-based 3DP and encountered difficulties in printing due to brittleness and high stiffness of the copolymer. Melt blending with a carrier polymer such as PCL improved flexibility and ductility thereby resolving the printability issue. Polyethylene oxide was also added to the formulation to reduce the negative impact of PCL on drug release profiles [32]. Melt blending PVP/VA with hydrophilic polymers such as HPMC and HPMCAS resulted in immediate release formulations [33].

TABLE 2.5 Typical physical, mechanical, and thermal properties of the cellulose polymers.

Properties	Klucel HPC[a]	Benecel HPMC	AquaSolve HPMCAS	Aqualon ethylcellulose
Molecular weight (Da)	40,000–1,150,000	20,000–1,200,000	55,000–93,000[d]	75,000–215,000[f]
Melting point (°C)	Softens at 130	190–200		156[f]
Glass transition temperature (°C)	0 and 120[b]	170–180	120–125	129–133[e]
Color	White to slightly yellow colored	White to off-white powder	White to off-white powder or granule[d]	White to light tan-colored powder[e]
Tensile strength (psi) (ASTM D882)	1450 (Klucel HPC EF)	6816 (Benecel HPMC E6)	5076 (HPMCAS L) 5366 (HPMCAS M) 5802 (HPMCAS H)[g]	6899
Elongation (%) (ASTM D882)	12 (Klucel HPC EF)	4 (Benecel HPMC E6)	11 (HPMCAS L) 19 (HPMCAS M) 16 (HPMCAS H)[g]	9
Modulus (psi) (ASTM D882)	200,000–630,000[c] (grade dependent)	367,090 (Benecel HPMC E6)	1574 (L) 1523 (M) 1494 (H)[g,h]	302,403

[a] *Adapted from Klucel HPC Physical and Chemical Properties Book (https://www.ashland.com/file_source/Ashland/Product/Documents/Pharmaceutical/PC_11229_Klucel_HPC.pdf),* [b] *Klucel HPC is a special polymer that can show dual* T_g *because it has a beta transition,* [c] *Reference [21],* [d] *Handbook of Pharmaceutical Excipients, Sixth Edition, 330–332,* [e] Handbook of Pharmaceutical Excipients, *Sixth Edition, 262–267,* [f] *Aqualon Ethylcellulose EC Physical and Chemical Properties, Product Brochure-PRO 250-42a,* [g] *PC-12624 AquaSolve HPMCAS Handbook,* [h] Handbook of Pharmaceutical Excipients, *Sixth Edition, 326–329.*

2.4.1 *Novel polymers in the market*

Melfil is a water-soluble filament of butanediol vinyl alcohol copolymer specifically designed for FDM 3DP. It offers superior water solubility and printability along with the flexibility to use as a support material or a water-soluble model (see the Nippon Gohsei—Melfil Product Brochure [53]).

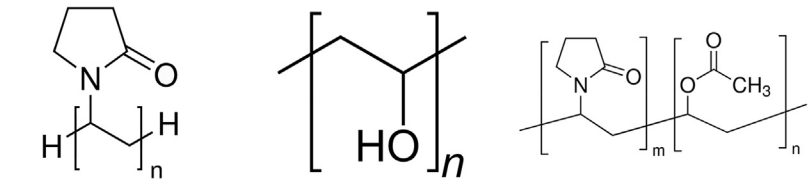
Thermoplastic polyurethanes (TPUs) are elastic and melt processable linear-segmented block copolymers. TPUs offer a unique advantage over other thermoplastic polymers because of their extreme material adaptability. This is due to the flexibility in modifying the molecular weight, ratio, and chemical composition of soft (polyether or polyester based) and hard segments (aliphatic or aromatic based) of the TPUs [34].

Polyether ether ketone (PEEK) and polyether imide (PEI, brand name ULTEM) are newer thermoplastic semicrystalline materials from the polyaryletherketone (PAEK) family of polymers currently used in FDM printers [35]. PAEK polymers can withstand high temperatures while maintaining mechanical strength [36]. PEEK is a superhigh-performance, biocompatible, chemically stable, semicrystalline plastic that offers the advantages of high-temperature resistance (melting point of 334°C, T_g of 143°C) and excellent mechanical properties, including high

TABLE 2.6 Typical chemical names and trade names of the representative acrylic polymers.

Generic name	Polymer dry weight content (%)	Trade name (supply form)	Manufacturer
Poly(butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate) 1:2:1	98% 12.5% 98%	Eudragit E 100 (granules) Eudragit E 12.5 (organic solution) Eudragit E PO (powder)	Evonik Industries
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2	97% 97% 30%	Eudragit RL 100 (granules) Eudragit RL PO (powder) Eudragit RL 30 D (aqueous dispersion)	Evonik Industries
Poly(methacrylic acid, ethyl acrylate) 1:1	95% 30% 95% 30% 30% 95%	Acryl-EZE (powder) Eudragit L 30 D-55 (aqueous dispersion) Eudragit L 100-55 (powder) Eastacryl 30 D (aqueous dispersion) Kollicoat MAE 30 DP (aqueous dispersion) Kollicoat MAE 100 P (powder)	Colorcon Evonik Industries Eastman Chemical BASF Fine Chemicals

Adapted from Handbook of Pharmaceutical Excipients.



Polyvinyl pyrrolidone (Povidone) | Polyvinylalcohol (PVA) | Polyvinylpyrrolidone vinyl acetate copolymer (Copovidone)

FIGURE 2.4 Representative chemical structures of vinyl polymers.

TABLE 2.7 Typical chemical names and trade names of the representative vinyl polymers.

Generic name	Polymer dry weight content (%)	Trade name (grades)	Manufacturer
Polyvinyl alcohol (PVOH/PVA)	Degree of hydrolysis 86.5–89.0	Goshenol EG Granules/Powder (EG-03P, EG-05P, EG-18P, EG-22P, EG-30P, EG-40P)	Nippon Synthetic Chemical Company
Polyvinylpyrrolidones (PVP, **P**ovidone)	K value- 25-90	Kollidon povidone Plasdone povidone	BASF Ashland
Polyvinylpyrrolidone: vinylacetate 6:4 (PVP/VA, **C**opovidone)	K value - 25.4-34.2[a,b]	Kollidon VA 64 copovidone Plasdone S630 copovidone	BASF Ashland

[a] http://www.nichigo.co.jp/english/lifechemical/pharma/index.html, [b] *From the Ashland brochure. Adapted from Handbook of Pharmaceutical Excipients.*

TABLE 2.8 Typical physical, mechanical, and thermal properties of the vinyl polymers.

Properties	PVA	Povidone	Copovidone[a]
Molecular weight (Da)	20,000–200,000[b]	28,000–1,150,000	45,000–75,000
Melting point (°C)	180–190 for partially hydrolyzed grades 228 for fully hydrolyzed grades	Softens at 150°C[c]	140
Glass transition temperature (°C)	85	120–175[d]	106
Color	White to cream-colored granular powder	White to creamy white powder[c]	White to off-white free-flowing powder
Tensile strength (psi)	44,961[e]	Films brittle; difficult to assess pure film properties	
Elongation (%)	2[e]		
Modulus (psi)	20,305[e]		

PVA, Polyvinyl alcohol. [a] *Specifications from the Ashland brochure*, [b] Handbook of Pharmaceutical Excipients, *Sixth Edition, 564–565*, [c] Handbook of Pharmaceutical Excipients, *Sixth Edition, 581–585*, [d] *Ashland Literature PTR-092 Plasticizer compatibility and thermal and theological properties of Plasdone povidone and copovidone polymers for hot-melt extrusion applications*, [e] *Hamied, S.F.A; Abd El-Kader, K.A.M. Preparation of poly (vinyl alcohol) films with promising physical properties in comparison with commercial polyethylene film.*

strength, elastic modulus, and fracture toughness [37]. PEI was developed by General Electric's plastics division in the 1980s (later acquired by SABIC) and demonstrates superior thermal properties and mechanical strength characteristics of the family.

2.4.2 *Additives*

Plasticizers, fillers, and lubricants are common additives used to improve printability by either modifying the melt and mechanical properties [33] or reducing the friction between the filament and walls of the printing extruder [10]. Commonly used additives include fillers such as talc, lactose, microcrystalline cellulose, magnesium stearate, and tricalcium phosphate, or plasticizers, such as triethyl citrate, triacetin, PEG 400, Tween 80, etc.

3. Technology details

3DP has been gathering significant attention from both industry and academicians. Research efforts have spanned the applications of both novel drug delivery to replacement/supplement of traditional manufacturing approaches. To accommodate these various manufacturing modes, different 3DP approaches are employed. This section reviews the available technologies along with their advantages and disadvantages from a technical point of view. In general, the technology is built on the principle that matter is converted from either liquid to solid or undergoes a transition from solid to liquid back to solid in a layer-by-layer approach either through chemical means or thermal energy. The contributing limitations to either print resolution or print speed are a result of the fundamental

mode of the physics used in the print process. ASTM ascribes seven different 3DP technologies (ASTM F2792). We discuss here the top three technologies that are most relevant for the pharmaceutical industry:

1. Vat photopolymerization
2. Powder-based processes
3. Material extrusion

The aim here is not to describe all of these technologies in detail but to cover the 3DP modes that have contemporaneous or direct immediate impact on the biopharmaceutical industry in their application of drug product prototyping and at-scale manufacture.

3.1 Vat photopolymerization

Vat photopolymerization carries alternative names with concurrent differing underlying technologies such as stereolithography apparatus (SLA), digital light processing (DLP), and continuous liquid interface production (CLIP). The fundamental principle of operation is that a liquid photopolymer resin formulation comprising a monomer, oligomer, and photoinitiator is cured through selective exposure to light using a specified light source (most typically a 450 nm laser) either in a raster mode or as a projected 2D image (e.g., DLP). The light source is controlled both in terms of energy supplied and in the amount of time that drives the photopolymerization reaction to cross-link the liquid formulation and convert it to solid polymer precisely at the regions where the light source is focused. Vat photopolymerization has the highest lateral and vertical print resolution in the range of 1–10 μm. Lateral resolution is defined by the positional control of the light source, whereas vertical resolution is controlled by the penetration depth of the light source and any light-absorbing additives that are added to photochemical resin to control any unwanted light-scattering events.

