



CHALMERS
UNIVERSITY OF TECHNOLOGY

Polymers in pharmaceutical additive manufacturing: A balancing act between printability and product performance

Downloaded from: <https://research.chalmers.se>, 2024-03-13 06:58 UTC

Citation for the original published paper (version of record):

Govender, R., Kissi, E., Larsson, A. et al (2021). Polymers in pharmaceutical additive manufacturing: A balancing act between printability and product performance. *Advanced Drug Delivery Reviews*, 177.
<http://dx.doi.org/10.1016/j.addr.2021.113923>

N.B. When citing this work, cite the original published paper.



Polymers in pharmaceutical additive manufacturing: A balancing act between printability and product performance

Rydvikha Govender^a, Eric Ofosu Kissi^{b,c}, Anette Larsson^a, Ingunn Tho^{b,*}

^a Department of Chemistry and Chemical Engineering, Chalmers University of Technology, SE-41296 Gothenburg, Sweden

^b Department of Pharmacy, University of Oslo, P.O. Box 1068 Blindern, NO 0316 Oslo, Norway

^c Nanoform Finland Oyj, Viikinkaari 4, 00790 Helsinki, Finland



ARTICLE INFO

Article history:

Received 2 May 2021

Revised 8 July 2021

Accepted 9 August 2021

Available online 11 August 2021

Keywords:

3D printing

Characterization

Oral drug delivery

Processability

Macromolecules

Excipients

Quality by design

Process analytical technology

Fused deposition modelling

Digitalization

ABSTRACT

Materials and manufacturing processes share a common purpose of enabling the pharmaceutical product to perform as intended. This review on the role of polymeric materials in additive manufacturing of oral dosage forms, focuses on the interface between the polymer and key stages of the additive manufacturing process, which determine printability. By systematically clarifying and comparing polymer functional roles and properties for a variety of AM technologies, together with current and emerging techniques to characterize these properties, suggestions are provided to stimulate the use of readily available and sometimes underutilized pharmaceutical polymers in additive manufacturing. We point to emerging characterization techniques and digital tools, which can be harnessed to manage existing trade-offs between the role of polymers in printer compatibility versus product performance. In a rapidly evolving technological space, this serves to trigger the continued development of 3D printers to suit a broader variety of polymers for widespread applications of pharmaceutical additive manufacturing.

© 2021 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Contents

1. Introduction	2
2. The role of polymers in printability	3
2.1. Feeding	3
2.2. Deposition	5
2.3. Adhesion	6
2.4. Polymerization	6
2.5. Pharmaceutically approved polymers underutilized in AM	7
3. The role of polymers in product performance: Case examples highlighting potential trade-offs between printability and product performance	9
3.1. Trade-offs between printability and achieving and stabilizing the solid state	9

Abbreviations: 3D, three dimensional; AM, additive manufacturing; c, concentration; CAD, computer-aided design; CLIP, continuous liquid interface production; CQAs, critical quality attributes; DLP, digital light processing; DMA, dynamic mechanical analysis; DoD, drop-on-demand; DoP, drop-on-powder; DPE, direct powder extrusion; DSC, differential scanning calorimetry; EC, ethylcellulose; FDA, United States Food and Drug Administration; FDM, fused deposition modelling; FTIR, Fourier transform infrared spectroscopy; HEC, hydroxyethyl cellulose; HME, hot-melt extrusion; HPC, hydroxypropyl cellulose; HPMC, hypromellose; HPMCAS, hypromellose acetate succinate; MCC, microcrystalline cellulose; mDSC, modulated differential scanning calorimetry; Mw, molecular weight; Na-CMC, carboxymethylcellulose sodium; NIR, near infrared spectroscopy; PAM, pressure-assisted microsyringe; PAT, process analytical technology; PCL, polycaprolactone; PEG, polyethylene glycol; PEGDA, polyethylene glycol diacrylate; Ph.Eur., European Pharmacopoeia; PLA, polylactic acid; PVA, polyvinyl alcohol; QbD, Quality-by-Design; SANS, small-angle neutron scattering; SAXS, small-angle x-ray scattering; SEM, scanning electron microscopy; SLA, stereolithography; SLS, selective laser sintering; SSE, semisolid extrusion; TGA, thermogravimetric analysis; T_{deg}, degradation temperature; T_g, glass transition temperature; T_m, melting temperature; TPI, terahertz pulsed imaging; XRPD, X-ray powder diffraction; X-ray μ CT, X-ray computed microtomography; WAXS, wide-angle x-ray scattering.

* Corresponding author at: Section of Pharmaceutics and Social Pharmacy, Department of Pharmacy, University of Oslo, P.O. Box 1068 Blindern, NO-0316 Oslo, Norway.

E-mail address: ingunn.tho@farmasi.uio.no (I. Tho).

<https://doi.org/10.1016/j.addr.2021.113923>

0169-409X/© 2021 The Authors. Published by Elsevier B.V.

This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

3.2.	Trade-offs between printability and drug delivery	11
4.	Characterization techniques used in additive manufacturing	12
4.1.	Thermal techniques	14
4.1.1.	Thermogravimetric analysis (TGA)	14
4.1.2.	Differential scanning calorimetry (DSC)	14
4.1.3.	Dynamic mechanical analysis (DMA)	14
4.1.4.	Defining printing temperature windows from several thermal techniques in combination	15
4.2.	Mechanical and powder flow techniques	15
4.2.1.	Compression, tensile, and indentation tests	15
4.2.2.	Interlayer adhesion test	16
4.2.3.	Powder flow	16
4.3.	Rheological techniques	16
4.4.	Techniques to measure surface tension	17
4.5.	Spectroscopic techniques	17
4.5.1.	Near infrared spectroscopy (NIR)	18
4.5.2.	Fourier transform infrared spectroscopy (FTIR)	18
4.5.3.	Raman spectroscopy	18
4.6.	Scattering techniques	18
4.6.1.	X-ray powder diffractometry	18
4.6.2.	Small- and wide-angle X ray scattering and small-angle neutron scattering	18
4.7.	Imaging techniques	18
4.7.1.	Scanning electron microscopy (SEM)	19
4.7.2.	X-ray computed microtomography	19
4.7.3.	Emerging imaging techniques	19
4.8.	Advanced use of characterization techniques for complex applications	19
4.8.1.	Process analytical technology (PAT)	19
4.8.2.	<i>In silico</i> techniques and other digital tools	20
4.9.	Choosing the right techniques for the right purpose	21
5.	Conclusion	21
6.	Expert opinion	22
	Funding	22
	Declaration of Competing Interest	22
	References	22

1. Introduction

Additive manufacturing (AM), colloquially termed 3D printing, encompasses a range of manufacturing technologies which are characterized by layer-by-layer material deposition to fabricate three-dimensional objects under digital control based on a computer-aided design (CAD) model or scan [1–10]. Beyond rapid prototyping, its utility over conventional pharmaceutical product fabrication has been mainly attributed to its high design freedom, which enables customization, its ability to form parts with complex internal and external geometries, and its ability to rapidly modify parts without the need for retooling [2,3,11,12]. Realizing these advantages relies on an intricate interplay between the design, the process parameters, the tooling, and the materials to be processed. A variety of materials have been used in AM in healthcare applications, including metals, ceramics, and polymers, with the latter being of primary relevance to pharmaceutical dosage forms [13,14].

The oral route of administration, especially the delivery of solid oral dosage forms, remains the predominant route of administration for pharmaceutical products for several reasons including its convenience, ease of handling and portability, suitability for self-administration, and so forth. Therefore, this review will focus on the role of polymeric materials in AM of oral pharmaceutical dosage forms, together with appropriate characterization methods for understanding and optimizing AM processability and product performance. Several reviews of polymers in AM have emerged recently, which specify pharmaceutical applications [15–23]. Comprehensive summaries and exemplification of polymers in AM can be found therein, with exhaustive lists of polymer types and characterization techniques used in AM. However, key questions

remain regarding the extent of utilization of pharmaceutically approved polymers across various AM technologies, i.e., which polymers are not yet used and why? In addition, how do polymer properties relevant to different stages of the AM process, e.g. feeding, deposition, and adhesion, compare across the various AM technologies used in pharmaceutical research? Lastly, are the characterization techniques already used to assess product performance equally suited to assess printability? To answer these questions, this review primarily highlights the interface between the polymer and key stages of the AM process that determine printability. Here, printability involves the capability to generate reproducible printed objects according to the specifications of the intended design [24]. By systematically clarifying and comparing selected polymer functional roles and properties for a variety of AM technologies, together with the means to characterize these properties, suggestions are provided to stimulate the use of underutilized but already available pharmaceutical polymers and emerging analytical tools to guide the evolution of AM for pharmaceutical applications. For the purposes of this review, process stages influencing printability are limited from process input to process output. Post-processing steps that can further enhance product quality or correct or mask print defects are considered out of scope.

Beyond this introduction in Section 1, Section 2 describes the various roles polymers need to exhibit to facilitate printability for different AM technologies. Section 3 highlights some trade-offs faced when balancing printability and product performance, with specific examples involving achieving the desired solid state and facilitating drug delivery. Section 4 summarizes current and emerging polymer characterization techniques as they relate to understanding, optimizing and monitoring printability of poly-

mers. Section 5 concludes the key findings of this review with an expert opinion provided in Section 6, where the authors offer perspective to guide further progress in this rapidly evolving field.

2. The role of polymers in printability

According to ISO/ASTM 52900, there are 7 process categories of additive manufacturing, each with several specific process examples [25]. These include material extrusion (e.g. fused deposition modelling (FDM), pressure-assisted micro-syringe (PAM) printing, melt extrusion deposition), material jetting (e.g. drop-on-demand (DoD) printing on a substrate), binder jetting (e.g. drop-on-powder (DoP) printing), powder bed fusion (e.g. selective laser sintering (SLS)), VAT polymerization (e.g. stereolithography (SLA), digital light processing (DLP), continuous liquid interface production (CLIP)), directed energy deposition (e.g. laser metal deposition), and sheet lamination (e.g. laminated object manufacture). Except for the latter two, these additive manufacturing process categories have been employed for pharmaceutical applications in the academic research setting. Furthermore, in 2015, the antiepileptic Spritam® (levetiracetam) from Aprelia Pharmaceuticals, fabricated by a binder jetting process patented as ZipDose® technology, gained market approval from the FDA [26]. More recently, in 2021, T19 from Triastek, fabricated by a material extrusion process called melt extrusion deposition, gained FDA clearance as an investigational new drug for rheumatoid arthritis [27,28]. For detailed descriptions of all operations for all AM technologies, which have different working mechanisms, the reader is referred to dedicated reviews on each AM technology [29–34]. In this section, we instead compare AM technologies across a few key process stages, namely feeding, deposition, and adhesion. These three process stages are not only highlighted because they are common to several (but not all) pharmaceutical AM technologies but also because they are key determinants of product quality upon 3D printing. Fig. 1 summarizes key polymer functions for common stages of the AM process, accompanied by the specific polymer properties that are required to elicit these functions. In the discussions of each of these important process steps in Sections 2.1–2.4, we describe some of

the key polymer functions required for printability, together with examples of currently used polymers. In Section 2.5, we identify some under-utilized pharmaceutically approved polymers which are still under-utilized in AM despite exhibiting potentially suitable properties for printability.

To select appropriate polymers for oral dosage forms fabricated by AM and critically examine their use in different AM technologies, the well-established Handbook of Pharmaceutical Excipients served as an important tool in this review [35], from which around 70 pharmaceutically approved polymers were identified. By subsequently inserting their common names and CAS numbers into SciFinder (© 2021 American Chemical Society), a list of search hits was generated. These were filtered for relevant examples of original research articles from the different AM technologies with products that could be orally administered. Polymers that are commonly used for biomedical purposes, such as agarose, polyetheretherketone, and polyurethanes, were excluded. More than 30 polymers were identified for use in pharmaceutical AM of oral dosage forms (Table 1). The reader is referred to the references listed within Table 1 for specific details on the exact functionality of each polymer and the compositions of the specific printed formulations.

2.1. Feeding

Feeding into the nozzle is a critical step towards printability. This function is discussed with respect to all process categories mentioned above, except for powder bed fusion and VAT polymerization, which lack nozzle-based working principles. Different AM processes are compatible with different forms of feedstock, giving rise to different material properties of relevance (Fig. 1).

During FDM, a melt extruded polymeric filament feedstock is fed through the nozzle via rotating drive gears. The feeding of the filament through the drive gears of the FDM machinery generates the pressure required to initiate deposition of high-viscosity melts [73,86]. The FDM feeding mechanism is therefore not only controlled by the AM machinery but also by the filament itself. The implication of this is that selection of the filament composition

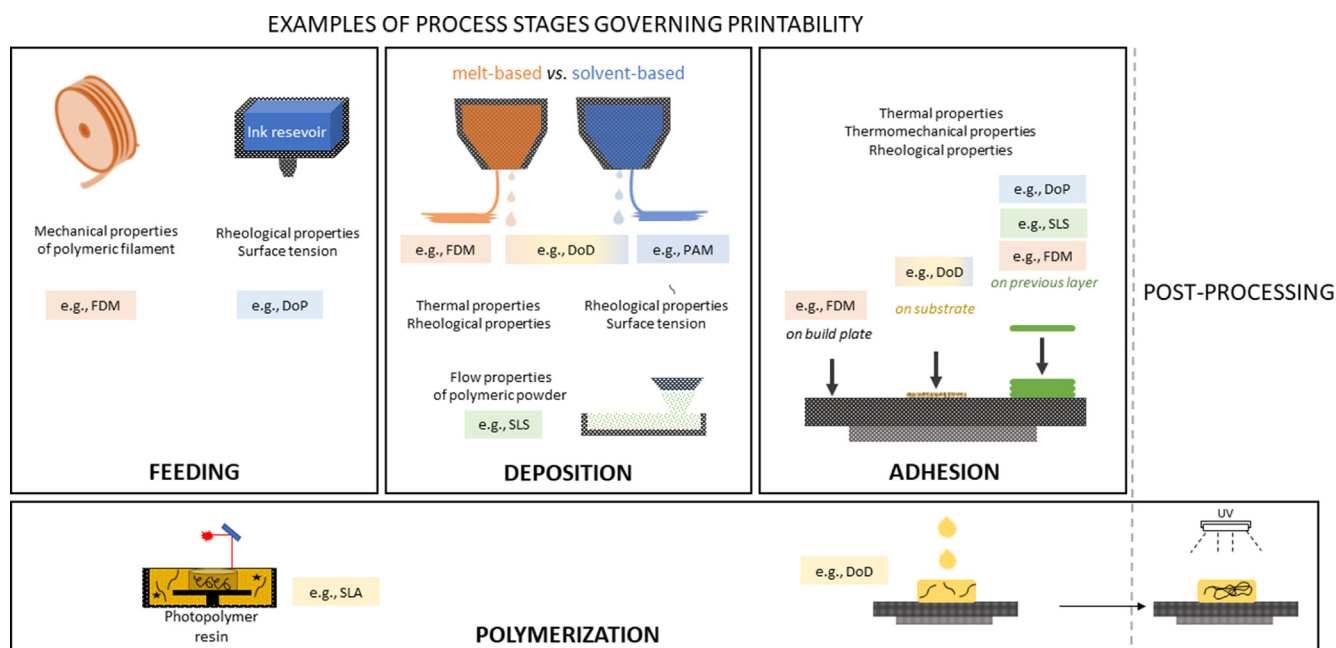


Fig. 1. A deconstructed AM process for selected AM technologies showing examples of key polymer properties of relevance at each stage. FDM = fused deposition modelling, SLS = selective laser sintering, DoD = drop-on-demand printing, PAM = pressure-assisted micro-syringe, DoP = drop-on-powder printing, SLA = stereolithography.

Table 1

List of pharmaceutically approved polymers with referenced examples indicating their oral drug delivery applications in various AM technologies. FDM = fused deposition modelling, PAM = pressure-assisted micro-syringe, SLS = selective laser sintering, DoP = drop-on-powder printing, DoD = drop-on-demand printing.

Polymer	AM Technology				
	Material Extrusion		Powder Bed Fusion SLS	Binder Jetting DoP	Material Jetting DoD
	FDM	PAM			
carbomer		[36]			
carboxymethylcellulose sodium (Na-CMC)		[37]			
cellulose acetate	[38]	[39]			
cellulose acetate phthalate	[40]				
cellulose (microcrystalline cellulose, MCC)		[36,41]	[42]	[43–45]	
copovidone (Kollidon® VA64)	[46–50]		[42,51]		
croscarmellose sodium		[37,52]			
crospovidone		[36]			
ethylcellulose (EC)	[47,49]		[53,54]	[55–57]	
gelatin		[41]			[58]
hydroxyethyl cellulose (HEC)	[59]	[60]			
hydroxypropyl cellulose (HPC)	[48,49,59,61–63]				
hypromellose (HPMC)	[46,47]	[39,41,52,64]	[51]	[55–57]	[65–67]
hypromellose acetate succinate (HPMCAS)	[68]				
hypromellose phthalate	[40,69]				
maltodextrin	[48]	[60,70]		[71]	
pectin		[70]			
poloxamer (Pluronic®)		[72]			[67]
polycaprolactone (PCL)	[40,73]		[74]	[75]	
polyethylene glycol (PEG)	[40,47–49,63,76]	[39]		[45,77]	[66,67]
polyethylene oxide (PEO)	[59,62,63,76]			[75]	
polylactic acid (PLA)	[50,78]				
polymethacrylates (Eudragit®)	[40,47]		[79]	[43,44,55]	
polyoxyethylene sorbitan fatty acid esters (Polysorbate 20, Tween® 20)	[46,76]			[44,71]	[80]
Polyoxylglycerides (Gelucire®)	[46]				
polyvinyl alcohol (PVA)	[38,47,49,50,76,78,81,82]				
polyvinyl alcohol/polyethylene glycol graft copolymer (Kollicoat® IR)	[48]		[53,79]		
polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer (Soluplus®)	[46,47,76]			[77]	
povidone (Kollidon® PVP)	[38,40,47,83]	[39,52]		[43–45,55,57,71]	[80]
pullulan		[84]			
sodium starch glycolate		[39]			
starch					[85]

is required to deliver both the required final product performance (e.g. in terms of appropriate and accurate dose, drug release, stability, and so forth) and enable the filament to facilitate printability by acting as a piston during FDM. In addition to facilitating printability during the feeding step, the polymers listed in Table 1 under the FDM category have additional functions in the formulations, for example, as drug carriers, compartment builders, or plasticizers. In the following paragraph, material properties exclusively for printability during the feeding stage will be addressed. Material properties for product performance will be introduced in Section 3 to elucidate the major balancing act between printability and product performance that needs to be solved to successfully integrate AM technologies into the pharmaceutical space.