3.1.1 *Stereolithography apparatus*

Fig. 2.5 depicts the principal components of a typical SLA printer. The platform is precisely controlled in concert with the position of the focused laser source and any mirrors used to direct the light source to sequentially scan or project the laser light source within a plane on the surface of the photosensitive resin formulation. The time spent on any individual 2D layer depends on the chemistry of the resin formulation to successfully complete the cross-linking reaction and convert the liquid formulation to solid polymer resin. The lateral (x–y) position of the laser is typically controlled with a pair of mirrors within servo-controlled galvanometers,

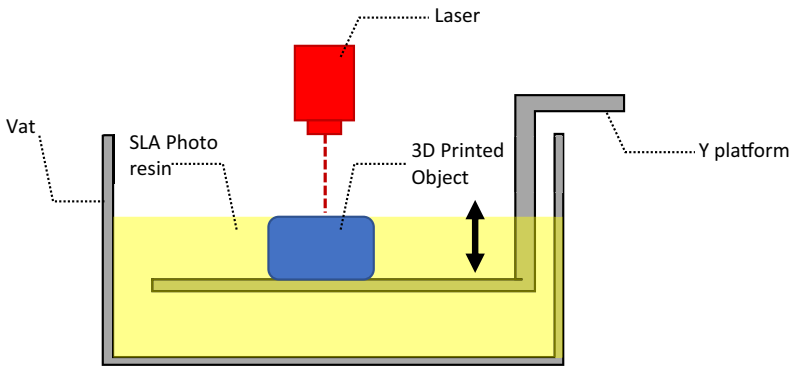


FIGURE 2.5 Principal components of a stereolithography apparatus (SLA) printer.

which are electromechanical instruments used to precisely control the position of the mirror and hence the position of the laser spot location. This process is conducted layer by layer whereby the slicing software converts the 3D image to be printed into a series of control statements that ascribe not only the position of the platform position, but also the laser energy pulse and well as the tilt angle of the mirrors used to position the $x-y$ position of the spot. A unique feature of photopolymerization 3D printers is the ability to resolve fine details by the application of galvanometer dithering (or high-frequency movements) to effectively process grayscale images that prescribe laser energy states between full on or full off. This technique allows for the creation of highly resolved surfaces. In general, photopolymerization techniques allow for highly resolved features and surfaces on the order of 1 μm. Their main disadvantages are extremely limited for use as a biopharmaceutically acceptable process in that they are using both toxic monomer and oligomer materials and usually have lengthy postprocessing steps to remove any unreacted monomer and oligomer as well as completely consume any unreacted free radicals as a result of photochemistry. The materials available for creating 3DP drug products from photochemical reactions are limited but research in this area is evolving.

3.1.2 Digital light processing

DLP is analogous to SLA because both processes use a controlled wavelength light source to selectively drive a photochemical reaction of a resin formulation. The main difference between SLA and DLP is that the light source in SLA acts as an $X-Y$ rastering, whereas in DLP the entire layer to be cured is projected onto the focal plane at one time. The technology used with DLP is the same technology used in overhead projectors, which allows for dithering as described in the SLA section earlier and for grayscale image processing and hence higher resolution features and smoother printed surfaces. Unlike SLA where the photochemical reaction is near the liquid/air interface and subject to oxygen inhibition less direct control of the photochemical cross-linking reaction, DLP 3D printers are controlled in the reverse direction where the reaction layer occurs at a plane immersed well below the liquid/air interface. An example of the application of DLP in 3DP is the work by Kim et al. with precision bioprinting of silk fibroin bioink for applications in building complex organ structures [38].

3.1.3 Continuous liquid interface production

The latest variety of vat photopolymerization is CLIP [39,40]. This technology addresses the major time-limiting step of both SLA and DLP, which is the required mechanical separation of the just-cured material from the vat of unpolymerized material. This 3DP technique uses an oxygen permeable membrane to inhibit polymerization at the interface nearest to the ultraviolet (UV) light source. This region creates a 10−100 μm "dead zone" where free radical polymerization does not occur. Just above this zone, light-catalyzed free radical polymerization occurs on the focal plane of the projected light. This innovation is key to facilitate a faster 3DP process because the need to refresh or recoat the region between the printed part and the light source using a mechanically activated platform is not needed. Using CLIP, this region is continuously present with uncured formulation and the 3D-printed part appears to "grow" out of the resin. Resolution of the part in the vertical direction is improved by increasing the concentration of the passive light absorber. This slows down the production speed because light penetration is in a smaller volume of the resin. By lowering the concentration of this additive, deeper penetration of light can be realized and hence faster production speeds. Part quality is also improved by removing the need to mechanically separate the part from the resin bath. This mechanical separation that is typical in most SLA 3D

printers causes undue stress on the part and can lead to feature distortion or even failure. CLIP allows for both high print quality and speeds and can produce parts with features below 100 μm at growth rates in the range of a vertical support plate speed of 1000−3000 mm/h.

3.2 Powder bed fusion processes

3.2.1 Selective laser sintering process/laser sintering process

Generally, laser sintering 3DP allows for many more materials over other 3DP techniques from high-performance thermoplastic polymers to even metal powders.

The operating principle behind powder-based SLS consists of powder deposition from the feed chamber to the build chamber by powder transfer and consists of build surface preparation by rolling and leveling with a scraper, laser rastering and particle melting and sintering, cooling and solidification, followed by the build chamber being lowered by one-layer thickness to repeat with a recoating of fresh material from the feed chamber. During the printing process, the laser, in most applications a 2 W blue diode laser (445 nm) light source, is rastered (∼100 mm/s) to match the geometry of the layer [27]. The light energy from the laser source is absorbed by the particles at the site of the laser focal spot, which in turn heats the material beyond the thermal transition (T_g or T_m) allowing for interparticle contact diffusion and binding. After removal of the light source the energy dissipates, and the newly formed coherent body solidifies. The unprinted material surrounding the printed material serves as an intrinsic support material. The fact that the 3D-printed parts are constantly surrounded by unprinted support material means that parts can be effectively stacked and printed together to make efficient use of the build volume but it also implies that a lengthy and "dirty" postprocessing is required to remove the bulk powder from the build chamber as well as the powder that is loosely adhered to the final printed part. Because of the impact of the heat-affected zone powder, not all of this unprinted powder can be reused, and it is good practice to blend virgin powder with this recycled material.

One key to this technique is for the process to proceed so that enough thermal mass is present, such that not only are the particles bonded within the as-printed 2D layer, but this layer also softens/melts and binds through the same diffusional process to the layer(s) just below to form our 3D-printed part. For thermoplastic materials, liquid-phase sintering drives capillary interactions between neighboring particles resulting in bonds due to the diffusion of polymer chains or chemical cross-linking.

One method that ensures a well-formed 3D-printed part is to keep the entire 3DP chamber at a temperature just below the softening or melting point of the material to decrease the processing time and reduce thermal gradients within the part, which can lead to part distortions caused by the relatively large volume changes in semicrystalline or amorphous polymers. In this method, maintaining an elevated environment is a key consideration in the processing of thermally sensitive materials (e.g., oxidation) and would need careful evaluation depending on the material that is used for printing. To provide the best part quality and minimal part warpage, the build volume is left to cool gradually over 24−48 h for both safety in handling and to avoid distortion caused by premature handling while the parts are in a softened condition.

One of the more critical criteria for this process to be effective is the flow and particle packing properties of the starting material. Because the powder deposition process between adjacent layers is done by depositing material

through a blade and roller recoating process, the distribution of the particles across the 2D plane to be printed directly impacts part quality. If the particles do not flow and fill in the region in a uniform manner there will be voids in the final printed part. The size and sphericity of the particle properties also directly influence the surface roughness and spatial print resolution of the manufactured parts. Part resolution on the order of 100 μm is typical for a printed part. Compressibility, or volume reduction, under the roller assembly can aid in powder bed uniformity and this predensification can enable the printing of higher-density final parts.

Many SLS 3D-printed parts undergo a series of postprocess finishing operations to provide more elegant surface properties. In addition, intrinsic to the type of 3DP, because of the use of powder as the starting material, final parts will be porous in nature, which may be considered as defects from a mechanical strength point of view or could aid in the disintegration of oral dosage forms as in traditional compressed tablets. For biomedical applications the porosity present in these 3D-printed parts could also serve as a scaffold for cell growth.

Regardless of the material used, the parts obtained by the powder bed fusion processes will typically exhibit a certain level of porosity. The amount of free volume is dependent on particle size distribution, material choice, and process parameters. The pores remaining within a green part after the additive manufacturing process represent potential weak points in models subjected to mechanical load. If high mechanical strength is required for a given application, it is therefore common practice to improve mechanical properties by means of isostatic pressing, infiltration with suitable resins, or sintering. On the positive side, SLS-fabricated parts are light and porosity can be advantageous in other applications that require large surface areas, for example, scaffolds for cell growth in tissue engineering. SLS is applicable to materials with vastly different bulk properties. Moreover, SLS powders for the same bulk material can also vary in their morphology, sintering, and melting behavior.

3.2.2 *Powder binding technology*

Like the SLS processes, in the first step of powder binding 3DP a powder layer is deposited using a roller/scraper assembly from a feeder chamber to the build chamber. Unlike SLS, which used a thermal method of binding powder, in liquid-phase powder binding 3DP, the powder is bound together with the use of a liquid that is dispensed using an inkjet printing head. The inkjet head will either contain a solvent (e.g., water) or a solvent–binder solution. In the former, the binder is contained within the powder formulation whereas if the inject print head has a solvent–binder solution the binder is dispensed from the print head. The finished 3D-printed part is then cleaned of any residual powder using a combination of a vibratory plate and airflow. Much like SLS, the particle properties drive product quality and final part resolution, but unlike SLS the inkjet print head spatial resolution is lower than that of a laser spot size. This technology offers the ability to print several materials because of two reasons: either the powder loaded into the feed chamber is a blend of multiple materials or the inkjet print head could also contain a different material such as an active ingredient or a colorant. This technology is likely the closest analogy to a traditional wet granulation process because of the similarities in materials that are used. In fact, the powder binding technology is the same core process that is used by Aprecia Pharmaceuticals to manufacture the Spritam tablet. The porous nature of the powder bed process creates a dosage form that instantaneously dissolves because of the formulation and the intrinsic capillary wicking action of the dosage form.

3.3 3D material extrusion—fused filament fabrication

3DP extrusion-based processes have seen a bolster of activity in recent years and cover a wider range of materials, including thermoplastic polymers, pastes, and thermo or UV curable gels. In this process a nozzle or piston (e.g., syringe) is fixed to a gantry that moves in $x-y$ space. After a single layer is deposited the extrusion head or build platform moves in z space to complete the next layer. The most common extrusion-based 3DP is known as fused filament fabrication (FFF), also known as FDM.

The operating principle is shown in Figs. 2.6–2.8, where the thermoplastic polymer filament with a round cross-section of 1.75 or 3.00 mm in diameter is mechanically fed using a gear-based extruder to a cartridge-heated

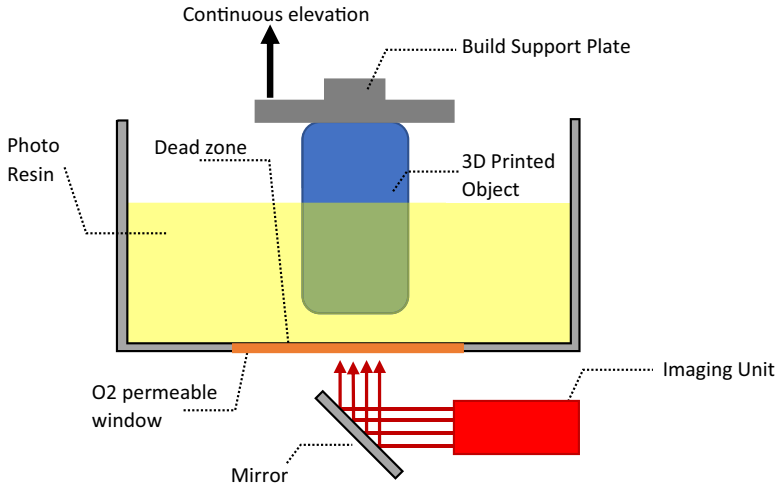


FIGURE 2.6 Schematic of continuous liquid interface production.

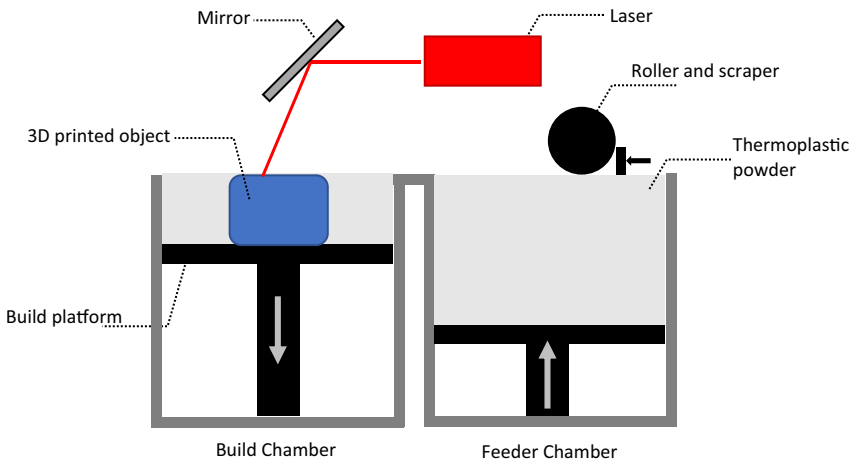


FIGURE 2.7 Schematic of selective laser sintering process.

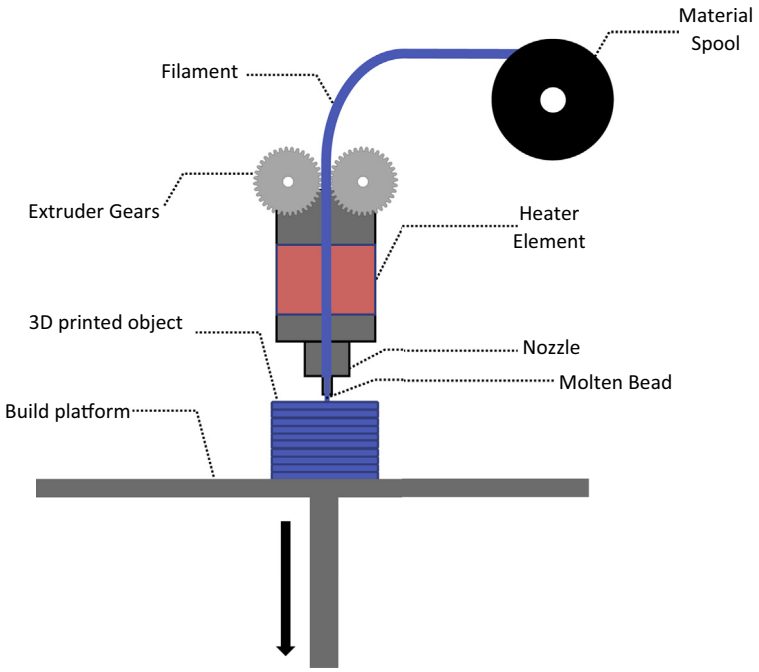


FIGURE 2.8 Operating principle of extrusion-based 3D printing process.

nozzle assembly. Process temperature is defined by the thermal properties of the polymer filament, which for amorphous polymers is above the glass transition temperature and for semicrystalline polymers is above the melting point. The melted filament forms a molten bead upon exit from the small nozzle orifice (0.1−1 mm diameter) and begins solidification at the location from which it was extruded. The resolution of an FFF-printed part is often defined by the diameter of the nozzle. Generally, a smaller nozzle results in a surface that more closely follows the profile of the 3D geometry; however, this results in an increase in print time because of the requirements of more nozzle traces to completely define the geometry as well as often slowing the print speed because of the increase in nozzle melt pressure as a result of the smaller diameter. The rheology of viscous thermoplastic polymer is often the limiting factor for this 3DP technique. Processing not only needs to consider the speed for appropriate bead deposition but also the temperature and time required for fusion of the deposited beads onto the adjacent layers that were previously printed.

Often in 3DP for a new polymer the impact of several parameters is often experimentally derived such as filament extrusion feed rate, temperature and thermal gradients, nozzle design, die swelling, polymer melt rheology, quench rate using convective air cooling, nozzle path direction, and part orientation. These parameters are optimized to improve 3DP efficiency, surface roughness, dimensional accuracy, mechanical properties, and isotropy. Many common thermoplastic materials (e.g., PLA, acrylonitrile-butadiene-styrene copolymers, polycarbonate, and polyamides), have been optimized for fused filament fabrication

3DP, while other more nascent thermoplastic polymers relevant for the pharmaceutical industry are still being experimented.

3.3.1 Postprocessing

Across most all 3DP technologies, the final part requires additional processing steps after completion of 3DP. Depending on the printing process these steps involve either mechanical removal of material used to improve adhesion to the printing plates, removal of support material used in the printing process, chemical and/or thermal treatment of unreacted surface material, removal of unbound surface powder, or heat treatment to reduce unwanted part residual stresses. Careful consideration and execution of the postprocessing steps is crucial to ensure that the part does not suffer undue damage.

4. Regulatory and quality considerations

The FDA recently issued a guidance for industry entitled "Technical Considerations for Additive Manufactured Medical Devices." Even though medical device and combination products are regulated by the Center for Devices and Radiological Health, many elements discussed in this document highlight key considerations for additive manufactured drug products that are regulated by the Center for Drug Evaluation and Research. This guidance like most offers supplementary regulatory guidance that covers 3DP-specific recommendations. The device-specific 3DP guidance document covers (1) design for 3DP, (2) patient-matched device design, (3) software workflows, (4) controls over materials used for 3DP, (5) postprocessing considerations, (6) process validation and product acceptance testing, (7) quality, and (8) device testing considerations. It is not the intention of this section to recount this guidance document but to direct the reader to key recommendations that are common for drug products. Generally, regulated products must fulfill standard Quality System requirements. Specific to 3DP of drug products, manufacturers must validate their process and establish and maintain procedures for monitoring and controlling processing parameters to ensure that the specifications of the drug product can be met with a high degree of confidence and the product performs as intended. There are numerous 3DP technologies described that can be used to manufacture drug products and hence there are different processing steps that are implemented to manufacture a quality drug product. Because of the relative novelty of 3DP, a higher level of scrutiny should be expected due to the integration of a novel manufacturing technique with traditional or novel materials that have been reprocessed or adapted to be enabled by 3DP. One unique regulatory consideration that is atypical from traditional pharmaceutical manufacturing is the utilization of software in both the design of the final product and in the control of the process to manufacture the final drug product. 3DP involves a multistep software process that is used to design and convert 3D dosage form shapes ranging from simple/traditional to complex (more on these designs will be highlighted in the sections that follow), into sliced 2D layers (using "slicer" software). This geometrical 2D information is then used as input into control software that then translates this information into print commands. To enable consistency across the industry, the FDA guidance proposes the utilization of a specific file format for additive manufacturing (ISO/ASTM 52915 "Standard specification for additive manufacturing file format"). The intention of this standard is to create a well-controlled and integrated file that describes the printed volume, material information, and the print controls and print location within the print volume. As will be highlighted later, and perhaps more unlike

other traditional pharmaceutical applications, software processes are as critical as and, in some instances, more critical of final product quality compared to traditional pharmaceutical process hardware/critical process parameters. Quality that is governed by software is not only process control over material being handled by the printer in terms of temperature and time as was pointed out earlier, but just as important is the structure and path for the printing tool that drives the printing of the drug product.

Just like other pharmaceutical processes, 3DP often uses environmentally sensitive material as a matrix and therefore needs to be handled and evaluated similarly. In addition, many physical and chemical attributes that govern product quality in traditional processes are just as important in 3DP. For example, particle size for SLS is a critical material attribute that defines not only final dosage form elegance but also mechanical strength and dissolution variability due to defect populations because of broad particle size distribution and insufficient sintering at specified locations because of voids.

TABLE 2.9 Examples of fused filament fabrication process critical process variables and failure modes.

Process variables	Failure modes
Hardware/software input/output	Voids between layers
Extrusion rate	Incomplete layer print
Retraction settings	Interlayer adhesion
Nozzle temperature	Plate–pill adhesion
Nozzle size	Stringing
Nozzle–platform gap	Temperature excursions
Platform surface type	Thermal degradation
Platform surface roughness	
Platform temperature	
Flow rate	
Print Speed	

Table 2.9 highlights some of the critical 3DP processing variables and failure modes that need to be considered when establishing the quality system for a drug product.