The success of the feeding step during FDM is primarily governed by the filament mechanical properties (Fig. 1) and includes measures of stiffness, flexibility, tensile strength, Young's modulus, toughness, yield strength, and ductility [29,73,87]. Melt-extruded filaments for pharmaceutical FDM are typically solid dispersions of the drug in a thermoplastic polymeric carrier (Table 1), with potential inclusion of additional excipients in the formulation. These excipients include polymeric additives acting as plasticizers to promote printability, such as PEG and Pluronic® [48,88]. Alternatively, drug-free polymeric filaments, containing PVA or PLA, for example, have been used to generate capsules or alternative compartmentalized product architectures [78,89]. In both cases, filament mechanical properties are dictated in part by the polymer type and content, particularly when the polymer(s) forms a large fraction of the composition. If the resulting filament is too brittle, it will break under the force of the drive gears. If the filament is

too soft, it will deform between the drive gears and fail to act as a piston to drive deposition from the nozzle. In addition to mechanical properties, material thermal properties are also highly relevant for FDM feeding. Firstly, thermal properties and mechanical properties are correlated. The thermal properties of relevance for the polymer include its glass transition temperature (T_g), melting temperature (T_m), thermal degradation temperature (T_{deg}) and heat distribution [15,76,90,91]. Since polymers could be semi-crystalline, the softening of polymers could occur at any point between the T_g and T_m and does not necessarily require melting to occur. Plasticizing the polymer with other excipients, plasticizing drugs, or moisture, leads to depression of T_g , which will alter both the thermal and mechanical behaviour. The inclusion of polymers which have too low a T_g or T_m , like gelatin ($T_m < 35^\circ\text{C}$) [92], will be unsuitable for feeding as an FDM feedstock, when included in high proportions as carriers, since this often results in filaments which are too soft for successful feeding. This challenge of filament feeding is further compounded with natural polymers, which exhibit an inherent variation of properties. For example, the T_g of shellac has been reported to vary between 33°C and 52°C [93]. Thermal properties and rheological properties are inter-related and together influence feeding. The primary rheological property of interest is viscosity [94,95]. High-viscosity melts at the nozzle end require tougher filaments to force it through the nozzle orifice at a given temperature. Low-viscosity melts at the nozzle end could result in failure of the piston mechanism if it results in pooling of molten material in the heating chamber above the nozzle. Using polymers which have sufficiently wide thermal processing windows between T_g or T_m and T_{deg} can help in optimizing the vis-

cosity of the material reaching the nozzle for optimal feeding. The viscosity of the polymer melt can also be controlled by using the same type of polymer at a different molecular weight for optimizing feeding. Several viscosity grades are available for PEO and HPMCAS for this purpose. An important consideration is that the short exposure time to heat during FDM feeding means that thermal gradients in polymer-based materials are expected to play a key role in obtaining the desired melt viscosity and therefore printability during the feeding step.

To circumvent the reliance on filaments with optimal mechanical properties during FDM feeding, an alternative but related technique has been introduced, namely direct powder extrusion (DPE) [96,97], also trademarked as melt extrusion deposition [28]. As the name suggests, this process allows direct feeding of raw materials or physical mixtures into a built-in extruder upstream of the printer nozzle. This process solves a critical and challenging material property encountered during FDM, specifically during the feeding stage of printing. In doing so, the range of processible materials is potentially expanded for DPE compared to FDM. In the authors' collective view, such an evolution of AM technologies towards enhanced material diversity will be a key deciding factor in the extent of applicability of AM to future pharmaceutical products. The development of DPE did not merely involve selection of an alternative existing filament-free AM technology but rather focused on the specific stage and specific material property that required improvement in a conventional FDM process. The material thermal properties and rheological properties discussed above remain relevant to the working principle of DPE. However, due to the use of raw materials or physical mixtures which do not require pre-processing and are in powder form when exposed to the relatively large heated surface and high shear of the built-in extruder, thermal gradients that exist with melt-extruded filaments and short residence times during FDM become a far less critical factor in determining printability in the feeding stage of DPE. Notably, melt-based DoD technologies offer a similar benefit for printability during feeding, especially when powder feedstocks are used. However, when pre-extruded and pelletized feedstocks are favoured for melt-based DoD, DPE offers greater process efficiency without its reliance on a separate upstream pre-processing unit operation.

Feeding of solvents instead of melts through a nozzle may occur for certain AM technologies for example, PAM and solvent-based DoD. Although PAM is often used interchangeably with semisolid extrusion 3D printing (SSE) in the pharmaceutical AM literature [30,84,98], there are also instances where SSE is described as a broader conceptual term encompassing different material extrusion mechanisms, for example, pneumatic extrusion, mechanical extrusion, and solenoid extrusion [99]. For this review, we exemplify the SSE category with PAM to represent the deposition of gels and pastes typically through non-heated nozzles (although heat could optionally be introduced). In addition to FDM mentioned above, both PAM and solvent-based DoD require an extra process step (i.e., dissolving and/or dispersing) before feeding into the AM technology. For solvent-based DoD, a drop generator is located above the orifice as part of the machinery, which is connected to a reservoir of ink via a channel that restricts flow and controls the refilling process. For the refilling process to function optimally, viscosity and surface tension are important attributes [100]. Polymers may be added to the solution to modify each of these properties, however, both surface tension and viscosity are typically optimized with priority on controlling drop dynamics during deposition and not the feeding. These properties and the role of the polymer in modifying them for solvent-based DoD printing as well as PAM will therefore be addressed in more detail in Section 2.2. Similar to DoD, the feedstock in PAM should have an appropriate viscosity to arrive at the nozzle orifice and the generation of this feedstock also requires an extra process step before PAM.

2.2. Deposition

One of the most crucial polymer functions that governs printability for several AM techniques is deposition from a nozzle. Deposition may occur through a heated or non-heated nozzle, each of which requires different polymer properties (Fig. 1).

Deposition through a heated nozzle occurs during FDM, melt extrusion deposition, and melt-based DoD printing on a substrate. These AM technologies require polymers to be thermoplastic, as mentioned in Section 2.1. Therefore, thermal and rheological properties are relevant for deposition through the heated nozzle. FDM deposition or melt extrusion deposition, which involve continuous extrusion from the heated nozzle, can occur above the T_g or above the T_m of the formulation. Notably, all melt-based AM technologies with continuous extrusion from the nozzle may give rise to die swell [101]. Melt-based DoD, however, is characterized by the deposition of droplets and therefore requires printing above the T_m to provide an appropriate melt viscosity for droplet formation and deposition [66,67].

Using polymers with a high T_g in AM technologies with heated nozzles typically requires decreasing of the T_g , which can be obtained by mixing with excipients which have more suitable thermoplastic properties [102]. A low T_g excipient can give rise to plasticization if it is compatible with and mixed well with a polymeric carrier with a higher T_g . These plasticizers may either be small molecules or polymers. One example of a commonly used polymeric plasticizer in AM applications is PEG [76,103]. Polymers with too low T_g that are processed alone without antiplasticization provided by other components in the formulation, may result in uncontrolled and inaccurate deposition from heated nozzles, due to low melt viscosities at the processing temperatures encountered during melt-based AM printing. An example of a polymer with a low T_g in the presence of moisture is polydextrose, which exhibits a T_g below room temperature at 50% relative humidity [104], potentially too low to achieve appropriate rheological properties on its own for processing through heated nozzles. In contrast, calcium alginate or barium alginate exhibit an increased T_g as the amount of ions increases and as the extent of cross-linking between the divalent cations and the polymer chains increases [105]. This may require a processing temperature which exceeds that which is possible with the heated nozzles in AM. This phenomenon is also observed for covalent cross-linked carboxymethylcellulose sodium [106]. Other polymers which have a high T_g , for example, methylcellulose, polymethyl vinyl ether/maleic anhydride, and zein ($T_g > 150^\circ\text{C}$) [35], may also hinder deposition when used alone, necessitating careful selection of plasticizers [107]. The potentially plasticizing effects of added of drugs and exposure to moisture also needs to be taken into account when optimizing the printability of the polymer formulation in heat-based AM.

For deposition through non-heated nozzles, polymer properties of interest are governed by whether the deposition process is extrusion-based or jetting-based. An example of the former is SSE via PAM. The polymers used in PAM (Table 1) have different functions in the formulations, for example providing appropriate rheological properties, providing the required solids content to the formulation, and achieving the desired final product performance. Rheological properties, particularly viscosity, yield point and yield stress under shear and pressure, are crucial [5]. The yield point refers to the stress required to initiate flow. For materials which have a high yield point, the deposition of the material will be limited by the maximum pressure applied by the printer and the maximum shear forces tolerated by the material. For materials which have too low a yield point, there could be uncontrolled leakage of material from the nozzle under the influence of gravity. The importance of rheology for PAM is demonstrated by the fact that

polymers used in PAM are traditionally classified as thickening (viscosity-increasing) agents (see Table 1, e.g. carbomer, HEC, HPMC and PVP). The semi-solid nature of formulations for PAM mean that polymer concentrations are often above the overlap concentration. However, in PAM, since the content of gel-forming polymer can be quite low, the formulations often include solid excipients that serve to increase the solid content of the dried dosage forms in order to shape and strengthen the structure or provide specific product properties or performance. These are polymers that are traditionally used in oral tablets or capsules, like diluents (Table 1, MCC) and disintegrants (Table 1, MCC, sodium starch glycolate, carboxymethylcellulose sodium). Since the solids content will influence the rheological properties of the paste, not only should it contribute to the final product structural integrity but it should also be optimized to ensure appropriate deposition.

With solvent-based jetting processes, surface tension and viscosity are the primary formulation properties of interest, which govern drop dynamics. Although the main carriers in these processes are solvents, polymers may be included to obtain the required properties [108]. Viscosity and surface tension act together to contribute to printability during DoD printing. For deposition to occur, sufficient pressure should be applied above the nozzle to overcome the viscous forces and surface tension of the liquid and deposit the droplet [108]. This pressure is supplied by piezoelectric, electrostatic, or thermal actuators [5]. Upon ejection of a liquid jet from the nozzle, the surface tension is a major factor responsible for droplet formation [109,110]. Sufficiently low surface tensions are required for droplet formation. At the same time, sufficiently high surface tensions are required to prevent leaking from the nozzle when deposition is not occurring [100,108,110]. An optimal surface tension working range has been reported to lie between 30 and 70 mN/m [8,12,111] and the optimal viscosity should be between 2 and 20 mPas, typically around 10 mPas [109], which is low enough to facilitate ejection from the nozzle and high enough to discourage the formation of satellite droplets [108,109]. The reader is referred to Alomari et al. [100], where surface tensions and viscosities for a range of printed formulations are tabulated. The inclusion of polymers in the formulation could contribute to achieving optimal surface tensions and viscosities of printing inks for successful deposition [109]. The most commonly used polymeric viscosity modifier for DoD technologies is PEG [100]. Examples of polymers that have been used for jetting techniques with the aim to control both surface tension and viscosity are amphiphilic cellulose derivatives like the commonly used HPMC, whereas others like HEC and HPC have the potential to be utilized more in future (Table 1). A further example of a polymer commonly used to control surface tension is the polymer-based surfactant, Tween®, whereas other surfactants like Pluronic® and polyoxyethylene stearates have not been as frequently used for jetting technologies thus far. The same properties apply for melt-based DoD printing with the added consideration that, where molten polymers are the primary carrier, viscosity and surface tension are temperature-dependent [67]. Although thermoplastic properties are specific to deposition from heat-based extrusion-based AM and surface tension is specific to the jetting processes, the above discussion reveals that viscosity plays a central role as a material property defining the success of deposition regardless of the distinct working principles of the nozzle-based AM technologies.

SLS, a powder bed fusion process, is an example of non-nozzle-based deposition, where polymer powder is fed from a reservoir to the build-plate using a sled. Therefore, polymer powder flow properties, governed in part by powder particle morphology and particle size distribution, are of primary importance [112].

2.3. Adhesion

Adhesion to the build-plate, an alternative substrate, or the preceding deposited layer, is another crucial polymer function that constitutes printability (Fig. 1). During FDM, adhesion to the build plate and previous printed layer has been related to surface tension, viscosity, and mechanical properties like brittleness [87], all of which can be modulated through polymer selection or the addition of plasticizers to formulations. Polymers which do not necessarily need to be included in the formulation can be specifically selected to act as a support structure, for example a raft, to improve first-layer adhesion and prevent warping. Such support structures can be removed once the pharmaceutical product has been constructed, as post-processing step [87]. Polymers which exhibit good adhesion to several other polymers are expected to be highly beneficial in encouraging first-layer adhesion of a variety of AM formulations. Specifically, for layer-to-layer adhesion, a semi-molten state with an appropriate relaxation time to allow the polymer to diffuse across the interface between deposited layers, is most desirable [4], making thermal properties an additional contributor to adhesion. At temperatures slightly above T_g , the polymer may exhibit a degree of stickiness, which can promote adhesion. Although a sufficiently low viscosity is required for spreading and adhesion onto the previous layer, viscosity should not be so low as to result in a flowing liquid or excessive spreading or coalescence of layers that would hinder the geometric accuracy of the printed construct. Notably, rapid cooling is also required after deposition of each layer to prevent layer to layer coalescence.

For solvent-based processes, like solvent-based DoD printing, the surface tension and viscosity of the formulation may be optimized through the inclusion of appropriate polymers to encourage adhesion without unwanted coalescence of droplets [108]. An interesting application of polymers in solvent-based DoD printing occurs during the layering of droplets, for example, to achieve the desired drug loading. Since droplets are expected to spread differently on the substrate versus on the previous deposited layer, drug-free polymeric layers could be deposited in between each drug-containing layer and on the substrate to improve or obtain consistent and predictable adhesion [108]. The polymers used in the jetting techniques can be classified as (i) polymers included in the printing ink or droplets, where they function in controlling the rheological properties and surface tension or (ii) polymers that serve as the powder or substrate onto which the droplets are deposited. Both play a role in achieving optimum adhesion. To some extent, this resembles PAM, where the initial dry raw material is wetted by a liquid commonly containing polymer binders, which not only contributes to the final product structural characteristics but is also key to promoting interlayer adhesion. Upon scrutinizing Table 1, it is therefore unsurprising that a few polymers like HPMC, PEG, PVP, and MCC are frequently used in both PAM and jetting processes.

During selective laser sintering, powder particle adhesion is central to its working principle and requires polymer stability against high laser temperatures, appropriate thermomechanical properties, and low melt surface tension to encourage powder particle coalescence [13]. Successful layer to layer adhesion during SLS without the formation of unwanted voids relies on having an appropriate particle morphology and narrow particle size distribution to provide a homogeneous powder bed prior to sintering.

2.4. Polymerization

Polymerization can occur as a post-printing solidification step after the 3D object is generated, for example in material jetting

by DoD printing or certain types of SSE 3D printing (Fig. 1) [99,113]. Appropriate cross-linkable materials are required for the chosen cross-linking mechanism. This could involve photopolymerization or thermal, ionic, or pH-induced cross-linking [113]. Solidification by photopolymerization as a post-processing step is currently encountered primarily in biomedical applications. Polymerization may also be an inherent part of generating the three-dimensional object, as is the case with VAT polymerization (e.g. SLA and DLP). Here, spatially controlled photopolymerization of a liquid polymer resin is initiated under computer control to generate a solid three-dimensional object [33]. The polymer needs to be a photopolymer which undergoes polymerization with the aid of a photoinitiator to form a cross-linked polymeric network, which may entrap the drug during formation of the network or allow for subsequent drug loading [33,114–116]. Unlike other additive manufacturing processes, where the process inputs or feedstocks are polymers, the liquid resins in VAT polymerization consist of multi-functional monomers, typically based on methacrylate or acrylic esters [33]. Both SLA and DLP have been used for drug delivery research [33]. SLA has been used specifically in oral drug delivery research with photopolymerizable resins containing primarily polyethylene glycol diacrylate 700 (PEGDA 700) or N-vinyl-pyrrolidone as the reactive oligomer or monomer and polyethylene glycol 300 (PEG 300) as the liquid non-reactive filler [114–117], together with the drug and photoinitiator. The first example of SLA for oral drug delivery involved the fabrication of paracetamol and 4-aminosalicylic acid tablets using PEGDA and PEG 300 [115]. More recently, mucoadhesive microreservoirs for oral drug delivery and enhanced mucoadhesion have also been demonstrated using SLA [118]. Although applications of VAT polymerization for oral drug delivery have been demonstrated in research, so far, most utilized photopolymers and the monomers

they are generated from are not generally recognized as safe or pharmaceutically approved. Indeed, Table 1 reveals that out of the 5 process categories of pharmaceutical AM, the main users of approved excipients are material extrusion, powder bed fusion, binder jetting and material jetting. Therefore, VAT polymerization is addressed in a limited manner henceforth in this review.

So far, this section has highlighted key polymer functions which aid printability and the polymer properties they require, with examples of specific polymers utilized that offer these properties for various AM processes. Since different AM processes have different specific requirements for printability, no single AM technology can process all pharmaceutically available polymers. Notably, the polymer properties required for printability are dependent on whether the AM technology is melt-based or solvent-based, with added considerations for whether they are based on continuous extrusion or jetting. Despite their unique working mechanisms, this may allow a degree of overlap in the polymers which are suitable for different process stages for different AM technologies. In a rapidly evolving technological space, such an insight should trigger the development of printers that support hybrid printing mechanism to suit a broader variety of polymers and potentially broader pharmaceutical applicability. The upcoming section will shed light on an identified research gap, where pharmaceutically approved polymers are pointed out, which demonstrate suitable properties for printability according to Sections 2.1 to 2.4 but are still not commonly utilized in specific pharmaceutical AM processes.

2.5. Pharmaceutically approved polymers underutilized in AM

Fig. 2 summarizes critical polymer functions for each stage of printing for each AM technology. By scrutinizing the three central

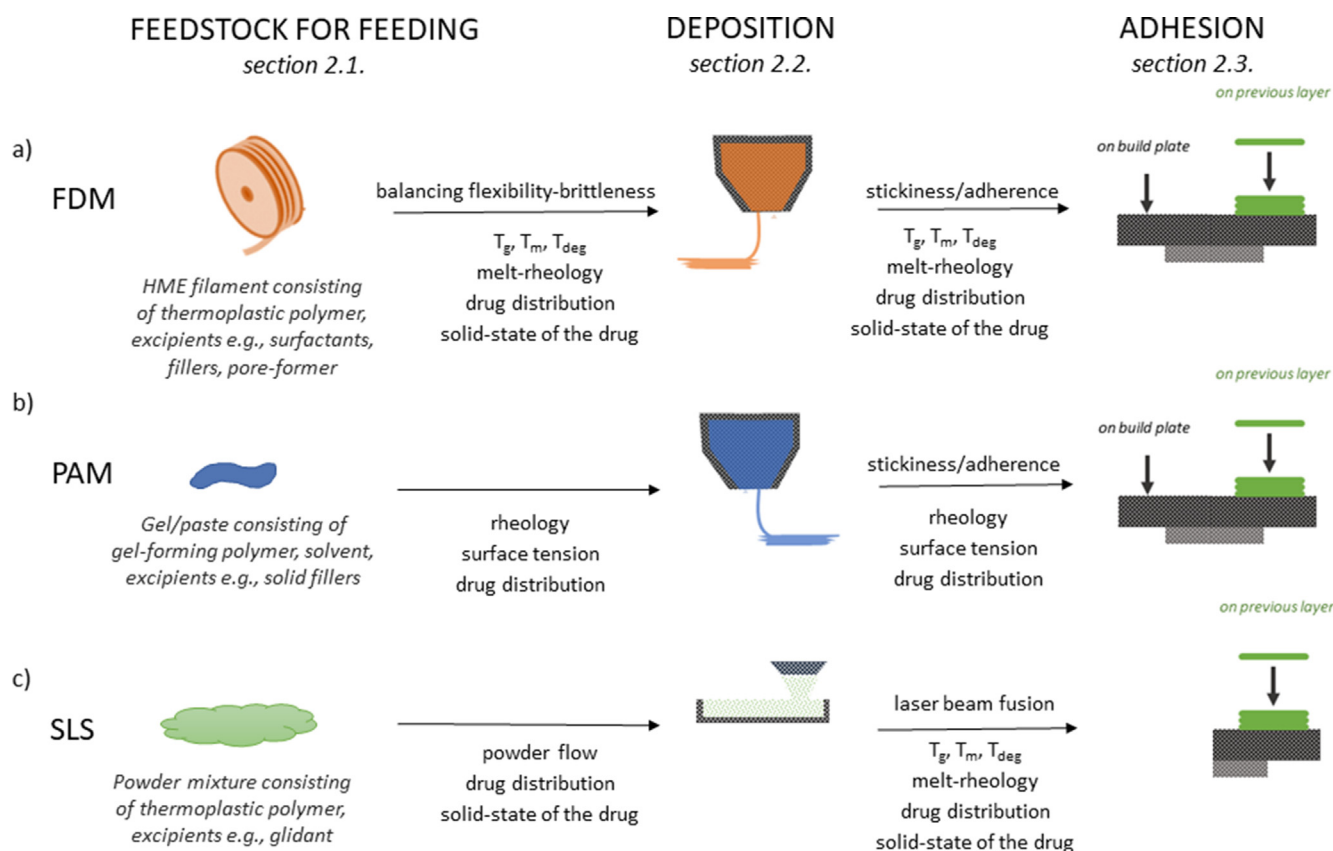


Fig. 2. Summary of generalized steps and typical polymer properties for the AM technologies further discussed in this review, a) FDM = fused deposition modelling, b) PAM = pressure-assisted micro-syringe, c) SLS = selective laser sintering, d) DoP = drop-on-powder printing, e) solvent-based DoD = drop-on-demand printing and f) melt-based DoD. T_g = glass transition temperature, T_m = melting temperature, T_{deg} = degradation temperature.

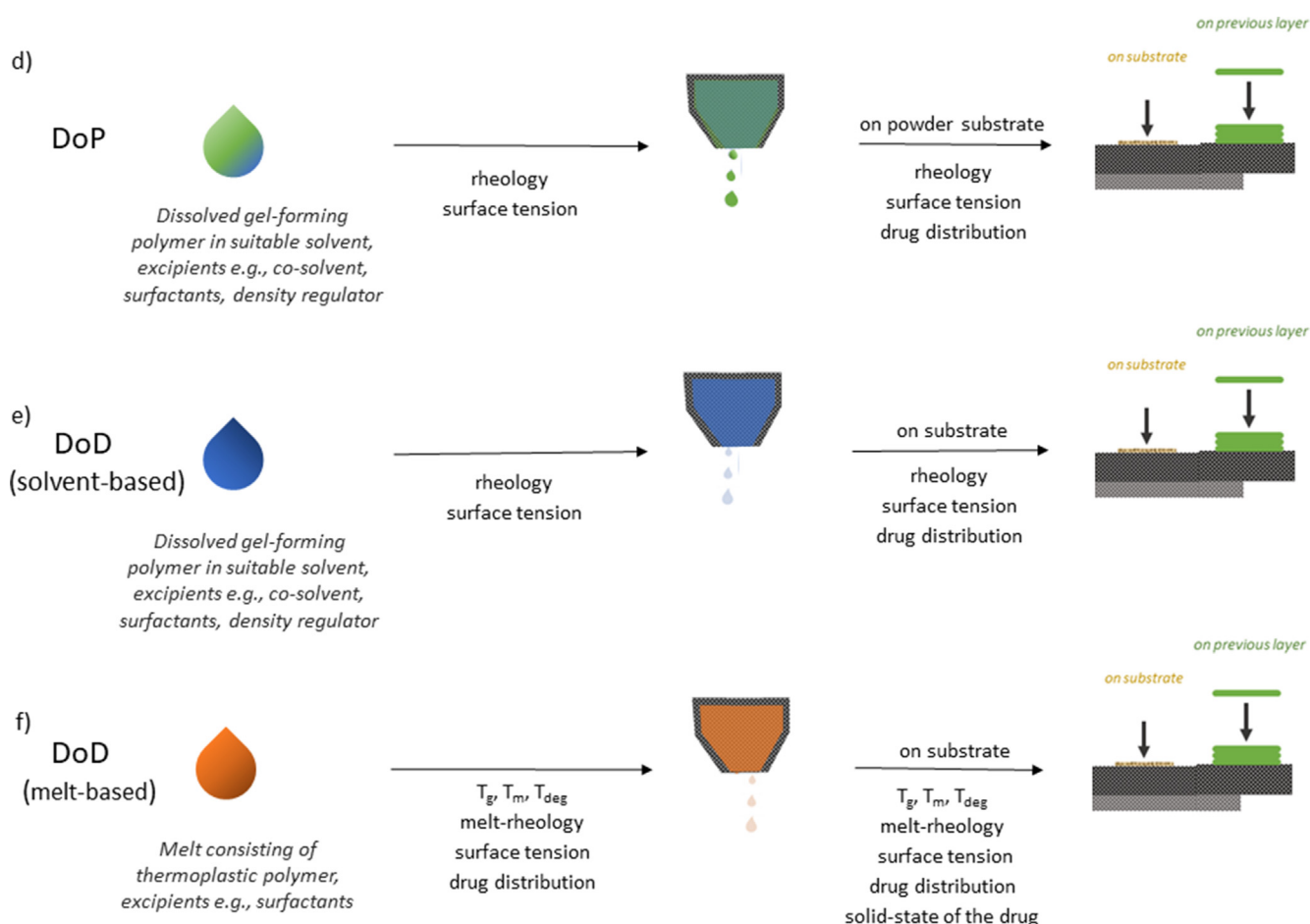


Fig. 2 (continued)

steps, feeding, deposition, and adhesion, across AM processes, we bring to light the similarities and differences between required polymer properties for different processes. This serves as a basis for suggesting appropriateness of underutilized pharmaceutically approved polymers for specific AM technologies. In doing so, we hope to stimulate scientists working in the pharmaceutical AM arena to explore well-known polymers beyond their current use.

All melt-based AM processes share polymer requirements when it comes to thermal properties and melt-rheology, therefore several of the polymers already used in FDM (Table 1) are also appropriate for melt-based DoD or even SLS. Most polymer examples used in FDM are traditionally intended for coating or film-forming applications [35] because these functions also require thermoplasticity. These include polyvinyl alcohol, polymethacrylates, cellulose acetate, hydroxypropyl methylcellulose, and copovidone, to name a few (Table 1). There are additional pharmaceutical polymers like aliphatic esters and povidone, which are not classified as coating agents or film formers but nevertheless have suitable T_g and/or T_m for deposition through heated nozzles. On the other hand, not all film formers are suitable on their own for deposition through heated nozzles due to thermoplastic properties which may be incompatible with the typical operating temperature ranges of heated nozzles in AM, for example, too high T_g . The process window for melt-based AM techniques should be below T_{deg} but above T_g or T_m . Excessively high T_g narrows the processing window, potentially compromising the optimization of printability. A high T_g relative to T_{deg} is a common feature for dry non-substituted polysaccharides, including starch, cellulose, xanthan, carrageenan, and so forth, making their poor thermoplastic properties unsuitable for melt-

based AM. Although Table 1 reveals one exception to the exclusion of non-substituted polysaccharides, namely, maltodextrin, the reported content of maltodextrin in the cited study was below 15%, where it functioned as a pore forming agent [48], not as the primary polymeric carrier. Unlike the non-substituted polysaccharides, many substituted polysaccharides, like CA, HPMC, EC, HPC, and so forth, do indeed exhibit appropriate thermoplastic properties to function as the primary polymeric carrier. Substituted polysaccharides exhibit a lower T_g than unsubstituted polysaccharides and maintain their T_{deg} due to the fact that hydrogen bonding between the hydroxyl groups in the polysaccharides are reduced to some extent by the addition of substituents [119,120]. Thus, the type of substituent and number of substituents largely impact the thermoplastic properties and could play a key role in widening thermal processing windows for melt-based AM.

Table 2 summarizes underutilized polymers together with examples of their functional properties and suggestions of which AM category they may be useful for. Two potential thermoplastic drug carriers or compartment builders that may show promise for FDM applications are ethylene vinyl acetate (T_m between 75 °C and 102 °C) and polyvinyl acetate phthalate (T_g approximately 42 °C) [35]. It is well-known that PEG and the amphiphilic surfactant, Pluronic®, referenced in Table 1, can be used as plasticizers. It is feasible that an under-utilized polymer class for melt-based AM, the “polymer-like” surfactants, with their strong amphiphilic character, may also find similar uses in melt-based AM. Examples include sorbitan fatty acid esters, polyoxyglycerides, polyoxyethylene sorbitan fatty acid esters, and polyoxyethylene stearates.

Table 2

Summary of examples of pharmaceutically approved polymers that are not commonly used in oral formulations produced by different AM technologies with suggestions of where their properties might promote printability alongside their current functionalities. Functional categories are obtained from [35], except where specific references are cited.

Polymers and polymeric containing surfactants	Melt-based AM technologies		Solvent-based AM technologies	
	Thermoplastic part	Additives	Solvent part	Dry part
Natural polymers (alginate-based polymers, carrageenan, ceratonia, chitosan, guar gum, polydextrose, tragacanth, zein)			Viscosity controlling agent	
Semi-synthetic polymers (low-substituted HPC, methylcellulose, hydroxyethylmethyl cellulose, calcium carboxymethylcellulose, hydroxypropyl starch, propylene glycol alginate)		Pore forming agent	Viscosity controlling agent, binder	Disintegrant, diluent
Synthetic polymers (ethylene vinyl acetate, polycarbophil, polyvinyl acetate phthalate, polymethyl vinyl ether/maleic anhydride, dimethicone)	Carrier [124]			Film substrate [123], stabilizer of solid dispersions [124], anti-foaming agent
Polymeric surfactants (polyoxyethylene alkyl ethers, sorbitan fatty acid esters, polyoxyglycerides, polyoxyethylene sorbitan fatty acid esters and polyoxyethylene stearates)		Plasticizer [125], lubricant [126]		Solubilizing agent, wetting agent

Similarities between the requirements on polymer functionalities can be found between SLS and melt-based AM techniques which feed polymers via a nozzle. Polymers like Kollidon VA64[®], EC, HPMC, PEG, and Kollicoat[®] IR are commonly used in both AM technologies, first in FDM and later in SLS. Perhaps, in future, the wide range of thermoplastic polymers already used in FDM, including PEO, PVP and PVA, to name a few, may continue this trend to find increased use in SLS.

Solvent-based AM processes, such as PAM, solvent-based DoD, and DoP, also exhibit similarities in the types of polymers that are useful. The largest category of polymers, identified from the Handbook of Pharmaceutical Excipients, which are not commonly used in AM for oral formulations is the water-soluble polysaccharides (e.g. guar gum, carrageenan, and alginic acid). Their traditional uses outside of AM include their functions as stabilizing agents for suspensions, emulsifiers, and viscosity-controlling agents [35]. The second largest category is the cellulose derivatives, including low-substituted HPC, carboxymethylcellulose calcium, and hydroxyethylmethyl cellulose, which have been used outside of AM as binding agent in tablets, emulsifying agents, and coating agents, respectively, in conventionally manufactured oral dosage forms [35]. In addition, the viscosity-increasing synthetic polymers (polyvinyl alcohol, polymethacrylates) are useful for PAM. All remaining aforementioned polymers are strong candidates for increased use in both PAM and other solvent-based AM processes. The natural polymers listed here are not typically encountered with PAM for oral drug delivery, but could have potential here, especially since some are already utilized in PAM for biomedical applications [121,122]. A related exception is the use of the polysaccharides, maltodextrin and pectin, to 3D print chewable oral dosage forms containing isoleucine and additional excipients using a modified gummy candy 3D printer, based on SSE 3D printing [70]. The use of these dosage forms in a clinical study paves the way for polymers already encountered in the food and confectionary AM industries to be directly applied to pharmaceutical formulations made by AM. In material jetting, where polymers can also be used as substrates often resembling flat films, ethylene vinyl acetate, a polymer commonly used in transdermal drug delivery system, could be a suitable polymer to apply [123].

This section has revealed that there are a few pharmaceutically approved polymers, which are not yet commonly utilized in specific AM processes for oral drug delivery despite their potential suitability. Furthermore, many polymers exist in several grades to allow appropriate tuning of properties and extended utilization across multiple AM technologies. To harness this advantage, com-

plete characterization of the desired properties of polymers is necessary. This can allow for optimization of polymer-process compatibility and can potentially apply the wide range of available polymers to the AM technologies they are not yet used in. The following section will exemplify a few trade-offs between printability and product performance that only become evident when beginning to apply polymers in AM to their intended pharmaceutical applications.

3. The role of polymers in product performance: Case examples highlighting potential trade-offs between printability and product performance

Pharmaceutical polymers are a bedrock in drug development and their uses in developing dosage forms traverse various pharmaceutical technology platforms [127]. This section aims at illustrating the complex role of polymers in AM, particularly with regards to balancing printability and product performance in specific applications. The use of polymers to stabilize the drug in its most appropriate solid state and the use of polymers in drug delivery applications are selected as two application examples, which serve to elucidate the potential trade-offs between printability and product performance that arise when translating AM technologies to pharmaceutical applications. Fig. 3 is an extension of Fig. 2, where product performance has been added to the printability depictions already present in Fig. 2, showing that a successful AM process flow relies on the satisfaction of both printability and product performance requirements.

3.1. Trade-offs between printability and achieving and stabilizing the solid state

The role of polymers regarding the solid state of products generated by pharmaceutical AM has primarily been reported as solubilisation of the drug and/or stabilizing the amorphous form of poorly soluble drugs upon amorphization by the AM technique. However, achieving this alongside printability may be met with key trade-offs, which need to be overcome to fully harness the potential of polymers in AM for these functions. A few examples will be discussed in this section in this regard.

Amorphization represents one means by which the apparent solubility and dissolution rate of poorly-water soluble drugs can be improved [128]. Several pharmaceutical AM technologies are well-suited to inducing amorphization of drugs and/or polymers.

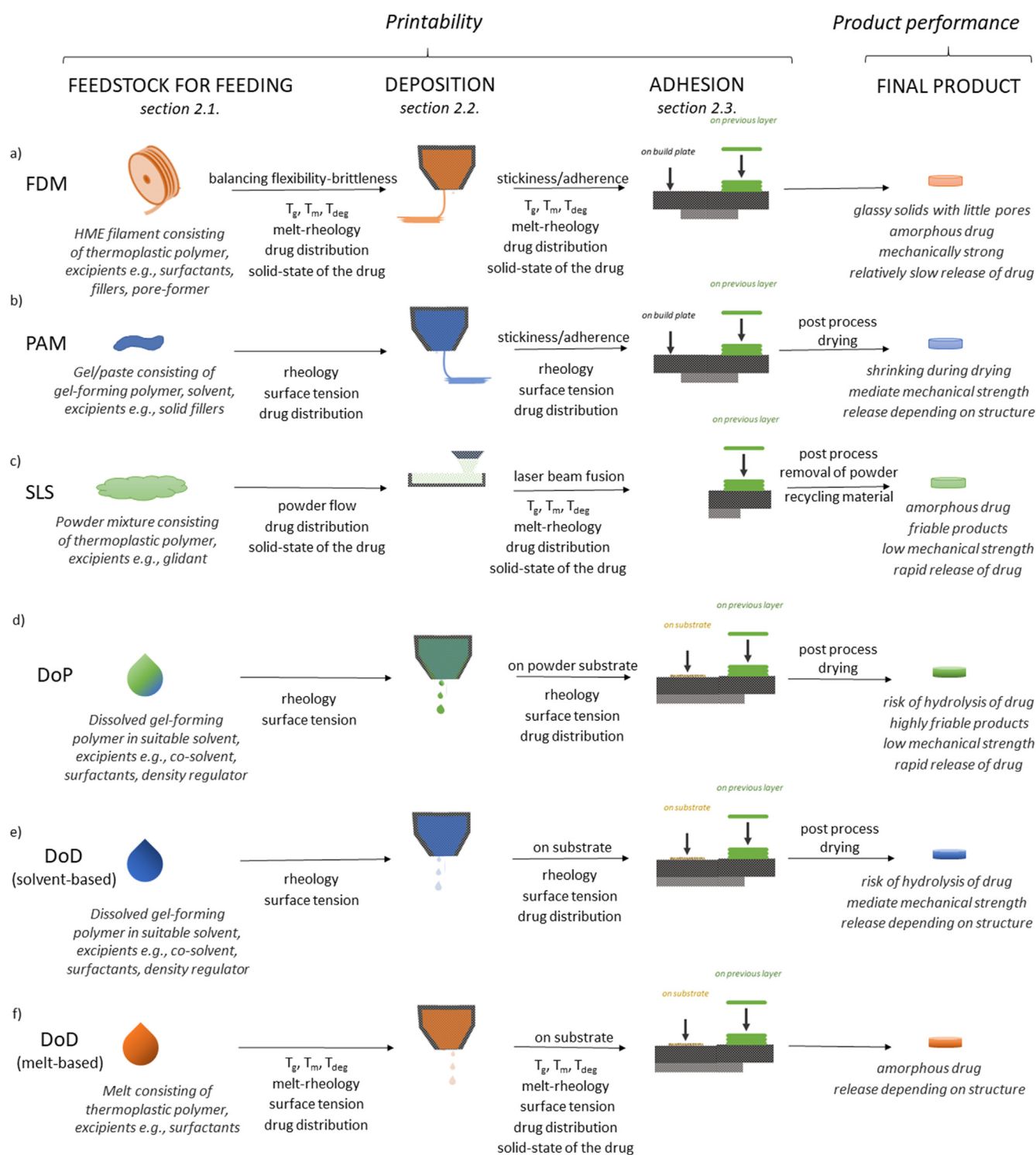


Fig. 3. Overview of desired polymer properties and examples of typical product performance attributes for various AM technologies. The figure is an extension of Fig. 2.