5. Pharmaceutical applications for drug delivery

The current advantages of using 3DP for pharmaceutical dosage forms are targeted at dosage form design and patient customization. Here we detail several published accounts of applying 3DP in the production of more traditional oral dosage forms, customized oral dosage forms that highlight the ability to tailor doses and release rates to meet patient needs, as well as nonoral dosage forms that aim to provide more patient complaint dosage forms through longer acting drug delivery. Another advantage of 3DP in drug product development is the ability to circumvent the long and complex clinical R&D process. This is especially true when the work requires: increasing drug solubility by converting the active ingredient from crystalline to amorphous using processes such as spray drying or HME, protecting the active ingredient from a specific region of the gut, or altering the drug release profile to overcome pharmacokinetic-related adverse events. 3DP can allow for production of dosage forms that overcome these common R&D challenges in a cost-effective and rapid approach in a single-step process.

5.1 Tunable release technologies

Currently, there are limited pharmaceutically acceptable materials available in filament form, which is the raw material feedstock for FDM printers. Many traditional polymer excipients do not have the appropriate thermal and

mechanical properties for filament processing or the physical properties are altered when drug is incorporated in the filaments. To have a robust filament the polymer must be sufficiently rigid to maintain its form as it is pushed from the compression gear through the hot end nozzle orifice of the printer. The polymer should be sufficiently tough so the extruder gear of the FDM printer can gently depress and grip the filament to generate an extrusion force greater than the resistance from the molten polymer flow out of the nozzle. In addition, the melting temperature or glass transition temperature must be significantly higher than the temperature inside the printing enclosure to allow forced air cooling to rapidly quench the extrudate. The melting temperature should also be below 250°C, which is the maximum temperature allowed in most commercially available FDM printers. Finally, to maintain proper molten flow, the thermoplastic material must not degrade while it is held at elevated temperatures during the printing process for extended periods of time, usually on the order of minutes. Once a filament is extruded, X-ray computed tomography can be used as a quality check for surface or volumetric defects [40a,40b]. Diameter variations in the filament tend to strongly correlate with the quality of the final print as most commercial printers do not dynamically change the extrusion rate based on the filament's instantaneous diameter. Typically, pharmaceutically acceptable polymers have been experimented with varying success. HPC has been used to print drug-free capsules that are manually filled and assembled postprinting [41]. Additional work has highlighted the difficulties and limitations of using FDM for printing PVA capsules where the dosage forms were printed for hand filling with placebo liquids, followed by manual assembly and sealing, and external and internal surface roughness of the printed capsule walls were investigated. Typically, however, the filament that is loaded into the FDM 3D printer is preprocessed using extrusion to incorporate active ingredients, which are then used to print the final dosage form. PVP [10,41a,41b] mixed with drug in an HME process has been used with FDM to construct oral dosage forms. PVA has been most commonly used due to its beneficial mechanical and thermal properties aiding the FDM process [6,8,30,40b,42–44]. Recent work on manufacturing filaments for 3DP examined the use of Eudragit EPO, a cationic acrylic polymer with dimethylamine-containing side chains, which is a polymer typically unsuitable for FDM due to its brittle properties [14]. This study showed that Eudragit EPO could be compounded with a plasticizer, triethyl citrate, and a nonmelting filler, tricalcium phosphate, to optimize the hardness and flexibility properties to enable printing of the filament. The same research group demonstrated the feasibility of printing an enteric-coated 3D-printed caplet using the same plasticizer and filler approach with PVP and drug-free Eudragit EPO [10]. Other extruded materials, where quinine was mixed individually with Eudragit RS, PCL, PLA, and ethyl cellulose at a 5 wt% drug loading, demonstrated viability for use as FDM filaments for preparing 3D-printed implants [44a]. It has also been demonstrated that soaking filaments in a poor or nonsolvent solution containing drug can result in diffusion of drug into the filament, although drug loading is intrinsically lower than extrusion methods [42]. To date, there are limited successful piloting examples of pharmaceutically acceptable filaments, and the surface quality of these printed dosage forms indicates more optimization is required before widespread adoption can be realized.

As of 2019, there are numerous examples of applying 3DP to produce dosage forms in a rapid prototyping method with variable and tunable release rates within the same manufacturing step. Several examples rely on incorporating an API into the filament used in extrusion-based 3DP using a typical HME process [1,2,5,9,10,41,43,45–48] or solvent-based diffusional processes [26,42]. The primary limitation with these approaches is the limited amount of drug that can be incorporated into the filament and hence the final 3D-printed dosage form with typical drug loadings in the 1–30 wt% range. The release rates of dosage forms made by this approach are governed by either diffusion or erosion for which the volume and geometry of the final dosage form play are key role. An advantage of this approach of manufacturing dosage forms directly from drug-loaded filament is that the final dosage forms are generally robust enough to be used immediately after printing. Figs. 2.9 and 2.10 highlights a well-known study by Ref. [5,8,43,44] where the dosage form surface area, surface area/volume, or mass were discretely controlled and thereby directly impacted the dissolution rate without changes to the formulation.

Another degree of freedom in 3DP is the modification of the infill parameters of the printed tablet, which can manipulate diffusional length scales as well as the dosage form buoyancy and hence the release rates [1–3].

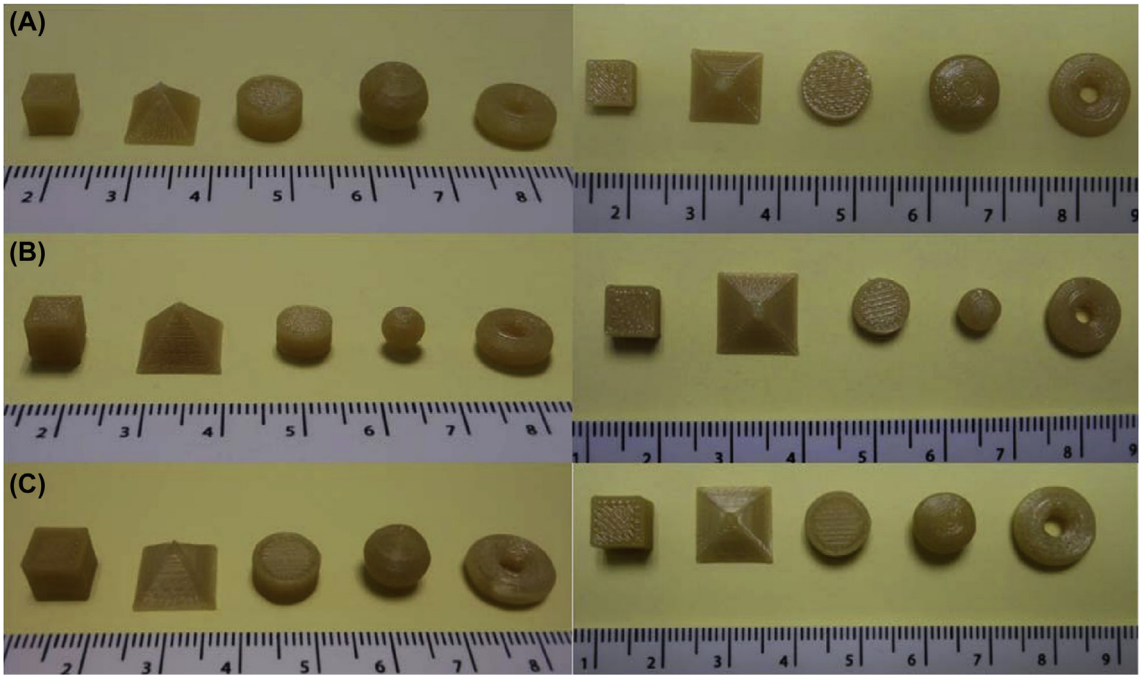


FIGURE 2.9 3D-printed dosage forms of various geometries using poly(lactide) as the primary matrix for tunable release rates at constant (A) surface area, (B) surface area/volume ratio, and (C) mass (scale bar in cm). *Adapted from Goyanes A, Chang H, Sedoug HD, Hatton GB, Wang J, Buanz A, Gaisford S, Basit AW. Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing. Int J Pharm 2015b;496:414–420; Goyanes A, Martinez PR, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. Int J Pharm 2015c;494:657–663; Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. Eur J Pharm Biopharm 2015a;89:157–162; Goyanes A, Wang J, Buanz A, Martínez-Pacheco R, Telford R, Gaisford S, Basit AW. 3D printing of medicines: engineering novel oral devices with unique design and drug release characteristics. Mol Pharm 2015d;12:4077–4084.*

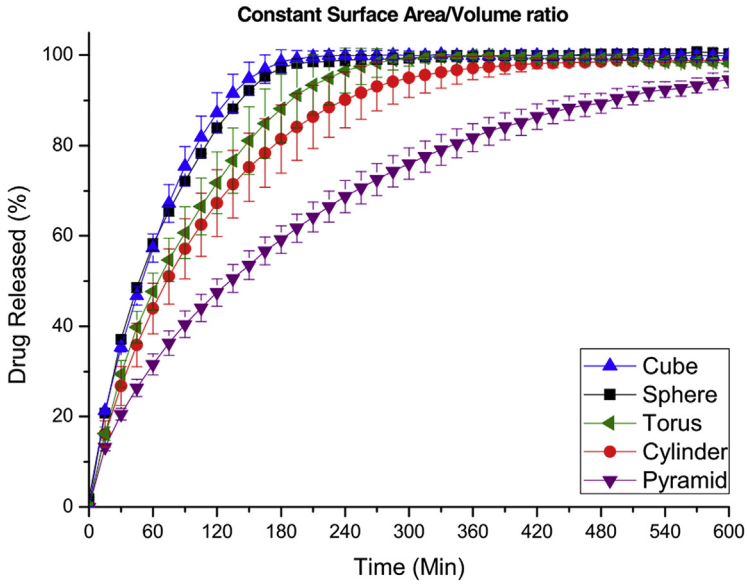


FIGURE 2.10 Paracetamol dissolution profiles from 3DP solid dosage with surface area/volume ratio 1 in phosphate buffer (pH 6.8). *Adapted from Goyanes A, Chang H, Sedoug HD, Hatton GB, Wang J, Buanz A, Gaisford S, Basit AW. Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing. Int J Pharm 2015b;496:414–420; Goyanes A, Martinez PR, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. Int J Pharm 2015c;494:657–663; Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. Eur J Pharm Biopharm 2015a;89:157–162; Goyanes A, Wang J, Buanz A, Martínez-Pacheco R, Telford R, Gaisford S, Basit AW. 3D printing of medicines: engineering novel oral devices with unique design and drug release characteristics. Mol Pharm 2015d;12:4077–4084.*

Infill is the process by which the print head will print an outer shell of the shape of the part and the inside of this shell is filled in with a particular pattern to accommodate a predefined volume percentage. The material that is printing between the outer shell is termed "infill" and can be controlled through software to define both the geometry of the infill material as well as the amount of infill.

In addition to their use in solid filament as the starting material for extrusion-based 3DP, viscous pastes and UV curable polymers have been shown to be viable feedstocks for extrusion-based 3DP of active dosage forms [46,47,49]. Preparing these starting materials as shown in Fig. 2.11 requires less process development as compared to an extrusion-based approach; however, these dosage forms typically require postprocessing, such as drying or active thermal curing, and the mechanical properties for the resulting dosage product have not been investigated thoroughly. With both of these approaches, API chemical and/or physical stability may be compromised. These paste formulations have been printed using similar equipment to an FDM printer, except the hot end is replaced with a closed shot canister. Using this approach, HPMC and polyacrylic acid (Carbopol 974P) [46], HPMC and lactose [47], and HPMC hydroalcoholic gels [49] have been printed. Notably, this approach has been used for polypills [47,49], which are single oral dosage forms that contain three or more isolated volumes each containing a different active ingredient. While paste formulations open doors to more material choices, this approach typically requires

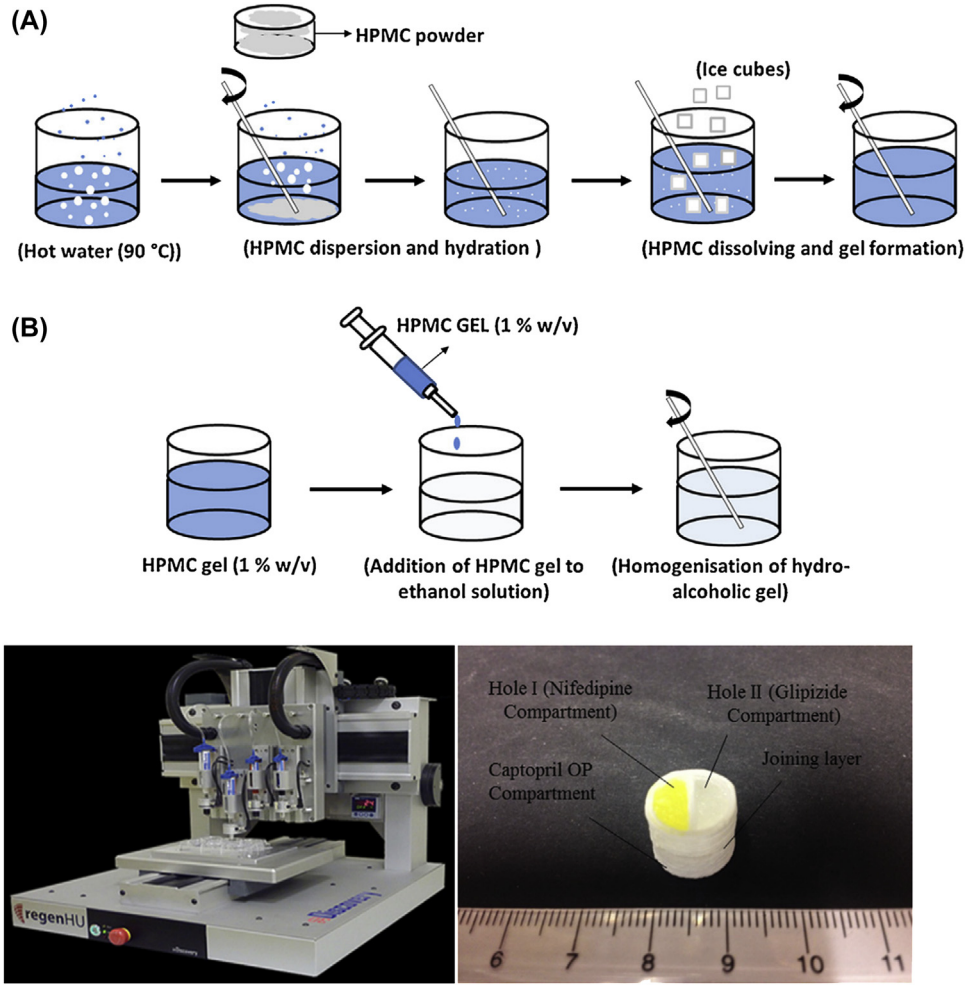


FIGURE 2.11 (i) Schematic diagrams of (A) the dispersion technique of hypromellose (HPMC) 2910 powder and (B) formulation of HPMC hydroalcoholic gel [46]. (ii) Photograph of a RegenHU 3D printer (*left*) RegenHU Switzerland (regnhu,com), and image of a multiactive tablet (*right*) (10.45 mm [height], 6 mm [radius]) composed of a captopril osmotic pump compartment (*bottom*), and nifedipine (hole I) and glipizide (hole II) sustained release compartments (*top*) and joining layer (*middle*).

subsequent steps such as overnight drying of the print to remove any solvent or water from the dosage form for long-term physical stability, and it is unclear at this time how the mechanical robustness of paste-printed dosage forms will endure secondary packaging and user handling.

These are existing examples of implementing 3DP technology into rapid prototype release rates using different strategies, largely focused on maintaining a similar material feedstock and using creative printing parameters to generate various releases. With all the following examples, at least one solid filament material is preprocessed to contain API. The extrusion of filaments or pastes has been used to manufacture what are termed core/shell tablets, where

the outer shell's thickness is varied, and has demonstrated the generation of distinct release rates. Core/shell tablets have been manufactured by using a second API-containing material [8] or a placebo material with the intent to mimic enteric-coated tablets [9,10], and have demonstrated the agility of 3DP to change the onset of the release of the core of the dosage form by as much as 2 h in vitro using the same material feedstock. While these strategies have been demonstrated to provide a software tuning knob for release rate manipulation while maintaining a constant material feedstock, all of these strategies rely on HME formulation of a printable filament for each API. Developing process conditions to incorporate API into an excipient-based solid filament is usually not trivial [11–14], and these filament processing developments add to the product development burden, reducing the rapid prototyping advantage 3DP brings to the table for early drug screenings.

Fina et al. [52] presented the first published work to utilize SLS for the production of oral dosage forms using two thermoplastic pharmaceutical-grade polymers, Kollicoat IR (75% polyvinyl alcohol and 25% PEG copolymer) and Eudragit L100-55 (50% methacrylic acid and 50% ethyl acrylate copolymer), with immediate and modified release characteristics. For this process to achieve printability and aid in the sintering process, pharmaceutical-grade silicate and oxide-based pigments are added to improve laser energy absorption and dissipation. In general, SLS-printed dosage forms have poorer surface quality and higher porosity as shown in the example from [52] (Fig. 2.12A). Control of the release rate of the SLS dosage forms based on the research thus far is governed more by the thermoplastic material than by the printing conditions as seen in Fig. 2.12B.

5.2 Paste/gel extrusion-based technologies

A unique approach that attempts to incorporate both filament-based and paste/gel extrusion-based technologies has been developed by Smith et al. [50,51]. The aim of their work was to take advantage of the printability of pharmaceutically acceptable polymers like PLA and PVA while limiting the processing of API to similar approaches shown earlier for paste, liquids, and gel-based formulations. They developed a single-step FDM 3DP process to manufacture thin-walled drug-free capsules, which can be filled with dry or liquid drug product formulations. Drug release from these systems is governed by the combined dissolution of the FDM capsule "shell" and the dosage form encapsulated in these shells. To prepare the shells, the 3D printer files (extension ".gcode") were modified by creating discrete zones, so-called "zoning process," with individual print parameters. Their work clearly shows several unique aspects of the difficulty in 3DP quality dosage forms that are elegant and water tight. The geometry of the dosage form requires a design that is specific to the 3DP process, breaking from the more traditional shapes to account for the physics of 3DP. In their work they highlight the need to redesign the shape with different angles (so-called zoning) using software that is commonly available to the public. Fig. 2.13 shows different colors within the dosage form to show where FDM thermal and mechanical process conditions are purposely changed to improve the quality of the final printed dosage form.

It is well known that the speed of FDM 3D printers is not particularly fast as compared to traditional dosage form manufacturing where a rotary tablet press can accommodate on the order of 1,000,000 tablets per hour. A 3D printer