These include the melt-based AM techniques, for example, FDM, melt-based DoD, and SLS, which provide sufficient energy input to convert the drug from crystalline to amorphous form (Fig. 3). Amorphization is not exclusive to melt-based AM. PAM or solvent-based DoD may also induce amorphization at low drug concentrations during the post-processing drying step.

Often, a binary system of polymer and drug is sufficient to achieve and stabilize an amorphous solid dispersion [129,130]. When such systems are directly printable, further addition of

excipients is not necessary. However, in cases where the polymer has too high a T_g for processability in melt-based AM (see Section 2.2.) or unsuitable mechanical properties for feeding as a filament in FDM (see Section 2.1.), additional excipients in the form of plasticizers are commonly incorporated [131]. Although this improves printability, plasticizers may compromise the physical stability of the system during storage by causing phase separation and subsequent recrystallization [132]. This is an example of a key trade-off between printability and product performance, which

must be overcome in order for AM to reach its full potential for pharmaceutical products. Another potential trade-off could occur when solubilizers or precipitation inhibitors are added to improve product performance by increasing bioavailability. These excipients often act as plasticizers, adversely influencing the mechanical properties of filament for FDM, compromising feeding and therefore printability. Both these trade-offs show that balancing printability and product performance is not a trivial task, with the role of the polymer in eliciting desired product performance and optimal printability playing a key role in this balancing act.

Sometimes, amorphization of the drug may not be desired or necessary, for example, in the case of highly water-soluble drugs, which may have better physical stability as crystalline solid dispersions [48]. Processing by AM may inadvertently induce amorphization of such drugs, compromising their physical stability. AM processes, which do not provide excessive energy input to the system are less prone to this phenomenon. An example includes solvent-based DoD, which also tends to incorporate higher drug loads, preventing unwanted amorphization.

Regardless of the polymer and process selection or modification to achieve and stabilize the desired solid state, additional product performance attributes, such as the target drug release profile, must still be preserved, all whilst maintaining optimal printability.

3.2. Trade-offs between printability and drug delivery

The role of polymers in formulation of conventional solid oral dosage forms is to facilitate processing of the drug into a dosage form and to tailor the release rate and site, amongst other product performance attributes. This role is preserved during AM. Pharmaceutically approved polymers with different properties (hydrophilic, hydrophobic, amphiphilic, pH dependent, etc.) enable manufacturing of systems ranging from conventional immediate release tablets to modified release systems with different capabilities, including sustained, delayed, extended, and pulsatile release of the drug. Formulations can be tailored to specific release sites, such as the stomach (e.g. floating or non-floating gastro-retentive systems), the intestine (enteric-coated systems), or be designed as dispersible or mucoadhesive systems. For a comprehensive overview of polymers in controlled release in AM, the reader is referred to a recent review by Borandeh et al. [21]. This section will illustrate some of the trade-offs between printability and drug delivery performance, with a few examples from the various AM technologies.

As emphasized earlier, the AM technologies are based on different working principles, which is reflected in the characteristic attributes of the printed products. Despite flexible design options, the melt-based technologies typically deliver printed formulations with a high concentration of thermoplastic polymers in order to meet the processability requirements. Such systems are typically more suited to slow release of the drug (Fig. 3) [47,79]. For melt-based printing, especially FDM, immediate release formulations that disintegrate rapidly to release the drug are more challenging to obtain than designing an extended release formulation. This is due to the generation of typically nonporous prints via FDM, unless porosity is designed into the model, for example, by varying infill densities or compartments. Looking at conventional compressed tablets, disintegration is facilitated by incorporation of hydrophilic polymers that swell in contact with water, creating a volume expansion that breaks up the dosage form into smaller fragments. Typical tablet disintegrants, such as hydroxypropylcellulose, croscopovidone, carboxymethylcellulose sodium, and microcrystalline cellulose, are also used in printing of immediate release formulations across the various platforms (Table 3). However, several of these polymers lack appropriate thermoplastic properties for printability via melt-based printing techniques, requiring additional excipients to increase their processability. Often, plasticizers are included in formulations to improve processability, especially in extruded filaments for FDM, however their inclusion may adversely alter not only the required drug release rate but also the product stability as discussed in Section 3.1. and even the surface texture of the printed product [48]. Once again, modification to polymer systems to facilitate printability may come at a considerable cost to final product performance, which is inadequately addressed in current pharmaceutical AM research, if at all.

One approach to manage trade-offs could be appropriate selection of the AM technology. Continuing the example above, where rapid disintegration is required as a product performance attribute but the polymers which facilitate it are not suitable for one AM process (FDM in the above example), they may be suitable for another AM process. DoP printing resembles wet granulation, where a binder solution is distributed over a powder bed, “gluing” powder particles together to form larger structures. These larger structures correspond to granules in wet granulation and porous dosage forms in DoP (Fig. 3). As highlighted for Spritam®, DoP is highly suitable for the manufacture of rapidly disintegrating systems and typical tablet excipients may be used, e.g., with an MCC-based powder bed and hydrophilic binder solutions (Table 3). The main challenge for printed formulations from DoP is balancing

Table 3
Description of selected examples of immediate release formulations from different AM technologies.

AM Technology	Composition	Printed Structure	Reference
FDM	<ul style="list-style-type: none"> 5–20 % drug (caffeine) hydrophilic polymers (HPC, Kollidon VA64®, Kollicoat IR®) plasticizer (PEG 4000) hydrophilic pore former (maltodextrin, xylitol) 	<ul style="list-style-type: none"> oblong shaped tablet one outer wall layer no top/bottom layer honeycomb infill pattern infill density 80%, 100% cylindrical tablet pore size 1 mm 	[48]
PAM	<ul style="list-style-type: none"> 24 % drug (carbamazepine) solubilizing polymer (hydroxypropyl-beta-cyclodextrin) hydrophilic polymer (HPMC, PVP, Na-CMC) 	<ul style="list-style-type: none"> cylindrical tablet 	[52]
SLS	<ul style="list-style-type: none"> 30% drug (clindamycin hydrochloride) 	<ul style="list-style-type: none"> cylindrical tablet 	[42]
DoP	<ul style="list-style-type: none"> Hydrophilic polymers (MCC, Kollidon® VA64) drug (amitriptyline hydrochloride) hydrophilic polymers (MCC) other powder excipients (lactose, dicalcium phosphate) hydrophilic binders (PEG, PVP) 	<ul style="list-style-type: none"> filled cylindrical tablet 	[45]
DoD	<ul style="list-style-type: none"> drug (haloperidol) hydrophilic polymer (HPMC) porosity enhancer (mesoporous fumed silica) plasticizer (glycerol) 	<ul style="list-style-type: none"> film substrate (prepared by solvent casting) DoD of ink solution 	[65]

varying aspects of product performance with each other, in this case rapid disintegration with the desired mechanical strength for handling and portability [45]. PAM can be considered as an alternative solution in this case. Analogous to the parallels between DoP and wet granulation, PAM may be compared to another conventional manufacturing technology, namely, wet extrusion for pelletization. Here, the powder mass is fully wetted and the binder liquid confers suitable rheological properties to be formable [52]. In order to achieve rapid disintegration in PAM, hydrophilic polymers are used in combination with geometrical designs containing voids, which could act as channels or pores for hydration and subsequent release. In the absence of the availability of a printer with each type of working principle, this extended case example shows that the future design of hybrid printers with combined alternative working principles may be a promising step in the right direction to manage trade-offs between printability and product performance through ease of switching between different working principles to process the wide range of polymers currently available for achieving a range of desired product performance attributes.

Compared to traditionally manufactured dosage forms, AM enables the printing of geometries that provide improved control over the available surface area for dissolution and drug release. However, this requires processibility of the desired polymers into final product geometries in a manner that closely represents the CAD model, imposing strict requirements on printability of such products. The geometric flexibility of AM also lends itself to the design and fabrication of several innovative stimuli-responsive systems, which change shape as a function of an external stimulus [133]. Examples of external stimuli that induce changes to the printed construct are temperature, ions, solvents, and time [134–136]. The latter paves the way for a relatively unexplored area in pharmaceutical AM, 4D printing, involving the fabrication of objects via 3D printing that change shape, properties or functionality as a function of time [135,137,138]. An interesting gastro-retentive device is presented in Fig. 4 [135]. This PVA device has a compressed helical shape, achieved using a 3D printed template, that expands upon exposure to water, which plasticizes the polymer, decreasing its T_g and allowing the expansion, which prevents transport through the pylorus. 3D printed concepts have the potential to expand the capabilities of AM to deliver advanced drug delivery solutions. However, regarding innovative applications of pharmaceutical AM, it is quite noticeable that the current literature is yet to address and tackle existing trade-offs between printability and product performance that may arise beyond proof-of-concept demonstrations.

Through selected examples of polymer applications in pharmaceutical additive manufacturing, namely, achieving and stabilizing the solid state and drug delivery, this section has demonstrated that choosing the optimal polymer which simultaneously satisfies

the requirements of printability and the requirements for product performance is no trivial task. Indeed, modifications to polymer systems to improve printability may sometimes hinder product performance and vice versa. This is one key reason why this review is not a guidance on polymer selection. Instead, we have highlighted polymer properties that lend themselves to printability for different AM processes and, through exemplification, how selecting polymers or material systems with these properties may not always result in the desired product performance. Addressing trade-offs in this manner is highly recommended in future to fill this knowledge gap and contribute to an improved balance between printability and product performance across AM technologies.

4. Characterization techniques used in additive manufacturing

Characterization techniques are multipurpose and their various applications range from screening to identify suitable polymers, process optimization [5,95], process monitoring in a Quality-by-Design (QbD) approach [94,139,140], and intermediate and final product quality attributes for subsequent optimization, for example, mechanical strength [86,141–144] or target drug release profiles [103,142,145–147]. Depending on their intended purpose, a range of characterization techniques are available and applied to study raw materials (such as polymers) or formulations containing drugs and/or polymers and/or non-polymeric excipients in the form of physical mixtures, product intermediates like filaments for FDM printing [141,142], or final dosage forms [139,140,148–150]. Some techniques may demand a sample preparation step, which modifies the material for subsequent analysis. Characterization techniques also vary between those that are destructive and those that are non-destructive to the sample, with the latter techniques gaining favour in real time quality assessments. The sample history plays a key role in determining the utility of the characterization technique for its intended purpose and at the very least requires careful scrutiny of the results of the analysis. This section introduces some of the most frequently encountered characterization techniques in pharmaceutical AM and points out a few emerging techniques. The characterization techniques are already primarily applied to assess product performance and/or raw material and pre-processed feedstock properties. We therefore highlight their specific value in assessing the role of the polymer in printability, where applicable. The techniques are categorized based on material properties and the analytical principles used to assess them. Table 4 provides an overview of these characterization techniques with selected examples of their typical applications and examples of the AM technologies they have been used in. Standardized characterization techniques that are essential for all solid dosage forms, for example, assessing uniformity of mass, drug content, disintegration, and dissolution behaviour, have been excluded

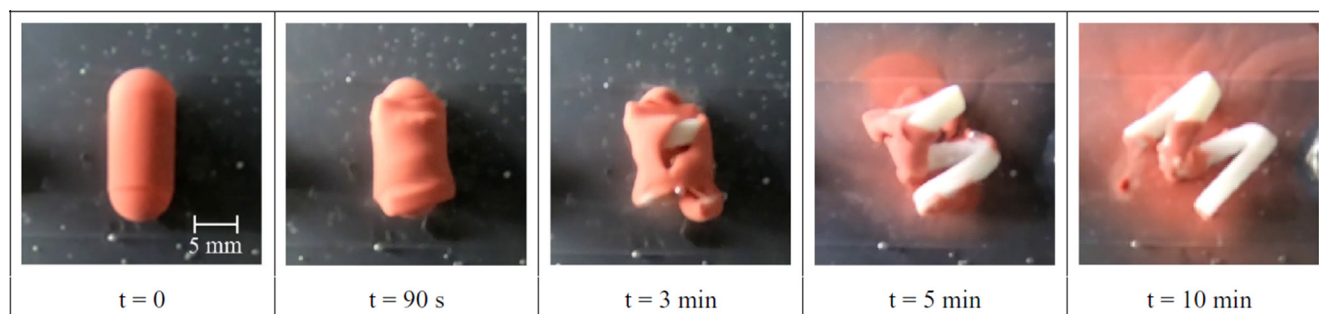


Fig. 4. Images of a helical PVA device inserted in a capsule and exposed to 0.1 N HCl at 37 °C at different times. The images illustrate how the shape of the prototype increases its dimensions and breaks the capsule [135]. Reprinted with permission.

Table 4

Overview of characterization techniques used in pharmaceutical AM with examples of their corresponding applications. TGA = thermogravimetric analysis, DSC = differential scanning calorimetry, DMA = dynamic mechanical analysis, NIR = near infrared spectroscopy, FTIR = Fourier transform infrared spectroscopy, XRPD = X-ray powder diffraction, WAX = wide-angle X-ray scattering, SANS = small-angle neutron scattering, SEM = scanning electron microscopy, X-ray μ CT = X-ray computed microtomography, TPI = terahertz pulsed imaging, ToF-SIMS = time of flight – secondary ion mass spectroscopy, T_{deg} = degradation temperature, T_g = glass transition temperature, T_m = melting temperature, E' = tensile storage modulus, E'' = tensile loss modulus, G' = shear storage modulus, G'' = shear loss modulus.

Characterization Techniques		Example of Application	AM Technology
Thermal techniques	TGA	Solid state (e.g. T_{deg})	FDM [151–155], PAM [156], SLA [157]
	DSC	Solid state (e.g. T_g , T_m)	FDM [73,86,142,149,153,158,159], PAM [60,160], SLS [51,79], DoD [58,161], SLA [116,157]
Mechanical techniques	DMA	Viscoelasticity (e.g. E' , E''), solid state (e.g. T_g)	FDM [73,86,130]
	Crushing strength	Final product breaking force	FDM [151,154,162,163], PAM [37,164], SLS [51,79], DoP [44,57,71]
	Friability	Robustness of final product handling and portability	FDM [151,162,163], PAM [37,164], SLS [79], DoP [44,57]
	Compression test e.g. Three-point bending	Stiffness and brittleness balance for feeding of intermediate filament (e.g. Tensile strength, yield strength, flexibility, ductility, Young's modulus)	FDM [73,142,146,149,158,159,165,166]
	Tensile test	Final product elasticity (e.g. Tensile strength, elongation, Young's modulus)	FDM [153,162,166], SLA [157]
	Indentation	Final product viscoelasticity	FDM [167,168], PAM [169]
Rheological techniques	Interlayer adhesion	Interlayer strength	FDM [140,146,170]
	Flow test	Feeding, deposition, and adhesion (e.g. viscosity, shear effects, yield point, gel point, gel strength)	FDM [171], PAM [37,169,172], DoD [173]
	Capillary test	Feeding, deposition, and adhesion (e.g. dynamic viscosity, intrinsic viscosity, melt-flow index)	FDM [86,162], PAM [169], DoD [85,111]
	Frequency sweep	Feeding, deposition, and adhesion (e.g. complex viscosity, viscoelasticity (G' , G'' , E' , E''), gel point, gel strength)	FDM [73], PAM [36,172,174]
	Creep test	Creep and die expansion or swelling	FDM [73], PAM [36]
	Pendant drop du Noüy ring	Optimization of droplet	DoD [111,173] DoD [85]
Spectroscopic techniques	NIR incl. NIR chemical imaging	Drug content and distribution	FDM [175] SLS [176] DoD [177]
	FTIR	Interactions between components	FDM [68,178,179] PAM [39] SLA [116] DoD [111]
	Raman incl. mapping and confocal Raman microscopy	Distribution and solid-state of drug	FDM [82,178,180] SLS [176] DoD [66,110,111,161]
Scattering and imaging techniques	XRPD	Solid-state	FDM [149,156,181–183], PAM [39], SLS [51,79,176], DoD [58,67,108,184], SLA [116,157]
	WAXS	Solid-state	FDM [155], PAM [160]
	SANS	Nanostructural information	FDM [185]
	SEM	Surface morphology	FDM [162,163,183], PAM [36], SLS [51,79], DoP [71] SLA [116,157]
	X-ray μ CT	Geometric assurance and image of inner structure/porosity	FDM [50,144,153,186,130], PAM [36], SLS [51,79], DoD [161]
	TPI	Microstructure information	FDM [186]
Computational techniques	ToF-SIMS	Spatial mapping of drug	DoD [161,187,188]
	Machine learning	Prediction of printing conditions and release rate of drug	FDM [139,189]

from this overview. Although they are essential for pharmaceutical products and are frequently employed to assess product performance in AM, as well-established Pharmacopoeial methods, they are not printability specific. Also, product-focused techniques for evaluation of chemical stability of the drug, polymer and other excipients, e.g., HPLC-based methods, are considered out of scope.

Several of the relatively simple and discrete characterization techniques highlighted in this section can be applied in a complex context, for example, serving as process analytical technologies (PAT) for real-time monitoring of an AM process or used for calibration and/or validation of *in silico* simulations and other digital methods. Such advanced applications are further discussed and exemplified in Section 4.8.