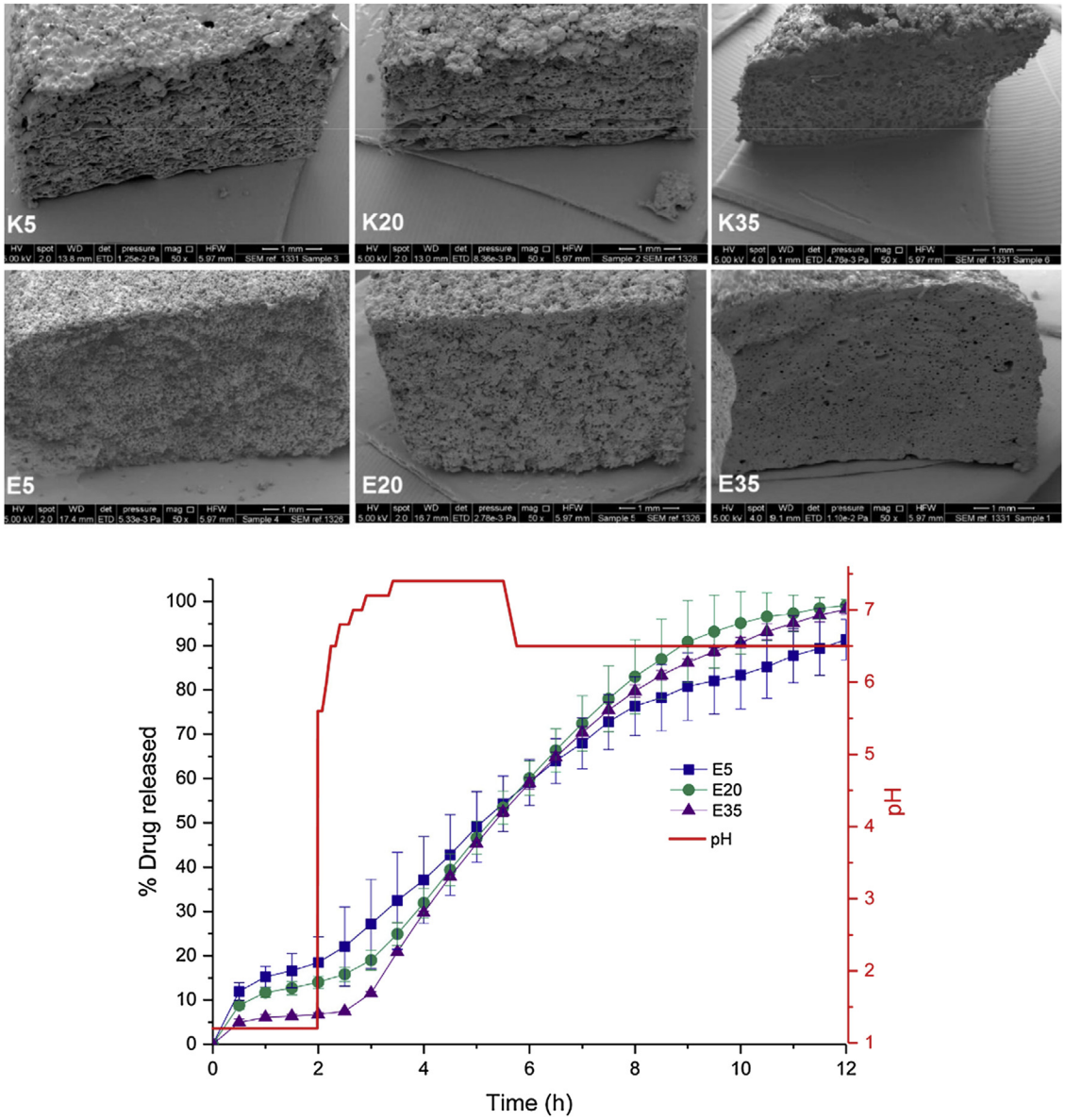


FIGURE 2.12 (A): Scanning electron microscopy images of the selective laser sintering of printlet vertical sections. On the top from left to right, Kollicoat IR K5, K20, and K35. On the bottom from left to right, Eudragit L100-55 E5, E20, and E35, where 5, 20, and 35 represent the wt% of paracetamol used as a model active pharmaceutical ingredient. (B) Drug dissolution from Eudragit SLS printlets. *Adapted from Fina F, Goyanes A, Gaisford S, Basit AW. Selective laser sintering (SLS) 3D printing of medicines. Int J Pharm 2017;529:285–293.*

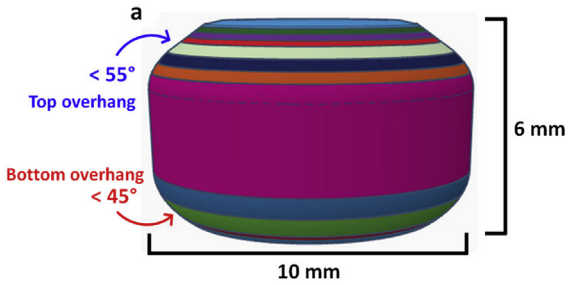


FIGURE 2.13 (A) Computer-aided design representation of a single-walled capsule with varying colors depicting the different print zones. (B, C) Top and side optical views, respectively, of polyvinyl alcohol (PVA) capsules printed on an Ultimaker 2+ at 60 mm/s with no zoning, and (D, E) with zoning. (F, G) Top and side optical views, respectively, of PVA capsules printed on a Hyrel 3D System 30M at 25 mm/s with no zoning, and (H, I) with zoning.

may have the ability to manufacture approximately 10–100 dosage forms per hour depending on many printing conditions. Controlling features that balance print speed and quality are nozzle diameter, layer height, and material flow rate (Fig. 2.14). Purposeful studies to optimize printing conditions are required to maximize dosage form throughput using FDM print technology that is available today. Smith et al. have also evaluated these conditions for dosage form quality and these are copied here (Fig. 2.15).

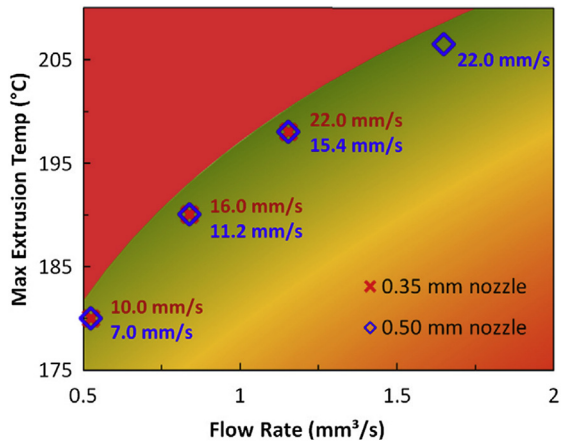


FIGURE 2.14 Graph of flow rate versus maximum sustainable extrusion temperature on a Hyrel 3D System 30M printer. The red region above data points indicates conditions at which the nozzle will clog due to polyvinyl alcohol degradation. The red region in the bottom right corner indicates poor print conditions resulting in poor mechanical properties of the printed capsule, or nonflow through the nozzle orifice. The green region indicates a stable print condition with better mechanical properties.

As stated earlier, a unique ability of 3DP is in the discrete control of one dosage form to create structures that control release rates. As shown in Fig. 2.16, using the software zoning process and knowledge of erosion rates of PVA, dosage forms can be designed to release at different regions in the gastrointestinal tract.

6. Conclusions

3DP has shown impressive R&D potential and commercial value in industries such as automotive, aerospace, and medical devices where product optimization and customization have had a significant benefit. In the pharmaceutical industry, 3DP offers a similar promise to rapid prototype dosage forms in a preclinical and clinical setting and significant future potential in commercial patient centric dosing. Additionally, pharmaceutical 3DP may evolve into manufacturing nodes at doctors' offices and local pharmacies. Addressing the known material and technology deficiencies will make this future state possible.

Utilization of 3DP technologies requires a unique presentation of material for the required phase transformation. For example, the need to have biopharmaceutically acceptable polymers in a filament form for FDM printing is not possible for all polymers because of the required technical specifications (e.g., mechanical strength and thermal degradation) that allow for successful printing conditions. The material challenges for successful SLS printing are governed by the ability to process thermoplastic materials into highly flowable (i.e., spherical),

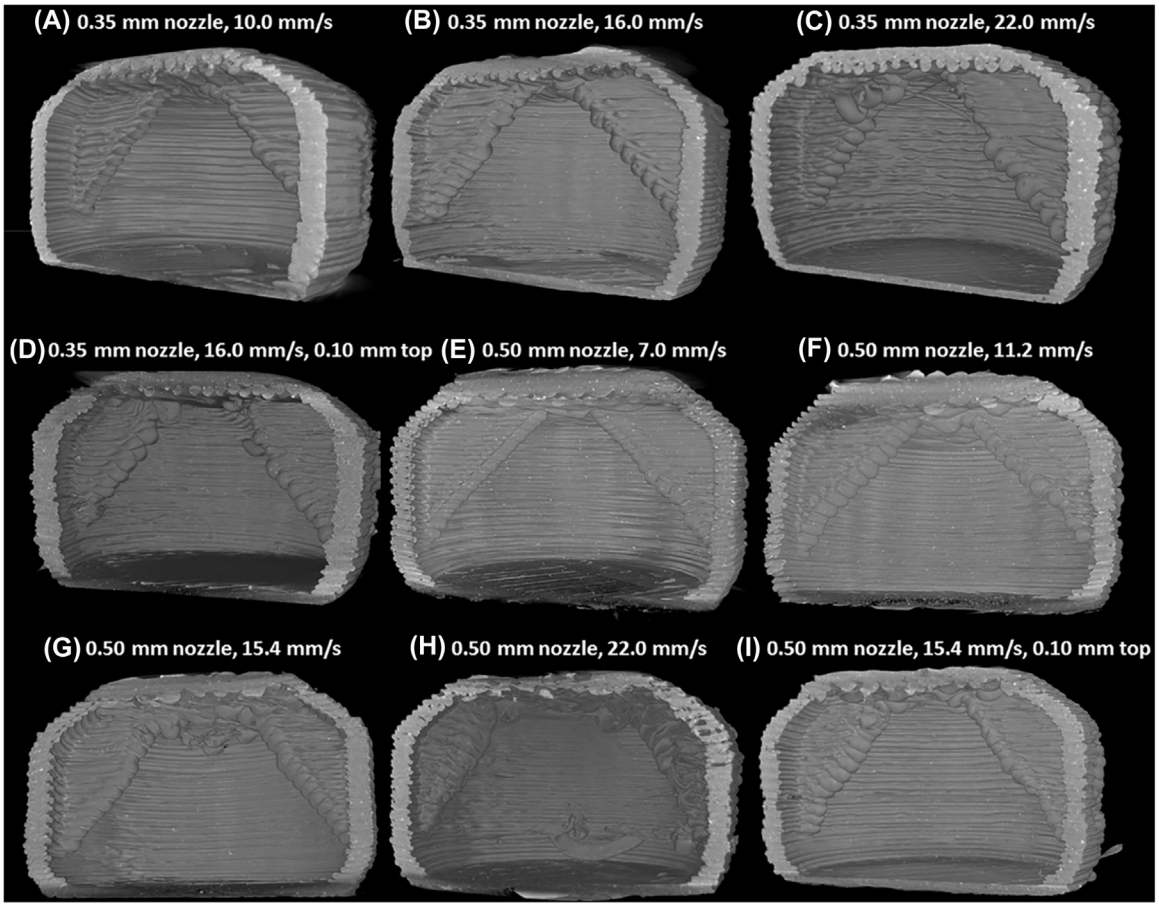


FIGURE 2.15 X-ray computed tomography reconstruction images of capsules with various print conditions on a Hyrel 3D System 30M printer, cropped to see the internal wall structure and shape. *Adapted from Smith D, Kapoor Y, Klinzing G, Procopio A. Pharmaceutical 3D printing: design and qualification of a single step print and fill capsule. Int J Pharm 2018a;544(2018):21–30; Smith D, Kapoor Y, Hermans A, Nofsinger R, Kesisoglou F, Gustafson T, Procopio A. 3D printed capsules for quantitative regional absorption studies in the GI tract. Int J Pharm 550;2018b:418–28.*

unimodal particles. In SLA, residual monomer/oligomer and free radical population in the printed dosage form are of primary concern for patient safety. Overcoming this challenge while defining a high-quality printable SLA formulation still needs a solution.