4.1. Thermal techniques

In the AM technologies which apply heat to the polymer, namely, FDM, melt-based DoD, and SLS, thermal transitions, such as T_g , T_m , and T_{deg} , are crucial to defining the optimal processing window for printability and product performance [87]. Thermoplastic polymers, with their relatively low T_m or T_g , are central excipients for these AM technologies [73,86,87]. However, for pharmaceutical AM, they are not typically used alone but instead contain the drug to form a solid solution of the drug molecularly dissolved in the polymer or a solid dispersion with the drug in crystalline or amorphous form. Importantly, the drug may alter the position of thermal transitions relative to those of the pure polymer, which may require defining of processing windows specific for each composition. The application of polymers in AM to achieve a particular solid state was discussed in Section 3.1. of this review. Three thermo-analytical techniques will be discussed in this section, namely thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and dynamic mechanical analysis (DMA), where the first two are the most frequently used.

4.1.1. Thermogravimetric analysis (TGA)

TGA measures changes in mass of a sample, specifically mass loss, as a function of temperature or time in a controlled atmosphere [190]. A typical thermogravimetric analyser achieves this by heating a sample at a predefined rate in a closed furnace and continuously measures its mass with a precision balance. The resulting TGA thermogram is expressed as mass or percentage of initial mass versus temperature or time. As such, mass loss occurring due to evaporation or thermal decomposition, for example, can be ascertained. For AM printing, determination of the onset of thermal degradation, assigned T_{deg} , defines the upper limit of processing temperature range to ensure thermal stability of the material [152,178]. TGA is a destructive analytical technique, which can be applied to raw materials, physical mixtures, intermediates or pre-processed feedstocks, and final products [151–153].

Below, T_{deg} , it may also be possible to perform multiple heating runs in a single TGA experiment to reveal the effect of double heat processing (e.g. hot-melt extrusion (HME) followed by FDM) on both the physicochemical stability and processing range of various materials. In addition, isothermal TGA measurements can provide valuable information on the effect of prolonged heating during printing, for example, when deposited polymer is in contact with a heated build-plate [191]. Even for AM technologies which do not typically apply heat directly to the polymer during processing, e.g. PAM, TGA can potentially provide information regarding the time and temperature required for desolvation and drying of final products during post-processing steps.

Due to its measurement principle, it follows that TGA is less useful for degradation that does not result in mass loss, even though such degradation defines material stability and could influence mechanical properties. To determine the stability of polymers

for SLS, a novel technique called stability estimate by crystallization analysis, has been introduced [192]. Based on fast scanning calorimetry, it is capable of heating materials by several thousands of Kelvins per second with the instrument time constants in the millisecond range, making it particularly useful for the short temperature exposure times in SLS. Even though not stipulated for other AM technologies, it could be advantageous for studying polymer stability during the short residence times encountered in the heated nozzle in FDM during rapid printing.

4.1.2. Differential scanning calorimetry (DSC)

DSC measures the difference in heat flow to a sample and a reference that is required to maintain both at the same temperature as the sample undergoes physical transformations, like phase transitions upon heating [193]. The total heat flow is proportional to the heat capacity of the material being analysed. Like TGA, DSC is also destructive to the analysed sample, which can be a raw material, physical mixture, intermediate or pre-processed feedstock, or final product. The resulting thermograms are expressed as a heat flow versus temperature. Several typical transitions can be observed in a DSC thermogram to determine the T_m (of crystalline polymers, crystalline parts of semi-crystalline polymers, or crystalline drugs), T_g (of amorphous polymers or amorphous regions of semi-crystalline polymers), dehydration, or relaxation, which are all endothermic transitions [190]. Exothermic transitions such as recrystallization of amorphous systems are also determined using DSC [190,193].

Heat flow analysis can be performed with a conventional DSC or a modulated DSC (mDSC). In the case of the latter, the difference in heat flow between a sample and reference is also measured as a function of temperature or time, however, unlike conventional DSC, mDSC applies a sinusoidal temperature modulation of predefined period and amplitude overlaying the linear heating profile. The consequence and advantage of applying this sinusoidal modulation over the linear temperature programme is that overlapping thermal transitions e.g. enthalpic relaxation, which could mask the glass transition in conventional DSC, can be resolved with mDSC [194].

For printability, DSC is particularly useful for determining the lower limit of the processing window, as defined by the T_g or T_m of the polymer. This lower processing temperature limit can also be altered through the addition of the drug or other excipients to the polymeric matrix, if plasticization occurs [159,195]. DSC can also be used to evaluate the thermodynamic solubility of the drug in the polymer [196]. This is important when developing formulations for heat-based AM techniques, since determining the amount of drug that is thermodynamically soluble in the polymer [197] is not just crucial for product performance but could also influence the efficiency of plasticization for improved mechanical properties of filaments for FDM (addressed in Section 4.2.) or altered rheological properties of droplets in melt-based DoD (addressed in Section 4.3.), for example.

4.1.3. Dynamic mechanical analysis (DMA)

DMA is a thermo-mechanical technique, which applies sinusoidal stress under a predefined frequency and temperature programme, to deform a sample and measure its strain response [198]. Specifically, DMA determines the phase angle between the applied sinusoidal stress and the resulting strain, from which viscoelastic behaviour is determined. This is translated to complex modulus via a mathematical treatment. A DMA thermogram presents the complex modulus as a function of either temperature, time, or frequency.

DMA can be performed on samples in the form of films or powders. The introduction of powder sample holders means that the utility of DMA can also be extended towards unprocessed raw

materials and physical mixtures. DMA has widespread applications from determinations of T_g and molecular mobility, viscoelastic properties, moisture content and its influence on complex modulus, dehydration of crystalline hydrates, crystallinity, and miscibility between polymers [65,73,86,198–203]. Many of these are key contributors to both product performance and the definition of processing parameters or screening of polymers for printability. For example, T_g determination by DMA can be used to define the lower temperature limit for printability using the AM technologies that apply heat to materials during processing. Indeed, specific thermal phenomena, such as the T_g , can be probed with DSC, DMA, or even dielectric spectroscopy [204], which all have different measuring principles and result in different absolute processing temperature ranges being reported for the same polymer [199,204,130]. Therefore, defining optimal thermal processing ranges to ensure printability and product performance requires careful consideration of the technique from which this information is derived.

4.1.4. Defining printing temperature windows from several thermal techniques in combination

Combining complementary information from TGA, DSC, and DMA allows the complete thermal processing range for printability to be defined (Fig. 5) [130]. Typically, during pharmaceutical AM, DSC and/or DMA is used to define the lower temperature limit for deposition through the nozzle in FDM and melt-based DoD as well as for adhesion to the build-plate, both based on T_g range determinations [205], whereas TGA is used to define the upper temperature limit of the processing range.

4.2. Mechanical and powder flow techniques

Mechanical tests are primarily relevant for optimizing and assuring final product performance. Analogous to solid dosage forms fabricated by conventional pharmaceutical manufacturing techniques, the mechanical properties of printed dosage forms should be within acceptable limits to facilitate handling, transport, and storage without breakage or material loss [15]. The European Pharmacopoeia (Ph.Eur.) describes two tests for the evaluation of

mechanical strength of solid dosage forms, namely *Friability of uncoated tablets* (Ph.Eur. 2.9.7) [206] and *Resistance to crushing of tablets* (Ph.Eur. 2.9.8) [207], both of which are applicable to all printed products, especially those that result in porous or fragile final dosage forms e.g. dosage forms fabricated by DoP printing or SLS (Fig. 3 and Table 4).

In addition to final product performance across all AM technologies, mechanical characterization plays a key role in determining printability of filaments for FDM [73]. During FDM, polymers which are extruded into brittle filaments are often incompatible with the rotating drive gears encountered in a typical FDM feeding mechanism, preventing automated feeding and optimal printability [208]. Here, mechanical tests which can assist in achieving an appropriate stiffness-flexibility-brittleness balance of the intermediate filament is essential for printability [29,73,87,144]. To the best of the authors' knowledge, no reports which systematically compare feeding of the same polymer through the drive gears of different FDM printers are available, however, it can be expected that different feeding mechanisms in different brands of FDM printers would alter what constitutes optimal measurement values for various mechanical properties. This section will highlight a few mechanical and powder flow techniques that are typically encountered in pharmaceutical AM literature.

4.2.1. Compression, tensile, and indentation tests

Compression, tensile, and indentation tests are performed with instruments that can record time-resolved force and displacement, for instance, a texture analyser or a material tester (Table 4), resulting in stress-strain profiles from which further information on the tensile strength, elongation to break, and Young's modulus, can be derived. The main differences between these tests lie in the different test setups and whether the applied force is compressing, extending, or crushing the sample. Filaments for FDM printing undergo both compressive and tensile forces under the applied force of the feeding drive gear. Compression tests provide valuable information on the material's resistance to crushing, similar to Ph. Eur 2.9.8. [207], for printability, in the case of FDM, and for final product performance, in the case of all AM technologies. There are different compression test methods including three-point

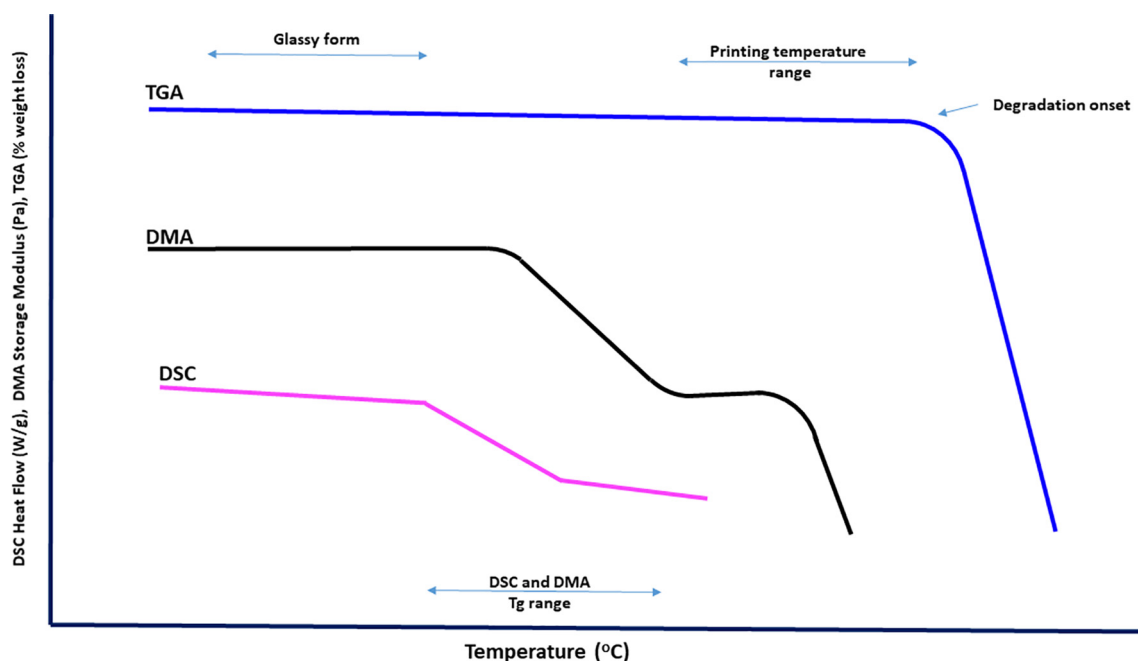


Fig. 5. Illustration of the combination of TGA, DSC, and DMA thermograms for defining the optimal processing temperature range for printability.

bending tests, vertical compression tests, and axial compression tests [158], which can all be performed on filaments for FDM printing. By analysing filaments in different orientations, they can be used to determine the stress at which plastic to elastic deformation occurs or at which a filament breaks [142,144]. In contrast to compression tests, tensile tests apply a force to extend the sample until rupture. Although tensile tests are typically used to determine the flexibility of thin samples, such as films [157], their use can, in principle, be extended towards material systems encountered in AM. Here, they can potentially be used to predict the flexibility of polymers to be extruded into filaments for FDM without the material wastage that occurs with larger batch sizes of potentially brittle filaments via melt extrusion upstream of FDM. Tensile tests may also offer value in determining the flexibility of polymers to be used as substrates in material jetting, which may, for example, require folding or rolling to fit into a capsule post-printing. Although compressive and tensile tests crush and rupture the sample, respectively, insight into material properties can also be obtained without sample destruction. Indentation tests position a small-diameter probe onto the sample and apply a compressive force until a pre-defined force value or displacement value is achieved. From this, the material's ductility and elastic properties can be determined.

4.2.2. Interlayer adhesion test

To evaluate the interfacial adhesion force between printed layers (discussed in Section 2.3), typical adhesion tests apply a force perpendicular to the layers of a printed structure. Alternatively, interlayer adhesion may be evaluated in tensile mode, where the upper and lower parts of an object are pulled apart until a detachment force is recorded. Due to the layer-by-layer deposition that characterizes AM technologies, the maximum interfacial adhesion force is relevant for most AM technologies and can provide a measure of adhesion either between layers of the same composition or between layers of different compositions [140,146,170], such as in multidrug dosage forms.

4.2.3. Powder flow

For all AM techniques involving the mixing and/or feeding of a powder, powder flow properties are crucial for obtaining consistent and homogeneous prints. Standard methods to assess powder flowability, such as flow rate through an orifice (g/sec), angle of repose, and estimation of the Hausner ratio or Carr index (derived from the bulk and tapped density of the powder), can be applied [209].

4.3. Rheological techniques

It is well established that polymers exhibit different rheological properties depending on a number of factors, including the chemical and physicochemical structure of the material itself, the physical state of the material (e.g. solid versus liquid), concentration of the material (e.g. melt/concentrated solution, semi-dilute solution, dilute solution), the environment (e.g. temperature, pressure), and the strain history. Although the physical state of the material and the polymer concentration in the formulation can vary widely between different AM technologies, ranging from the sintered solid polymers in SLS to molten polymers in FDM and melt-based DoD to semi-solid gels or pastes in PAM to dilute solutions in DoP printing or solvent-based DoD printing, the basic flow theory remains the same. Fig. 6 provides an overview of polymer rheology, as a guide for the discussion in this section.

Viscosity describes the resistance of a material to flow and is modulated by shear and/or temperature, where shear viscosity is the ratio of shear stress to shear rate. Elasticity describes a material's internal resistance to deform and restore its original state when the applied force is removed. Polymers are viscoelastic and therefore exhibit the viscous properties of liquids and the elastic properties of solids, depending on the timescale of the deformation. Viscoelasticity is expressed as a shear storage modulus (G' , elasticity) and a shear loss modulus (G'' , plasticity). Due to the time-dependent plasticity component, polymers respond differently to different shear stresses and shear rates. However, due to


Polymer concentration			
Description - characterized by	melt/concentrated solution	semi-dilute solution $c > c^*$ entanglements	dilute solution $c < c^*$ separate polymer chains
Rheological behaviour	elastic	viscoelastic	viscous
Analysed using - example of configuration	oscillatory measurements (rheometer) e.g. plate-cone, plate-plate	rotational viscometer e.g. cup-spindel, cone-plate	capillary viscometer e.g. Ubbelohde
Parameters assessed - examples	complex viscosity, storage and loss moduli (G' , G'') relaxation, gel strength	viscosity, yield point shear effects	dynamic viscosity kinematic viscosity
AM techniques	SLS/FDM/melt-based DoD	PAM/DoP/solvent-based DoD	Solvent-based DoD/DoP

Fig. 6. Overview of polymer rheology, associated characterization techniques, and relevance in AM (c = concentration, c^* = overlap concentration, G' = shear storage modulus, G'' = shear loss modulus).

the elasticity component, they tend to recover their original properties over time. In oscillatory tests, the time dependence can be evaluated by varying the frequency of the applied stress or strain, with high frequencies corresponding to short time scales and low frequencies corresponding to longer time scales. Insight into these parameters allows better prediction of a polymer's behaviour during processing [90,91,94,210].

For melt-based AM technologies, where thermoplastic polymers are typically the major component in the formulation, temperature is used to soften or melt the polymer, with a corresponding change in its viscosity [67,76,90]. Several recent publications, which emphasize the importance of melt rheology during melt extrusion, are equally applicable to melt-based AM [94,95,171]. The temperature required in FDM printing is often higher than in HME because of the lower shear in the printer extruder combined with low residence time in the nozzle compared to HME [94]. To assess rheological properties of melts temperature-controlled rheometers are used in various configurations, including parallel-plate and cone-plate geometries [95,171,211]. Typical parameters assessed are complex viscosity and storage and loss moduli. Melts and concentrated polymer solutions have similarities in characterization techniques and assessed parameters and are therefore categorized together (Fig. 6).

Another relevant parameter for extrusion-based AM technologies, including PAM, is the yield point, above which the material starts to flow [5,94]. Too low viscosity will result in uncontrolled deposition of material from the nozzle. High viscosity would necessitate higher forces to push the material out of the nozzle, resulting in excessive shear forces being exerted on the material. Too high viscosity could inhibit deposition altogether. Beyond uneven deposition, inconsistent and suboptimal flow could entrap air within the printed product or result in inhomogeneous and poor-quality prints. Undesirable viscoelastic behaviour can also result in creep and die expansion, both of which are likely to generate products with inaccurate dimensions and/or poor dimensional stability [36,73,95]. During PAM, the polymer exists in a semi-solid state as various forms, for instance, gels, pastes, or emulsion gels [95,172,174]. Typically, the polymer chains overlap ($c > c^*$) in a semi-dilute solution forming a three-dimensional network from polymer chain entanglements. Therefore, in addition to viscosity and yield point, gel strength is also crucial for controlling deposition from the PAM nozzle. Both oscillatory measurements in rheometers and rotational viscometers can be used to characterize semi-dilute systems, depending on the polymer concentration as well as the content of fillers or dry excipients in a formulation.

Low polymer concentrations forming dilute polymer solutions, where the polymer chains do not interact with each other ($c < c^*$), could be encountered in solvent-based DoD or DoP printing if polymers are included in the solvent. Here, an optimal viscosity contributes to the controlled deposition of primary droplets without the generation of unwanted satellite droplets [109]. Alongside viscosity, surface tension is another useful parameter to assess drop dynamics (Section 4.4). Dilute polymer solutions typically show plastic or pseudoplastic flow with a yield point. Shear thinning effects are also frequently observed. These systems are evaluated with either rotational viscometers or simple capillary viscometers, such as Ubbelohde or Ostwald viscometers [212].

Rheological analyses have been shown to provide a deeper understanding of processability of the polymer or formulation [5,10,141,147,149,174,213]. Rheological tools are also useful for formulation development, for studying drug-polymer interactions [7,210,214], polymer blends [210,214], the effect of added excipients [215], and for tailoring and predicting product performance, such as dissolution and drug release behaviour [103,139,147]. Several options exist to optimize the rheological properties specific to the AM process of interest. These include a combination of process

parameters (e.g. temperature, printing rate) and formulation parameters (e.g. polymer type-considering chain flexibility, branching, chain length, Mw; mixing of polymers-considering different copolymer ratios, Mw; and addition of drug(s) and excipients such as plasticizers or fillers) [103,171,210,216,216]. Although rheological characterization is performed routinely in the polymer industry to evaluate processability of polymers, it remains somewhat underutilized in pharmaceutical additive manufacturing [95].

4.4. Techniques to measure surface tension

Drop dynamics is a crucial part of printability during melt-based and solvent-based DoD printing, where surface tension is a key property, alongside viscosity [4,108,110,217]. Here, measurements of surface tension by drop shape analysis [111] or tensiometry [218] for example, by utilizing a du Noüy ring [85], have been reported (Table 4). In the case of the former, the pendant drop method has been used. Here, both the surface tension and weight of a droplet contributes to its shape when suspended from a needle, therefore, by analysing an image of the drop, its surface tension can be determined. In addition, several dimensionless quantities exist to characterize drop dynamics including the Reynolds number, Weber number, Ohnesorge number, and Fromm's number [67]. Although lower and upper limits for acceptable values exist for Newtonian fluids, more research is required to determine what values are considered optimal for viscoelastic liquids such as polymer melts during melt-based DoD [67]. Contact angle measurements have also been utilised to ascertain whether the material has an appropriate surface tension for optimal adhesion [3].

Regardless of whether solvent-based or melt-based DoD printing is employed, the surface tension of the liquid at the nozzle needs to be sufficiently high to prevent leakage from the nozzle orifice when deposition is not occurring, to form spherical droplets after liquid is ejected as a jet from the nozzle, and to prevent potentially undesirable spreading and droplet coalescence onto a substrate during adhesion [100,109,110]. At the same time, surface tension needs to be sufficiently low such that the pressure pulses originating from piezoelectric, electrostatic, or thermal actuators can overcome the surface tension to eject the droplets during deposition [5]. Surface tension also influences refilling of the drop generator, together with viscosity [100]. Although most studies in pharmaceutical AM relate surface tension to DoD printing, surface tension measurements are not exclusively applicable to DoD technologies. They may also be advantageous in understanding adhesion to a build plate, substrate, or previous printed layer, which has been harnessed during FDM [87]. Surface tension is also crucial for successful printing during SLS. Here, low melt surface tension is desirable to encourage coalescence between powder particles [13].

4.5. Spectroscopic techniques

Rapid, specific, and non-destructive analytical techniques for assessment of drug content, drug distribution, and the solid-state form of drugs are desired in quality control of all pharmaceutical products. Selected spectroscopic methods are highly attractive since they can be used for real-time analysis in-line and on-line during processing, in addition to or as an alternative to off-line analysis [219]. As such, the spectroscopic techniques are key tools in PAT (see Chapter 4.8.1). In this section, the vibrational spectroscopic methods near infrared (NIR), Fourier-transform infrared (FTIR), and Raman spectroscopy will be discussed, and their use in AM exemplified. FTIR and Raman are often considered complementary techniques. In order to extract and quantify information in an efficient manner, spectral data are often accompanied by

chemometric treatment of data and multivariate analysis [220,221].

4.5.1. Near infrared spectroscopy (NIR)

NIR spectroscopy is a rapid and non-destructive analytical technique with wide and varied applications in pharmaceutical analysis. This technique is based on the absorption of electromagnetic radiation from the visible (780 nm) to the mid-infrared region (2500 nm) [220]. NIR spectra comprise chemical information (e.g. content of drug, content of excipient, contamination, water content, and batch-to-batch variability), physical information (e.g. crystalline form, polymorphism, and particle size), and is frequently applied for process monitoring (e.g. of chemical or physical information, end-point detection) (Ph.Eur. 2.2.40. *Near-infrared spectroscopy*) [222]. Its use in combination with AM can be found across different technologies with an emphasis on product performance. For example, Trenfield et al. quantified the drug content in SLS printed dosage forms with NIR [10], Vakili et al. used NIR hyperspectral imaging to study inkjet printed systems [177], and Khorasani et al. created chemical maps of drug and excipients by NIR chemical imaging for the prediction of the spatial distribution of drug in FDM printed films [175].

4.5.2. Fourier transform infrared spectroscopy (FTIR)

FTIR is another rapid and non-destructive analytical technique based on the absorption of infrared radiation. FTIR operates by converting a time domain interferogram to a frequency spectrum. The spectrum serves as a fingerprint of a molecule and can be used to elucidate molecular structure and reveal interactions between molecules [223]. FTIR is often used to examine possible interactions between the components of the formulation, such as the drug and the excipients. This is not the most widespread method in AM but has still been used in a variety of the technologies, such as FDM [68,178,179], PAM [39], SLA [116], and solvent-based DoD [111].

4.5.3. Raman spectroscopy

Raman spectroscopy is a versatile non-destructive analytical technique that uses the secondary radiation “Raman scattering” to determine vibrational modes of molecules [224,225]. The hyperspectral information provides a structural fingerprint from which chemical identity, quantitative analysis, and solid-state form of drug molecules can be extracted [226]. As stated in the Ph.Eur. (2.2.48. *Raman spectroscopy*), Raman spectroscopy is useful for chemical, physical, and process analysis [227]. Coupling a Raman spectrometer with fiber-optic probes allow operational flexibility and remote systems that can be built into equipment for process monitoring. They can also function as small hand-held equipment for rapid analysis [224,225]. Raman microscopes can perform localized sample analysis, enabling hyperspectral chemical imaging or mapping, whereas confocal Raman microscopy can also discriminate axial signals originating from selective depth within the sample [224]. Although Raman has been used to monitor HME processes [228,229], to the best of our knowledge, it has not yet been implemented into FDM printers. Nevertheless, Raman spectroscopy has widespread use in confirming the product performance of 3D printed products. For example, Raman mapping has been used to assess drug distribution and solid-state form of the drug in FDM [82,147,180], in melt-based DoD [66], and in SLS [176]. Other authors have used confocal Raman microscopy for the evaluation of FDM printed matrices [178] and solvent-based DoD [111,161].

4.6. Scattering techniques

Pharmaceutical polymers processed by AM are available in amorphous or semi-crystalline form. AM processing can intention-

ally alter the solid-state form of the polymer (e.g. from semi-crystalline to amorphous form in melt-based AM), unintentionally alter the polymer solid state form, or even aid in maintaining the polymer in its original solid-state form, if desired. Scattering techniques are typically used to evaluate the solid-state form of drugs during pharmaceutical AM but this property is also strongly influenced by the type and concentration of polymer that is incorporated into the AM formulations. Current applications of scattering techniques are used almost exclusively for product performance and stability, not printability. This section summarizes X-ray powder diffraction (XRPD), small-angle x-ray scattering (SAXS), wide-angle x-ray scattering (WAXS), and small-angle neutron scattering (SANS) with a focus on the polymer solid-state. XRPD is currently the most widespread of these in AM. Since this review focuses on the role of polymers for printability rather than only product performance, these techniques will only be briefly addressed for information purposes.

4.6.1. X-ray powder diffractometry

An X-ray diffractometer is equipped with an X-ray tube for generating X-ray radiation. The emitted X-rays interact with the sample, placed on a sample stage, and are diffracted. The intensity of the diffracted beam is then recorded by a detector at various diffraction angles. During diffraction of crystalline materials, long range molecular order is present, which produces a constructive interference pattern. This interference pattern is read out as peaks in the diffractogram [230]. The diffraction pattern for a crystalline form is unique, therefore X-ray diffractometry can be used for material characterization and crystal structural elucidation [230–232]. For amorphous materials, which lack long range molecular order, no constructive interference occurs, resulting in a halo pattern in their diffractogram [230]. Several pharmaceutical polymers are either amorphous or semi-crystalline and are therefore characterized by either a halo or low intensity diffraction peaks, respectively [233]. In AM, when a crystalline drug is embedded in the amorphous polymer, less intense diffraction peaks have been observed [183,233–235]. For the purposes of product performance and stability, X-ray diffraction can be performed under varying temperatures and/or humidities [232].

4.6.2. Small- and wide-angle X ray scattering and small-angle neutron scattering

WAXS can provide similar information to XRPD on the solid-state form of the polymer [155], without requiring sample milling. SAXS probes considerably smaller angles than WAXS [236], providing information on longer length scales, for example, thickness of amorphous or crystalline layers, which may be useful to probe heterogeneity in intermediates or final products. In the case of the former, this could clarify the processability or lack thereof of certain material systems. Furthermore, scanning SAXS can potentially be used in future to study controlled spatial deposition of drugs and polymers with different solid-state forms during AM printing.

SANS is a technique that has been used previously to understand structures on a nanometer scale, which has been related to properties of interest in FDM-printed constructs outside of pharma [185]. In pharmaceutical AM, it may, for instance, be applied similarly to study polymer alignment and orientation at the interface between printed layers or troubleshoot potential printability issues related to structure, such as delamination.

4.7. Imaging techniques

Most microscopic imaging techniques are non-destructive and have a long history in the study of pharmaceuticals. Various imaging techniques have proven useful in visualising and understand-

ing morphological features, spatial distribution, particle size distribution, and feature dimensions, on surfaces and sections of 3D printed products and solid intermediates [153]. As mentioned in Chapter 4.5., both NIR and Raman are also used for imaging or mapping [111,147,175,177].

4.7.1. Scanning electron microscopy (SEM)

One of the most prevalent imaging techniques is scanning electron microscopy (SEM). SEM uses an electron microscope to scan sample surfaces or sections with an electron beam. These electrons interact with the sample, producing backscattered and secondary electrons, which are used to generate a 2D image containing compositional, topographical, and morphological information on the sample, for example surface roughness, porosity, layer height, and layer structure [237,238]. Although SEM techniques generate a 2D image, they may provide a 3D impression of morphological features. In addition to providing information about final product quality and performance, for example, by elucidating the microstructure to explain mechanical properties or drug release [178,239], SEM can also be used to reveal potential relationships between filament microstructure and feeding during FDM.

In addition, other forms of SEM imaging such as focused ion beam-SEM and SEM with energy dispersive X-ray analysis [240,236,241] can be used to study the distribution of drug and polymer in extruded filaments for FDM or polymeric substrates with deposited drug in DoD printing, which can provide insights into the flexibility or physical stability of these printed products.

4.7.2. X-ray computed microtomography

X-ray computed microtomography (X-ray μ CT) is a non-destructive 3D imaging technique that has gained significant use in visualizing 3D printed samples. It is based on the principle that an object will attenuate incident X-rays to different extents in regions with different densities. The resulting 2D shadow projections are subsequently reconstructed to generate a 3D X-ray image [242]. One of the major uses of X-ray μ CT is the determination of porosity in 3D printed constructs. Due to the high geometric design flexibility of several AM processes, an internal pore network can be intentionally designed into the 3D printed construct, if desired, to modulate drug release kinetics, for example. In addition to porosity determination, X-ray μ CT can be used to determine the structural integrity of printed constructs. Its non-destructive nature and ability to generate 3D visualizations makes X-ray μ CT especially suitable for geometric assurance, i.e., to determine how closely the printed object resembles the intended CAD model [50,180]. Modification of process parameters and material inputs can thereafter be carried out to optimize printability and product quality.

4.7.3. Emerging imaging techniques

More advanced imaging techniques are also explored for printed pharmaceuticals. Using time of flight – secondary ion mass spectroscopy (ToF-SIMS), microscale heterogeneity between surfaces and bulk can be revealed, which can provide insights into potential physical instability or crystallization of the drug [161,187,188]. In addition, spatial mapping of drug distribution as a function of depth can be obtained, which has been shown to provide complementary evidence to Raman spectroscopy within the bulk of printed structures by melt-based DoD [161,187]. Since ToF-SIMS is surface sensitive, with a measuring depth of approximately 1 nm, typically only substances on the surface can be analyzed. However, ToF-SIMS has also been used in combination with focused ion beams to probe the chemical interface between printed surfaces containing silver nanoparticles and polymers like polystyrene or poly(methyl methacrylate) [187]. Scoutaris et al. have also shown that it is possible to determine the chemical content in dry ink-jet droplets containing both drugs (felodipine and

hydrochlorothiazide) and polymers (PVP, PLGA) by using ToF-SIMS [243].

Terahertz pulsed imaging is based on the reflection of terahertz pulses as they encounter media with different refractive indices [186,244]. This technique has been used to determine coating layer thickness on solid dosage forms [244,245]. Terahertz radiation is capable of penetrating most polymers. Recently, Markl et al. showed that this non-destructive imaging technique is another option to characterize microporous structures within 3D printed products [186].

4.8. Advanced use of characterization techniques for complex applications

Several of the simple characterization techniques described above in Section 4 can also be combined and implemented for more complex purposes, such as process monitoring in a PAT approach or combined with computational methods or digital tools to calibrate and validate models for *in silico* simulations and predictions. Examples of such applications within AM are addressed in the following sub-sections.

4.8.1. Process analytical technology (PAT)

Implementation of PAT to monitor AM processes and secure critical quality attributes (CQAs) in the final product has been explored in a Quality-by-Design (QbD) approach. PAT tools are intended to rapidly and non-invasively collect and analyse data in real-time. To this end, spectroscopic techniques, such as Raman, near infrared, and UV/Visible spectroscopy have been employed in the study of drug content, content uniformity, and degradation-induced changes in the solid state, to name a few examples [73,228,229,246]. The spectroscopic techniques are generally recognized among the main PAT tools and are even described in the recent monograph on PAT in the European Pharmacopoeia (Ph. Eur. 5.25. *Process analytical technology*) [247]. They are considered key elements of pharmaceutical continuous manufacturing [248]. Recently, several reviews on pharmaceutical AM technologies also discuss the PAT tools required for continuous manufacturing. For example, Bandari et al. discuss the coupling of HME and FDM to a continuous line [29], Rahman and Quodbach discuss the required PAT tools for PAM [30] and Awad et al. does the same for SLS [32]. In this context, not only are spectroscopic PAT tools needed but techniques that specifically provide real-time information on processability and/or identification of failure modes leading to geometry defects whilst processing, would have considerable potential, and should be further explored. The following paragraphs provide a few examples to highlight the value of other PAT tools for pharmaceutical AM.

Various imaging techniques using cameras or laser profile sensors can be applied in-line to track the printed geometry using digital image analyses. Real-time images can therefore be continuously compared with the CAD model to identify printing defects and errors [43,45,249]. For melt-based AM technologies, thermal imaging may prove particularly beneficial in providing information on potential hotspots, which could lead to thermal degradation [73]. Thermal imaging could also be useful for monitoring the cooling phase in melt-based AM. Optimal cooling is critical to solidify the printed product and avoid deformation under its own weight whilst at the same time facilitating optimal adhesion to the build-plate, substrate, or preceding printed layer [171].

For extrusion-based techniques, in-line pressure transducers are useful tools to monitor material flow [94,171]. Nozzle clogging is a frequently occurring process error that could impact the resulting geometric accuracy and mechanical properties of the printed construct. Tlegenov et al. proposed a dynamic model for current-based nozzle condition monitoring [249]. Anderegg et al. designed

a nozzle that enabled in-situ measurements of material temperature and flow rate to reduce fluctuations in pressure during FDM processing [250]. Recently, in-line rheological monitoring for FDM was described by Coogan and Kazmer [94,140]. Here, a modified printer nozzle with an invasive thermocouple and pressure transducer provided real-time monitoring of melt temperatures and viscosities encountered during FDM processing. Translating several such developments from non-pharmaceutical AM to pharmaceutical applications will likely provide a considerable step forward in the widespread implementation of controlled pharmaceutical AM processes.

4.8.2. In silico techniques and other digital tools

Pharmaceutical AM technologies are actively moving towards integrating more computational methods and digital tools to predict and optimize process parameters, eliminate material usage, reduce trial and error, and improve cost- and time-efficiency, to name a few examples. Nevertheless, all computational approaches require calibration and/or validation with experimental data at some point. In this section, the potential or established utility of simulations, digital twins, artificial intelligence, and specifically, machine learning, will be addressed. Where relevant, their contribution to elucidating or optimizing the role of the polymer in AM will be highlighted. The interested reader is referred to a recent review on artificial intelligence for pharmaceutical AM [251].

Simulations play an important role in predicting experimental outcomes, such as the influence of material properties on printability and product performance, in a rapid and efficient manner. By attaining practical feedback through simulations, the performance of current designs can be ascertained, and several alternate designs can be tested without physically fabricating them in the early design phases and without initially extensive and costly experimentation. Subsequently, the characterization techniques described earlier in Section 4 may be employed in a potentially more resourceful manner towards optimizing processes and systems.

Molecular dynamics simulations have been used to predict the influence of plasticizers, like glycerol, on T_g , even for hydrophilic polymers like starch [252]. In addition, the T_g of materials systems comprising ibuprofen or theophylline in Eudragit® has been predicted by Maus et al. [253] (Fig. 7). The T_g of a polymer is expected to have a considerable influence on the choice of printing temper-

atures for AM technologies based on melting and sintering, for example, FDM and SLS. Such insights from molecular dynamics simulations are therefore invaluable for process and material optimization. Beyond its uses in manufacturing by AM, such simulations also facilitate rapid prototyping in early design and development phases. Alternative types of simulations are also available for these purposes.

Yuan et al. have developed numerical simulations, which consider printing speed, thermal convection coefficient, nozzle diameter, and latent heat of crystallisation, to predict evolution of crystallization of polymers by a simulation method known as the finite element method [254]. This approach is particularly critical to understand the interplay between polymer and process for preventing unwanted crystallization of the drug and/or polymer for product performance and/or printability.

In addition to simulations, a second example of the potential manifestation of digitalization in the evolving pharmaceutical AM landscape is that of digital twins. A digital twin is defined as “a set of virtual information constructs that fully describes a potential or actual physical manufactured product from the micro atomic level to the macro geometrical level” [255]. A digital twin consists of three basic components, namely, a physical component, a virtual component, and automated data communications that integrate these components. Digital twins have various potential applications in pharmaceutical AM, including but not limited to, understanding the roles of various process parameters, understanding the sensitivity of product quality to process variations, prediction of productivity, material tracking, and quality assurance [256]. For polymers in AM, a potential benefit foreseen in this review stems from the variety of AM processes and their utilization of different classes of polymers to ensure printability. Here, digital twins could guide polymer selection for a wide variety of AM technologies such that the optimal polymers and grades are selected not only for printability but also for product performance. In addition, since geometric design freedom is touted as one of the principal advantages of AM, digital twins may have a high potential for geometry assurance of printed products and for evaluating the contribution of varying inputs such as polymers with different physicochemical properties to enhanced geometric flexibility and accuracy.