So far, the pharmaceutical industry has adapted 3DP technologies that have existed previously and were built to handle engineering materials for the purposes of rapid prototyping. As discussed earlier, researchers have had to accommodate and transform materials to be able to print using 3D technologies that were not designed for pharmaceutical materials. One example that was described in this chapter focused on the need for strong interlayer adhesion of more than one thermoplastic pharmaceutical material in FDM for oral-controlled delivery. This particular challenge is because of the low T_g of pharmaceutical materials as compared with engineering materials as well as material interfacial incompatibility.

3DP offers a paradigm change for our industry across manufacturing, regulatory, and

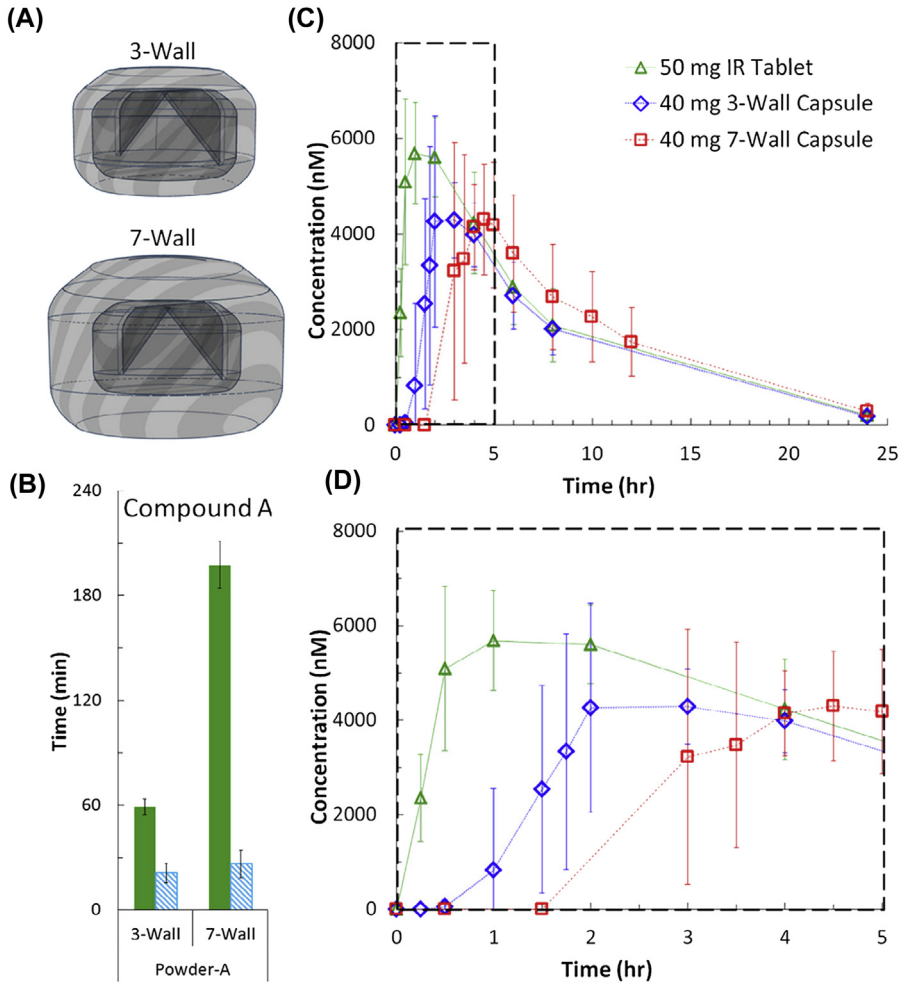


FIGURE 2.16 (A) Computer-aided design images of 3-wall and 7-wall polyvinyl alcohol capsules, (B) burst (green *[dark gray in printed version]* bars) and 85% release (blue *[dark gray in printed version]* patterned bars) graphs in vitro dissolution for 3-wall and 7-wall powder-A filled capsules, (C) in vivo drug concentrations in blood in dogs for the 50 mg immediate release (IR) tablet and 40 mg 3-wall and 7-wall powder-A filled capsules, and (D) enlarged inset of (C) for the first 5 h.

quality functions. As of now, 3DP is not considered as a mass production technology due to limitations in hardware and material and has been used for products requiring moderate throughput. However, should the pharmaceutical industry look to leverage distributed manufacturing and personalized medicine, 3DP is poised to disrupt traditional pharmaceutical mass production. From a quality point of view, the current mode of releasing pharmaceutical product relies on the testing of a statistically relevant subset of the aforementioned mass-produced product, whereas 3DP layered with process analytical technology has the potential to offer an advantage of in-depth analytical prosecution for every dosage form being produced. Due to the intrinsic layer-by-layer construction of the 3D-printed dosage form, process analytical technologies can evaluate these layers during production, which is not

capable with traditional pharmaceutical processing. As discussed earlier, because of the novelty of this technology, regulatory guidance does not exist for drug products but as industry and academicians push forward R&D into commercial space, we anticipate alignment and regulation as has happened historically for other process technologies.

The primary advantage that is offered and frequently discussed by 3DP is with customization. To this end, one version of the pharmaceutical industry future looks to address patient centric dosing in terms of combining multiple medications and controlling for drug release rates that are tuned to maximize efficacy and minimize side effects based on a patient's phenotype and genotype. Traditional pharmaceutical process technologies do not offer this level of per dosage form customization and 3DP is on the verge of disrupting this industry to provide dosage forms that accomplish these goals. The key to achieving this relies on the repurposing of traditional materials and development of novel materials that provide the level of quality needed for meeting drug product specifications. Material and 3DP vendors and academic and industrial research units have shown significant progress for pushing the technology for pharmaceutical applications and the authors believe that this trend will continue in the foreseeable future.

References

[1] DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceuticalindustry: new estimates of R&D costs. J Health Econ 2016;47:20–33.

[1a] Herper M. The cost of creating a new drug now $5 billion, pushing big pharma to change. 2013.

[1b] Chai X, Chai H, Wang X, Yang J, Li J, Zhao Y, Cai W, Tao T, Xiang X. Fused deposition modeling (FDM) 3D printed tablets for intragastric floating delivery of domperidone. Sci Rep 2017;7:2829.

[2] Goyanes A, Fina F, Martorana A, Sedough D, Gaisford S, Basit AW. Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing. Int J Pharm 2017.

[3] Yang Y, Wang H, Li H, Ou Z, Yang G. 3D printed tablets with internal scaffold structure using ethyl cellulose to achieve sustained ibuprofen release. Eur J Pharm Sci 2018;115:11–8.

[4] Arafat B, Wojsz M, Isreb A, Forbes RT, Isreb M, Ahmed W, Arafat T, Alhnan MA. Tablet fragmentation without a disintegrant: a novel design approach for accelerating disintegration and drug release from 3D printed cellulosic tablets. Eur J Pharm Sci 2018b; 118:191–9.

[5] Goyanes A, Chang H, Sedoug h D, Hatton GB, Wang J, Buanz A, Gaisford S, Basit AW. Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing. Int J Pharm 2015b;496:414–20.

[6] Skowyra J, Pietrzak K, Alhnan MA. Fabrication of extended-release patient tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. Eur J Pharm Sci 2015;68:11–7.

[7] Tagami T, Nagata N, Hayashi N, Ogawa E, Fukushige K, Sakai N, Ozeki T. Defined drug release from 3D-printed composite tablets consisting of drug-loaded polyvinylalcohol and a water-soluble or water-insoluble polymer filler. Int J Pharm 2018;543: 361–7.

[8] Goyanes A, Martinez PR, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. Int J Pharm 2015c;494:657–63.

[9] Li Q, Wen H, Jia D, Guan X, Pan H, Yang Y, Yu S, Zhu Z, Xiang R, Pan W. Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing. Int J Pharm 2017;525:5–11.

[10] Okwuosa TC, Pereira BC, Arafat B, Cieszynska M, Isreb A, Alhnan MA. Fabricating a shell-core delayed release tablet using dual FDM 3D printing for patient-centred therapy. Pharm Res 2017;34:427–37.

[11] Korte C, Quodbach J. Formulation development and process analysis of drug loaded filaments manufactured via hot-melt extrusion for 3D-printing of medicines. Pharm Dev Technol 2018:1–11.

[12] Korte C, Quodbach J. 3D printed network structures as controlled-release drug delivery systems: dose adjustments, API release analysis and prediction. AAPS PharmSciTech 2018b;19(8):3333–42.

[13] Nasereddin JM, Wellner N, Alhijjaj M, Belton P, Qi S. Development of a simple mechanical screening method for predicting the feedability of a pharmaceutical FDM 3D printing filament. Pharm Res 2018;35:151.

[14] Sadia M, Sośnicka A, Arafat B, Isreb A, Ahmed W, Kelarakis A, Alhnan MA. Adaptation of pharmaceutical excipients to FDM 3Dprinting for the fabrication of patient-tailored immediate release tablets. Int J Pharm 2016;513:659–68.

[15] Guvendiren M, Molde J, Soares RMD, Kohn J. Designing biomaterials for 3D printing. ACS Biomater Sci Eng 2016;2(10):1679–93.