Importantly, digital twins are still in their first generation and yet to be implemented into pharmaceutical AM. In the meantime, the reader is referred to two recent reviews, the first by Chen et al. [256] on digital twins in biopharmaceutical manufacturing, which explores generalized applications without a specific mention of AM and the second by Zhang et al. [257] on digital twins in additive manufacturing in several industries but not pharma. Taken together, these recent reviews allude to a potential opportunity noted in this review that is yet to be explored, that is, digital twins in pharmaceutical additive manufacturing and more specifically, digital twins to guide the selection and utilization of a wider variety of approved polymers in pharmaceutical additive manufacturing.

Yet another emerging trend in pharmaceutical AM is artificial intelligence, particularly machine learning [251]. A few examples will be outlined in this paragraph. Elbadawi et al. used machine learning to predict the drug release rate from FDM-printed PCL units based on melt rheology data (i.e., shear and complex viscosity as a function of shear rate and oscillation frequency, respectively, at different temperatures). Three different machine learning techniques, namely, multi-linear regression, decision trees, and support vector machines, were used in this study [139]. Whilst this study used a small training set of eight formulations and tested the machine learning methods on data from one formulation, in another study, Elbadawi et al. used data from 614 drug-loaded formulations to predict the selection of printing temperature based

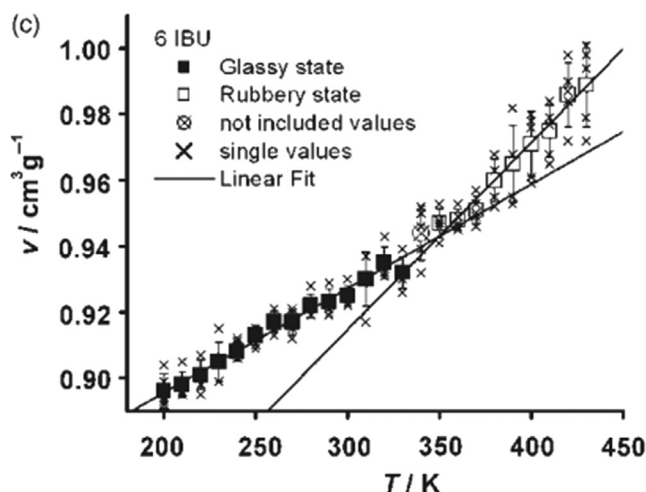


Fig. 7. Plot of the computed specific volume (v) versus temperature (T) for ibuprofen in Eudragit®. The intersection between the two lines, resulting from a linear regression of the data points, corresponds to the glassy and rubbery states determined by the simulated T_g values. Figure reproduced with permission [253].

on six machine learning techniques (multivariate linear regression, k-nearest neighbours, support vector machines, random forests, neural networks, and deep learning) [189]. M3DISEEN is a web application that was developed based on the used machine learning techniques to, for example, predict process temperatures for melt extrusion and printing of drug-polymer formulations [189]. The data inputs to M3DISEEN were based on 145 different materials. Interestingly, the random forest machine learning method reveals that the choice of polymer has a larger influence on the melt extrusion temperature, filament mechanical characteristics, and printability, than plasticizers, lubricants, drugs, disintegrants, surfactants, and so forth. However, the choice of added lubricant and plasticizer were shown to have somewhat higher influence on the printing temperatures than the choice of polymer [189]. With these early adaptations of artificial intelligence in pharmaceutical AM, expanding opportunities towards the improved use of rheological information to predict both drug release rates and printing performance by machine learning, for example, is possibly not far away. Further examples can be found in the review [251].

4.9. Choosing the right techniques for the right purpose

This section has explored the variety of characterization techniques that are currently available to assess properties of the raw materials or intermediates to ensure printability with selected AM processes and/or to optimize product performance and/or to monitor the printing process. As illustrated in Fig. 8, the same techniques may be useful for several of these purposes. The current prevalence of different characterization techniques in AM literature is expected to be biased by the relative use of each AM technique in pharmaceutical research. Relative use may, in turn, depend on ease of access to various instruments, cost barriers, and so forth. Consequently, the higher prevalence of one technique over another cannot be used as a direct proxy for their relative suitability or usefulness of each characterization technique.

This review has revealed several emerging techniques with respect to adoption in AM, such as more powerful X-ray techniques like X-ray μ CT, SAXS and WAXS, and highly specialized techniques, such as ToF-SIMS and Terahertz pulsed imaging, which are still underutilized and should be further explored for their benefits in pharmaceutical AM. The incorporation of advanced computational methods and digital tools for improved printability and product performance could contribute to improved understanding of the interplay between these functions and could potentially broaden the range of polymers and applications of polymers in pharmaceutical AM.

5. Conclusion

At the beginning of this review, three key questions were posed, which this review has begun to answer. Firstly, regarding the extent of utilisation of pharmaceutically approved polymers across various AM technologies, i.e., which polymers are not yet used and why?

Although this review revealed that more than 30 pharmaceutically approved polymers are currently used in various AM techniques, some are used more frequently than others. Interestingly, polymers that have widespread use in a given AM technique, lack use in other AM techniques based on similar polymer transformation principles e.g. melting. Several polysaccharides, cellulose derivatives, and polymer-based surfactants have been highlighted in this review for their potential in specific AM technologies. Currently, AM in biomedical, food, and confectionary industries provide a good indication of which pharmaceutically approved polymers could be adopted into pharmaceutical AM for oral drug delivery in future. A driving force for exploring today's underutilized polymers is the emergence of new pharmaceutical challenges, e.g. delivery of biological drugs, where the need for combining diverse polymers with innovative AM platforms may become even more critical in contributing to the effectiveness of the next generation of pharmaceutical products.

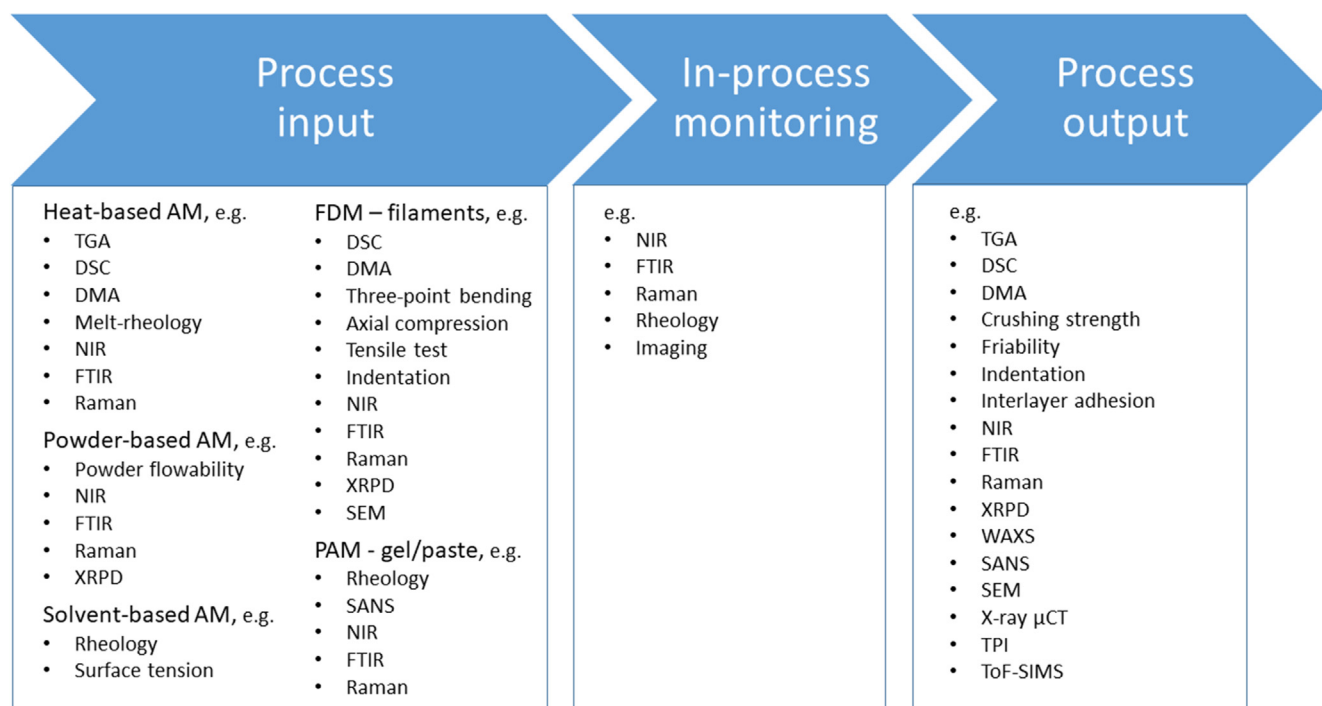


Fig. 8. Overview exemplifying the diversity of techniques used for characterization of feedstock or process input, in-process monitoring, and end-products or process output across AM of pharmaceutical oral products.

The second question posed was how do polymer properties relevant to different stages of the AM process, e.g. feeding, deposition, and adhesion, compare across the various AM technologies used in pharmaceutical research? This review revealed that required polymer properties for successful feeding, deposition, and adhesion were similar across the various melt-based techniques (FDM, SLS and melt-DoD) and across the various solvent-based techniques (PAM, solvent-based DoD and DoP). The most important polymer properties for melt-based AM are thermal properties and melt rheology. For solvent-based AM, rheology and surface tension of printing inks are critical. In addition, based on the feedstock form, polymer properties that are crucial include mechanical properties (for FDM filament feedstocks), viscosity (for solution or molten feedstocks), and powder flow (for powder-based feedstocks).

The last question posed involved addressing whether the characterization techniques already used to assess product performance are equally suited to assess printability. Indeed, this review has highlighted that most of the characterization techniques already used to assess product performance are equally suitable for assessing material suitability for printability. Looking to the future, further opportunities like enhanced use of PAT tools, *in silico* techniques, and even certain infrequently used characterization methods like advanced scattering techniques or specialized techniques like TOF-SIMS and terahertz spectroscopy, show potential in not only clarifying the role of polymers for AM but achieving this much-needed balance between printability and product performance across AM technologies with existing pharmaceutical polymers.

By demonstrating and discussing trade-offs between printability and product performance through simple case examples, including achieving and stabilizing the solid state and facilitating drug delivery applications, this review has shed a light on the inadequate exploration of printability versus product performance trade-offs which are anticipated for future bridging of proof-of-concept demonstrations to mainstream realization of pharmaceutical AM. This knowledge gap is crucial to address in order to optimally balance printability and product performance and harness the full potential of pharmaceutical AM.

6. Expert opinion

Materials (e.g. polymers) and manufacturing processes (e.g. AM) share a common purpose of enabling the pharmaceutical product to perform as intended. For them to carry out this purpose, compatibility between polymers and AM processes to allow printability is one crucial aspect. This review revealed that there is no shortage of pharmaceutically approved polymers, designed to elicit a variety of product performance attributes. Despite the wide range of available polymers, the current material diversity of each AM process appears to be quite restricted by their different working principles. Interestingly, by approaching this review from an overarching perspective of whether AM technologies are melt-based or solvent-based processes, whether they use continuous extrusion or jetting, whether they require pre-processing of feedstocks or not, and so forth, we have learned that distinct working principles do not necessarily imply a distinct set of appropriate polymers for each process. On the contrary, by assessing polymer suitability based on required properties during feeding, deposition, and adhesion stages of printing, several underutilized but suitable polymers for the desired product performance and for printability have become evident. However, an added complication to fully harnessing available polymers in AM is the trade-offs between printability and product performance that exist but are, surprisingly, given limited attention in progressing this field. Until all encountered trade-offs between product performance and print-

ability are solved, selecting polymers (and entire materials systems) for optimal product performance to suit patient needs will always be a priority over printability. This runs the risk of avoidance of AM implementation in favour of alternative manufacturing approaches. The consequence is that the unique advantages of AM for complex, personalized products and advanced drug delivery applications, may not progress from proof-of-concept to widespread adoption. When faced with a choice between introducing new materials to suit the current state of AM printers or developing printers to suit the current scope of pharmaceutically approved polymers, we strongly favour the latter. From an industrial perspective, introduction of new excipients, including polymers, is typically a time- and cost-intensive endeavour. Moreover, AM is in the midst of a rapid and ongoing technological evolution, which is equipped to maximize compatibility between emerging AM printing and a broader range of polymers than are currently used. We anticipate that, in future, high performing multifunctional or hybrid printers that combine several AM processes with different working principles will play a key role in expanding material diversity and enabling industrial applicability and adoption in the pharmaceutical space.

Funding

This project was carried out as part of Nordic POP (Patient Oriented Products), a Nordic University Hub funded by NordForsk (project number 85352).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] M. Attaran, The rise of 3-D printing: The advantages of additive manufacturing over traditional manufacturing, *Bus. Horiz.* 60 (2017) 677–688.
- [2] A. Mohammed, A. Elshaer, P. Sareh, M. Elsayed, H. Hassanin, Additive Manufacturing Technologies for Drug Delivery Applications, *Int. J. Pharm.* 580 (2020) 119245.
- [3] S.A.M. Tofail, E.P. Koumoulos, A. Bandyopadhyay, S. Bose, L. O'Donoghue, C. Charitidis, Additive manufacturing: scientific and technological challenges, market uptake and opportunities, *Mater. Today* 21 (2018) 22–37.
- [4] M. Trivedi, J. Jee, S. Silva, C. Blomgren, V.M. Pontinha, D.L. Dixon, B. Van Tassel, M.J. Bortner, C. Williams, E. Gilmer, A.P. Haring, J. Halper, B.N. Johnson, Z. Kong, M.S. Halquist, P.F. Rocheleau, T.E. Long, T. Roper, D.S. Wijesinghe, Additive manufacturing of pharmaceuticals for precision medicine applications: A review of the promises and perils in implementation, *Addit. Manuf.* 23 (2018) 319–328.
- [5] J. Zhang, A.Q. Vo, X. Feng, S. Bandari, M.A. Repka, Pharmaceutical Additive Manufacturing: a Novel Tool for Complex and Personalized Drug Delivery Systems, *AAPS PharmSciTech* 19 (2018) 3388–3402.
- [6] A. Awad, S.J. Trenfield, A. Goyanes, S. Gaisford, A.W. Basit, Reshaping drug development using 3D printing, *Drug Discov Today* 23 (2018) 1547–1555.
- [7] J. Goole, K. Amighi, 3D printing in pharmaceuticals: A new tool for designing customized drug delivery systems, *Int. J. Pharm.* 499 (2016) 376–394.
- [8] S. Jacob, A.B. Nair, V. Patel, J. Shah, 3D Printing Technologies: Recent Development and Emerging Applications in Various Drug Delivery Systems, *AAPS PharmSciTech* 21 (2020) 220.
- [9] M.O. Oyewumi, 3D Printing Technology in Pharmaceutical Drug Delivery: Prospects and Challenges, *J. Biomol. Res. Therapeut.* 04 (2015) e141.
- [10] S.J. Trenfield, A. Awad, A. Goyanes, S. Gaisford, A.W. Basit, 3D Printing Pharmaceuticals: Drug Development to Frontline Care, *Trends Pharmacol. Sci.* 39 (2018) 440–451.
- [11] A. Melocchi, M. Uboldi, A. Maroni, A. Foppoli, L. Palugan, L. Zema, A. Gazzaniga, 3D printing by fused deposition modeling of single- and multi-compartment hollow systems for oral delivery – A review, *Int. J. Pharm.* 579 (2020) 119155.
- [12] M.A. Alhnan, T.C. Okwuosa, M. Sadia, K.W. Wan, W. Ahmed, B. Ararat, Emergence of 3D Printed Dosage Forms: Opportunities and Challenges, *Pharm. Res.* 33 (2016) 1817–1832.