[16] Ligon SC, Liska R, Stampfl J, Gurr M, Mulhaupt R. Polymers for 3D printing and customized additive manufacturing. Chem Rev 2017;115(15):10212–90.
[17] Turner BN, Strong R, Gold SA. A review of melt extrusion additive manufacturing processes: I. Process design and modeling. Rapid Prototyp J 2014;20(3): 192–204.
[18] Panaitescu DM, Frone AN, Chiulan I. Nanostructured biocomposites from aliphatic polyesters and bacterial cellulose. Ind Crops Prod 2016;93:251–66.
[19] Chiulan I, Frone AN, Brandabur C, Panaitescu DM. Recent advances in 3D printing of aliphatic polyesters. Bioengineering 2018;5:2–18.
[20] Brady J, Dürig T, Lee PI, Li JX. Chapter 7- polymer properties and characterization. Developing solid oral dosage forms. 2nd ed. Pharmaceutical Theory and Practice; 2017. p. 181–223.
[21] Pinto E, Dürig T. Chapter 5- Cellulose ethers for extrusion application. In: Melt extrusion: materials, technology and drug product design; 2013. p. 123–44.
[22] Zhang J, Feng X, Patil H, Tiwari RV, Repka MA. Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets. Int J Pharm 2017;519: 186–97.
[23] Kozin ED, Black NL, Cheng JT, Cotler MJ, McKenna MJ, Lee DJ. Design, fabrication, and in vitro testing of novel three-dimensionally printed tympanic membrane grafts. Hear Res 2016. 203, 340:191.
[24] Handbook of pharmaceutical excipients. 6th ed. p. 525–533.
[25] Jamróz W, Kurek M, Łyszczarz E, Szafraniec J, KnapikKowalczuk J, Syrek K. 3D printed orodispersible films with aripiprazole. Int J Pharm 2017;533: 413–20.
[26] Beck RCR, Chaves PS, Goyanes A, Vukosavljevic B, Buanz A, Windbergs M, Basit AW, Gaisford S. 3D printed tablets loaded with polymeric nanocapsules: an innovative approach to produce customized drug delivery systems. Int J Pharm 2017;528:268–79.
[27] Fina F, Goyanes A, Gaisford S, Basit AW. Selective laser sintering (SLS) 3D printing of medicines. Int J Pharm 2017;529:285–93.
[28] Katstra WE, Palazzolo RD, Rowe CW, Giritlioglu B, Teung P, Cima MJ. Oral dosage forms fabricated by three dimensional printing (TM). J Control Release 2000;66:1–9.
[29] Bühler V. In: Kollidon® Polyvinylpyrrolidone excipients for the pharmaceutical industry. 9th revised ed. 1992. p. 14.
[30] Tagami T, Fukushige K, Ogawa E, Hayashi N, Ozeki T. 3D printing factors important for the fabrication of polyvinylalcohol filament-based tablets. Biol Pharm Bull 2017;40:357–64.
[31] Konta AA, Pina Garcia M, Serrano DR. Personalized 3D printed medicines: which techniques and polymers are more successful? Bioengineering 2017;4:79. https://doi:10.3390/bioengineering4040079.
[32] Fuenmayor E, Forde M, Healy AV, Devine D,M, Lyons JG, McConville C, Major I. Material considerations for fused-filament fabrication of solid dosage forms. Pharmaceutics 2018;10:44. https://doi.org/10.3390/pharmaceutics10020044.
[33] Solanki NG, Tahsin M, Shah AV, Serajuddin ATM. Formulation of 3D printed tablet for rapid drug release by fused deposition modeling: screening polymers for drug release, drug-polymer miscibility and printability. J Pharm Sci 2018;107:390–401.
[34] American Chemical Council- Introduction to Polyurethanes: Thermoplastic Polyurethanes. https://polyurethane.americanchemistry.com/Introduction-to Polyurethanes/Applications/Thermoplastic-Polyurethane//.
[35] Tan KD, Maniruzzanan M, Nokhodchi A. Advanced pharmaceutical applications of hot-melt extrusion coupled with Fused deposition modelling (FDM) 3D printing with personalized drug delivery. Pharmaceutics 2018;10:203. https://doi.org/10.3390/pharmaceutics10040203.
[36] Hou MM. 3D printed filaments: what's the deal with ULTEM and PEEK? 2017. https://www.engineering.com/3DPrinting/3DPrintingArticles/ArticleID/14465/3D-Printing-Filaments-Whats-the-Deal-with-ULTEM-and-PEEK.aspx.
[37] Wu WZ, Geng P, Zhao Y, Rosen DW, Zhang HB. Manufacture and thermal deformation analysis of semicrystalline polymer polyether ether ketone by 3D printing. Mater Res Innov 2014;18. https://doi.org/10.1179/1432891714Z.000000000898.
[38] Kim SH, Yeon YK, Lee JM, Chao JR, Lee YJ, Seo YB, Lee JS. Precisely printable and biocompatible silk fibroin bioink for digital light processing 3D printing. Sang Jin Lee James J. Yoo 2018;3(17). https://doi.org/10.1038/s41467-018-03759-y.
[39] Bloomquist CJ, Mecham MB, Paradzinsky MD, Januszewicz R, Warner SB, Luft JC, DeSimone JM. Controlling release from 3D printed medical devices using CLIP and drug-loaded liquid resins. August 2017 J Control Release 2018;278:9–23. https://doi.org/10.1016/j.jconrel.2018.03.026.
[40] Tumbleston JR, Shirvanyants D, Ermoshkin N, Januszewicz R, Johnson AR, Kelly D, Desimone JM. Continuous liquid interface production of 3D objects. Science 2015;347(6228):635–9.
[40a] du Plessis A, le Roux SG, Steyn F. Quality investigation of 3D printer filament using laboratory X-ray tomography. 3D print, Additive Manuf 2016;3:262–7.

[40b] Markl D, Zeitler JA, Rasch C, Michaelsen MH, Müllertz A, Rantanen J, Rades T, Bøtker J. Analysis of 3D prints by X-ray computed microtomography and terahertz pulsed imaging. Pharm Res 2017;34:1037–52.

[41] Melocchi A, Parietti F, Loreti G, Maroni A, Gazzaniga A, Zema L. 3D printing by fused deposition modeling (FDM) of a swellable/erodible capsular device for oral pulsatile release of drugs. J Drug Deliv Sci Technol 2015;30:360–7.

[41a] Okwuosa TC, Pereira BC, Arafat B, Cieszynska M, Isreb A, Alhnan MA. Fabricating a shell-core delayed release tablet using dual FDM 3D printing for patient-centred therapy. Pharm Res 2017;34:427–37.

[41b] Okwuosa TC, Stefaniak D, Arafat B, Isreb A, Wan K-W, Alhnan MA. A lower temperature FDM 3D printing for the manufacture of patient-specific immediate release tablets. Pharm Res 2016;33:2704–12.

[42] Goyanes A, Buanz AB, Basit AW, Gaisford S. Fused-filament 3D printing (3DP) for fabrication of tablets. Int J Pharm 2014;476:88–92.

[43] Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. Eur J Pharm Biopharm 2015a;89:157–62.

[44] Goyanes A, Wang J, Buanz A, Martínez-Pacheco R, Telford R, Gaisford S, Basit AW. 3D printing of medicines: engineering novel oral devices with unique design and drug release characteristics. Mol Pharm 2015d;12:4077–84.

[44a] Kempin W, Franz C, Koster L-C, Schneider F, Bogdahn M, Weitschies W, Seidlitz A. Assessment of different polymers and drug loads for fused deposition modeling of drug loaded implants. Eur J Pharm Biopharm 2017;115:84–93.

[45] Arafat B, Qinna N, Cieszynska M, Forbes RT, Alhnan MA. Tailored on demand anti-coagulant dosing: an in vitro and in vivo evaluation of 3D printed purpose-designed oral dosage forms. Eur J Pharm Biopharm 2018a;128:282–9.

[46] Khaled SA, Burley JC, Alexander MR, Roberts CJ. Desktop 3D printing of controlled release pharmaceutical bilayer tablets. Int J Pharm 2014;461:105–11.

[47] Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. J Control Release 2015a;217:308–14.

[48] Melocchi A, Parietti F, Maroni A, Foppoli A, Gazzaniga A, Zema L. Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling. Int J Pharm 2016.

[49] Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3D printing of tablets containing multiple drugs with defined release profiles. Int J Pharm 2015b;494:643–50.

[50] Smith D, Kapoor Y, Klinzing G, Procopio A. Pharmaceutical 3D printing: design and qualification of a single step print and fill capsule. Int J Pharm 2018a;544(2018):21–30.

[51] Smith D, Kapoor Y, Hermans A, Nofsinger R, Kesisoglou F, Gustafson T, Procopio A. 3D printed capsules for quantitative regional absorption studies in the GI tract. Int J Pharm 2018b;550:418–28.

[52] Fina F, Madla CM, Goyanes A, Zhang J, Gaisford S, Basit AW. Fabricating 3D printed orally disintegrating printlets using selective laser sintering. Int J Pharm 2018;541:101–7.

[53] Nippon Gohsei. Melfil™ product brochure. 2016. http://www.nippon-gohsei.com/cache/downloads/7m5hyx0hc1wkc08cg8k40occ4/MELFIL%20Brochure%202016%20English.pdf.

Further reading

Laulicht B, Tripathi A, Schlageter V, Kucera P, Mathiowitz E. Understanding gastric forces calculated from high-resolution pill tracking. Proc Natl Acad Sci 2010;107:8201–6.

Lennernäs H, Ahrenstedt Ö, Hällgren R, Knutson L, Ryde M, Paalzow LK. Regional jejunal perfusion, a new in vivo approach to study oral drug absorption in man. Pharm Res 1992;9:1243–51.

Maroni A, Melocchi A, Parietti F, Foppoli A, Zema L, Gazzaniga A. 3D printed multi-compartment capsular devices for two-pulse oral drug delivery. J Control Release 2017;268:10–8.

Martinez PR, Goyanes A, Basit AW, Gaisford S. Influence of geometry on the drug release profiles of stereolithographic (SLA) 3D-printed tablets. AAPS PharmSciTech 2018:1–7.

Melocchi A, Parietti F, Maccagnan S, Ortenzi MA, Antenucci S, Briatico-Vangosa F, Maroni A, Gazzaniga A, Zema L. Industrial development of a 3D-printed nutraceutical delivery platform in the form of a multicompartment HPC capsule. AAPS PharmSciTech 2018:1–12.

Okwuosa TC, Soares C, Gollwitzer V, Habashy R, Timmins P, Alhnan MA. On demand manufacturing of patient-specific liquid capsules via co-ordinated 3D printing and liquid dispensing. Eur J Pharm Sci 2018;118:134–43.

Sun Q, Rizvi G, Bellehumeur C, Gu P. Effect of processing conditions on the bonding quality of FDM polymer filaments. Rapid Prototyp J 2008;14:72–80.

Wang J, Goyanes A, Gaisford S, Basit AW. Stereolithographic (SLA) 3D printing of oral modified-release dosage forms. Int J Pharm 2016;503:207–12.