- [13] S.C. Ligon, R. Liska, J. Stampfl, M. Gurr, R. Mulhaupt, Polymers for 3D Printing and Customized Additive Manufacturing, *Chem. Rev.* 117 (2017) 10212–10290.
- [14] J.J. Water, A. Bohr, J. Boetker, J. Aho, N. Sandler, H.M. Nielsen, J. Rantanen, Three-dimensional printing of drug-eluting implants: preparation of an antimicrobial polylactide feedstock material, *J. Pharm. Sci.* 104 (2015) 1099–1107.
- [15] M.A. Azad, D. Olawuni, G. Kimbell, A.Z.M. Badruddoza, M.S. Hossain, T. Sultana, Polymers for Extrusion-Based 3D Printing of Pharmaceuticals: A Holistic Materials-Process Perspective, *Pharmaceutics* 12 (2020).
- [16] A. Jain, K.K. Bansal, A. Tiwari, A. Rosling, J.M. Rosenholm, Role of Polymers in 3D Printing Technology for Drug Delivery - An Overview, *Curr. Pharm. Des.* 24 (2018) 4979–4990.
- [17] J.W. Stansbury, M.J. Idacavage, 3D printing with polymers: Challenges among expanding options and opportunities, *Dent. Mater.* 32 (2016) 54–64.
- [18] C.M. González-Henríquez, M.A. Sarabia-Vallejos, J. Rodríguez-Hernandez, Polymers for additive manufacturing and 4D-printing: Materials, methodologies, and biomedical applications, *Prog. Polym. Sci.* 94 (2019) 57–116.
- [19] I. Jasiuk, D.W. Abueidda, C. Kozuch, S. Pang, F.Y. Su, J. McKittrick, An Overview on Additive Manufacturing of Polymers, *JOM* 70 (2018) 275–283.
- [20] S.D. Nath, S. Nilufar, An Overview of Additive Manufacturing of Polymers and Associated Composites, *Polymers (Basel)* 12 (2020).
- [21] S. Borandeh, B. van Bochove, A. Teotia, J. Seppälä, Polymeric drug delivery systems by additive manufacturing, *Adv. Drug Deliv. Rev.* 173 (2021) 349–373.
- [22] S.K. Patel, M. Khoder, M. Peak, M.A. Alhnan, Controlling drug release with additive manufacturing-based solutions, *Adv. Drug Deliv. Rev.* 174 (2021) 369–386.
- [23] A. Abaci, C. Gedeon, A. Kuna, M. Guvendiren, Additive Manufacturing of Oral Tablets: Technologies, Materials and Printed Tablets, *Pharmaceutics* 13 (2021).
- [24] S. Naghie, D. Chen, Printability – a Key Issue in Extrusion-based Bioprinting, *J. Pharm. Anal.* (2021).
- [25] International Organization for Standardization [ISO], ISO/ASTM 52900:2015 Additive manufacturing-General principles-Terminology, 2015. <https://www.iso.org/standard/69669.html#:~:text=ISO%2FASTM%2052900%3A2015%20establishes,into%20specific%20fields%20of%20application>.
- [26] U.S. Food and Drug Administration, CY 2015 CDER Drug and Biologic Calendar Year Approvals, 2015. <https://fda.report/media/95885/CDER-Drug-and-Biologic-Approvals-for-Calendar-Year-2015.pdf>.
- [27] H. Everett, Triastek Receives FDA IND Clearance for 3D Printed Drug to Treat Rheumatoid Arthritis-3D Printing Industry, 2021. <https://3dprintingindustry.com/news/triastek-receives-fda-ind-clearance-for-3d-printed-drug-to-treat-rheumatoidarthritis-184159>.
- [28] Y. Zheng, F. Deng, B. Wang, Y. Wu, Q. Luo, X. Zuo, X. Liu, L. Cao, M. Li, H. Lu, S. Cheng, X. Li, Melt extrusion deposition (MED™) 3D printing technology – A paradigm shift in design and development of modified release drug products, *Int. J. Pharm.* 602 (2021) 120639.
- [29] S. Bandari, D. Nyavanandi, N. Dumpa, M.A. Repka, Coupling hot melt extrusion and fused deposition modeling: Critical properties for successful performance, *Adv. Drug Deliv. Rev.* 172 (2021) 52–63.
- [30] J. Rahman, J. Quodbach, Versatility on demand - The case for semi-solid micro-extrusion in pharmaceuticals, *Adv. Drug Deliv. Rev.* 172 (2021) 104–126.
- [31] C. Parulski, O. Jennotte, A. Lechanteur, B. Evrard, Challenges of fused deposition modeling 3D printing in pharmaceutical applications: Where are we now?, *Adv. Drug Deliv. Rev.* 175 (2021) 113810.
- [32] A. Awad, F. Fina, A. Goyanes, S. Gaisford, A.W. Basit, Advances in powder bed fusion 3D printing in drug delivery and healthcare, *Adv. Drug Deliv. Rev.* 174 (2021) 406–424.
- [33] X. Xu, A. Awad, P. Robles-Martinez, S. Gaisford, A. Goyanes, A.W. Basit, Vat photopolymerization 3D printing for advanced drug delivery and medical device applications, *J. Control. Release* (2020).
- [34] V.M. Vaz, L. Kumar, 3D Printing as a Promising Tool in Personalized Medicine, *AAPS PharmSciTech* 22 (2021), 49–49.
- [35] Handbook of Pharmaceutical Excipients, 6 ed., Pharmaceutical Press and American Pharmacists Association, London and Chicago, 2009.
- [36] A. Zidan, A. Alayoubi, S. Asfari, J. Coburn, B. Ghamraoui, S. Aqueel, C.N. Cruz, M. Ashraf, Development of mechanistic models to identify critical formulation and process variables of pastes for 3D printing of modified release tablets, *Int. J. Pharm.* 555 (2019) 109–123.
- [37] M. Cui, Y. Li, S. Wang, Y. Chai, J. Lou, F. Chen, Q. Li, W. Pan, P. Ding, Exploration and Preparation of a Dose-Flexible Regulation System for Levetiracetam Tablets via Novel Semi-Solid Extrusion Three-Dimensional Printing, *J. Pharm. Sci.* 108 (2019) 977–986.
- [38] C.I. Giomouxouzis, E. Tzimtzimis, O.L. Katsamenis, A. Dourou, C. Markopoulou, N. Bouropoulos, D. Tzetzis, D.G. Fatouros, Fabrication of an osmotic 3D printed solid dosage form for controlled release of active pharmaceutical ingredients, *Eur. J. Pharm. Sci.* 143 (2020) 105176.
- [39] S.A. Khaled, J.C. Burley, M.R. Alexander, J. Yang, C.J. Roberts, 3D printing of five-in-one dose combination polyfill with defined immediate and sustained release profiles, *J. Control. Release* 217 (2015) 308–314.
- [40] W. Kempin, V. Domsta, I. Brecht, B. Semmling, S. Tillmann, W. Weitschies, A. Seidlitz, Development of a dual extrusion printing technique for an acid- and thermo-labile drug, *Eur. J. Pharm. Sci.* 123 (2018) 191–198.
- [41] Y. Yang, X. Wang, X. Lin, L. Xie, R. Ivone, J. Shen, G. Yang, A tunable extruded 3D printing platform using thermo-sensitive pastes, *Int. J. Pharm.* (Amsterdam, Neth.) 583 (2020) 119360.
- [42] E.M. Mohamed, S.F. Barakh Ali, Z. Rahman, S. Dharani, T. Ozkan, M.A. Kuttolamadom, M.A. Khan, Formulation Optimization of Selective Laser Sintering 3D-Printed Tablets of Clindamycin Palmitate Hydrochloride by Response Surface Methodology, *AAPS PharmSciTech* 21 (2020) 232.
- [43] C.W. Rowe, W.E. Katstra, R.D. Palazzolo, B. Giritlioglu, P. Teung, M.J. Cima, Multimechanism oral dosage forms fabricated by three dimensional printing, *J. Control. Release* 66 (2000) 11–17.
- [44] W.E. Katstra, R.D. Palazzolo, C.W. Rowe, B. Giritlioglu, P. Teung, M.J. Cima, Oral dosage forms fabricated by three dimensional printing, *J. Control. Release* 66 (2000) 1–9.
- [45] K. Sen, R. Mukherjee, S. Sansare, A. Halder, H. Kashi, A.W.K. Ma, B. Chaudhuri, Impact of powder-binder interactions on 3D printability of pharmaceutical tablets using drop test methodology, *Eur. J. Pharm. Sci.* 160 (2021) 105755.
- [46] M. Saydam, S. Takka, Improving the dissolution of a water-insoluble orphan drug through a fused deposition modelling 3-Dimensional printing technology approach, *Eur. J. Pharm. Sci.* 152 (2020) 105426.
- [47] K. Shi, J.P. Salvage, M. Maniruzzaman, A. Nokhodchi, Role of release modifiers to modulate drug release from fused deposition modelling (FDM) 3D printed tablets, *Int. J. Pharm.* 597 (2021) 120315.
- [48] M. Fanous, S. Gold, S. Hirsch, J. Ogorka, G. Imanidis, Development of immediate release (IR) 3D-printed oral dosage forms with focus on industrial relevance, *Eur. J. Pharm. Sci.* 155 (2020) 105558.
- [49] S. Ayyoubi, J.R. Cerda, R. Fernandez-Garcia, P. Knief, A. Lalatsa, A.M. Healy, D. R. Serrano, 3D printed spherical mini-tablets: Geometry versus composition effects in controlling dissolution from personalised solid dosage forms, *Int. J. Pharm.* (Amsterdam, Neth.) 597 (2021) 120336.
- [50] R. Govender, S. Abrahamsen-Alami, A. Larsson, A. Borde, A. Liljeblad, S. Foestad, Independent Tailoring of Dose and Drug Release via a Modularized Product Design Concept for Mass Customization, *Pharmaceutics* 12 (2020) 771.
- [51] F. Fina, C.M. Madla, A. Goyanes, J. Zhang, S. Gaisford, A.W. Basit, Fabricating 3D printed orally disintegrating printlets using selective laser sintering, *Int. J. Pharm.* (Amsterdam, Neth.) 541 (2018) 101–107.
- [52] J. Conceição, X. Farto-Vaamonde, A. Goyanes, O. Adeoye, A. Concheiro, H. Cabral-Marques, J.M. Sousa Lobo, C. Alvarez-Lorenzo, Hydroxypropyl-β-cyclodextrin-based fast dissolving carbamazepine printlets prepared by semisolid extrusion 3D printing, *Carbohydr. Polym.* 221 (2019) 55–62.
- [53] A. Awad, F. Fina, S.J. Trenfield, P. Patel, A. Goyanes, S. Gaisford, A.W. Basit, 3D Printed Pellets (Miniprintlets): A Novel, Multi-Drug, Controlled Release Platform Technology, *Pharmaceutics* 11 (2019) 148.
- [54] F. Fina, A. Goyanes, C.M. Madla, A. Awad, S.J. Trenfield, J.M. Kuek, P. Patel, S. Gaisford, A.W. Basit, 3D printing of drug-loaded gyroid lattices using selective laser sintering, *Int. J. Pharm.* 547 (2018) 44–52.
- [55] D.G. Yu, X.L. Yang, W.D. Huang, J. Liu, Y.G. Wang, H. Xu, Tablets with material gradients fabricated by three-dimensional printing, *J. Pharm. Sci.* 96 (2007) 2446–2456.
- [56] D.G. Yu, C. Branford-White, Z.H. Ma, L.M. Zhu, X.Y. Li, X.L. Yang, Novel drug delivery devices for providing linear release profiles fabricated by 3DP, *Int. J. Pharm.* 370 (2009) 160–166.
- [57] D.G. Yu, C. Branford-White, Y.C. Yang, L.M. Zhu, E.W. Welbeck, X.L. Yang, A novel fast disintegrating tablet fabricated by three-dimensional printing, *Drug Dev. Ind. Pharm.* 35 (2009) 1530–1536.
- [58] M. Palo, K. Kogermann, I. Laidmae, A. Meos, M. Preis, J. Heinamaki, N. Sandler, Development of Oromucosal Dosage Forms by Combining Electrospinning and Inkjet Printing, *Mol. Pharm.* 14 (2017) 808–820.
- [59] F. Fina, A. Goyanes, M. Rowland, S. Gaisford, A.W. Basit, 3D printing of tunable zero-order release printlets, *Polymers (Basel)* 12 (2020) 1769, <https://doi.org/10.3390/polym12081769>.
- [60] J. Elbl, J. Gajdziok, J. Kolarczyk, 3D printing of multilayered orodispersible films with in-process drying, *Int. J. Pharm.* 575 (2020) 118883.
- [61] G. Gorkem Buyukgoz, D. Soffer, J. Defendre, G.M. Pizzano, R.N. Dave, Exploring tablet design options for tailoring drug release and dose via fused deposition modeling (FDM), *Int. J. Pharm.* 591 (2020) 119987.
- [62] J.J. Ong, A. Awad, A. Martorana, S. Gaisford, E. Stoyanov, A.W. Basit, A. Goyanes, 3D printed opioid medicines with alcohol-resistant and abuse-deterrent properties, *Int. J. Pharm.* (Amsterdam, Neth.) 579 (2020) 119169.
- [63] M. Tidau, A. Kwade, J.H. Finke, Influence of High, Disperse API Load on Properties along the Fused-Layer Modeling Process Chain of Solid Dosage Forms, *Pharmaceutics* 11 (2019) 194.
- [64] P. Panraksa, S. Udomsom, P. Rachtanapun, C. Chittasupho, W. Ruksiriwanich, P. Jantrawut, Hydroxypropyl Methylcellulose E15: A Hydrophilic Polymer for Fabrication of Orodispersible Film Using Syringe Extrusion 3D Printer, *Polymers (Basel)* 12 (2020) 2666.
- [65] M. Edinger, D. Bar-Shalom, N. Sandler, J. Rantanen, N. Genina, QR encoded smart oral dosage forms by inkjet printing, *Int. J. Pharm.* 536 (2017) 138–145.
- [66] E. Icten, A. Giridhar, Z.K. Nagy, G.V. Reklaitis, Drop-on-Demand System for Manufacturing of Melt-based Solid Oral Dosage: Effect of Critical Process Parameters on Product Quality, *AAPS PharmSciTech* 17 (2016) 284–293.
- [67] E. Icten, A. Giridhar, L.S. Taylor, Z.K. Nagy, G.V. Reklaitis, Dropwise additive manufacturing of pharmaceutical products for melt-based dosage forms, *J. Pharm. Sci.* 104 (2015) 1641–1649.

- [68] R. Thakkar, A.R. Pillai, J. Zhang, Y. Zhang, V. Kulkarni, M. Maniruzzaman, Novel On-Demand 3-Dimensional (3-D) Printed Tablets Using Fill Density as an Effective Release-Controlling Tool, *Polymers* (Basel) 12 (2020) 1872.
- [69] G.K. Eleftheriadis, C.S. Katsiotis, N. Bouropoulos, S. Koutsopoulos, D.G. Fatouros, FDM-printed pH-responsive capsules for the oral delivery of a model macromolecular dye, *Pharm. Dev. Technol.* 25 (2020) 517–523.
- [70] A. Goyanes, C.M. Madla, A. Umerji, G. Duran Piñero, J.M. Giraldez Montero, M. J. Lamas Diaz, M. Gonzalez Barcia, F. Taherali, P. Sánchez-Pintos, M.-L. Couce, S. Gaisford, A.W. Basit, Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: First single-centre, prospective, crossover study in patients, *Int. J. Pharmaceut.* 567 (2019).
- [71] K.J. Lee, A. Kang, J.J. Delfino, T.G. West, D. Chetty, D.C. Monkhouse, J. Yoo, Evaluation of critical formulation factors in the development of a rapidly dispersing captopril oral dosage form, *Drug Dev. Ind. Pharm.* 29 (2003) 967–979.
- [72] A.P. Haring, Y. Tong, J. Halper, B.N. Johnson, Programming of Multicomponent Temporal Release Profiles in 3D Printed Polypills via Core-Shell, Multilayer, and Gradient Concentration Profiles, *Adv Healthc Mater* 7 (2018) e1800213.
- [73] J. Aho, J.P. Botker, N. Genina, M. Edinger, L. Arnfast, J. Rantanen, Roadmap to 3D-Printed Oral Pharmaceutical Dosage Forms: Feedstock Filament Properties and Characterization for Fused Deposition Modeling, *J. Pharm. Sci.* 108 (2019) 26–35.
- [74] G.V. Salmoria, P. Klauss, K.M. Zepón, L.A. Kanis, The effects of laser energy density and particle size in the selective laser sintering of polycaprolactone/progesterone specimens: morphology and drug release, *Int. J. Adv. Manuf. Technol.* 66 (2013) 1113–1118.
- [75] B.M. Wu, S.W. Borland, R.A. Giordano, L.G. Cima, E.M. Sachs, M.J. Cima, Solid free-form fabrication of drug delivery devices, *J. Control. Release* 40 (1996) 77–87.
- [76] M. Alhijaj, P. Belton, S. Qi, An investigation into the use of polymer blends to improve the printability of and regulate drug release from pharmaceutical solid dispersions prepared via fused deposition modeling (FDM) 3D printing, *Eur. J. Pharm. Biopharm.* 108 (2016) 111–125.
- [77] K. Shi, D.K. Tan, A. Nokhodchi, M. Maniruzzaman, Drop-on-powder 3D printing of tablets with an anti-cancer drug, 5-fluorouracil, *Pharmaceutics* 11 (2019) 150.
- [78] D.M. Smith, Y. Kapoor, G.R. Klinzing, A.T. Procopio, Pharmaceutical 3D printing: Design and qualification of a single step print and fill capsule, *Int. J. Pharm.* 544 (2018) 21–30.
- [79] F. Fina, A. Goyanes, S. Gaisford, A.W. Basit, Selective laser sintering (SLS) 3D printing of medicines, *Int. J. Pharm.* 529 (2017) 285–293.
- [80] H.K. Cader, G.A. Rance, M.R. Alexander, A.D. Goncalves, C.J. Roberts, C.J. Tuck, R.D. Wildman, Water-based 3D inkjet printing of an oral pharmaceutical dosage form, *Int. J. Pharm.* 564 (2019) 359–368.
- [81] A. Goyanes, A.B. Buanz, A.W. Basit, S. Gaisford, Fused-filament 3D printing (3DP) for fabrication of tablets, *Int. J. Pharm.* 476 (2014) 88–92.
- [82] A. Goyanes, J. Wang, A. Buanz, R. Martinez-Pacheco, R. Telford, S. Gaisford, A. W. Basit, 3D Printing of Medicines: Engineering Novel Oral Devices with Unique Design and Drug Release Characteristics, *Mol. Pharm.* 12 (2015) 4077–4084.
- [83] T.C. Okwuosa, B.C. Pereira, B. Arafat, M. Cieszyńska, A. Isreb, M.A. Alhnan, Fabricating a Shell-Core Delayed Release Tablet Using Dual FDM 3D Printing for Patient-Centred Therapy, *Pharm. Res.* 34 (2017) 427–437.
- [84] M. Elbadawi, D. Niljoo, T. Gustafsson, S. Gaisford, A.W. Basit, Pressure-assisted microsyringe 3D printing of oral films based on pullulan and hydroxypropyl methylcellulose, *Int. J. Pharm.* 595 (2021) 120197.
- [85] A.B. Buanz, M.H. Saunders, A.W. Basit, S. Gaisford, Preparation of personalized-dose salbutamol sulphate oral films with thermal ink-jet printing, *Pharm. Res.* 28 (2011) 2386–2392.
- [86] E. Fuenmayor, M. Forde, A.V. Healy, D.M. Devine, J.G. Lyons, C. McConville, I. Major, Material Considerations for Fused-Filament Fabrication of Solid Dosage Forms, *Pharmaceutics* 10 (2018).
- [87] G.G. Pereira, S. Figueiredo, A.I. Fernandes, J.F. Pinto, Polymer Selection for Hot-Melt Extrusion Coupled to Fused Deposition Modelling in Pharmaceutics, *Pharmaceutics* 12 (2020).
- [88] S. Wachirahuttapong, C. Thongpin, N. Sombatsompom, Effect of PCL and Compatibility Contents on the Morphology, Crystallization and Mechanical Properties of PLA/PCL Blends, *Energy Procedia* 89 (2016) 198–206.
- [89] W. Jamroz, M. Kurek, J. Szafraniec-Szczesny, A. Czech, K. Gawlak, J. Knapik-Kowalczyk, B. Leszczynski, A. Wrobel, M. Paluch, R. Jachowicz, Speed it up, slow it down...An issue of bicalutamide release from 3D printed tablets, *Eur. J. Pharm. Sci.* 143 (2020) 105169.
- [90] A. Melocchi, F. Briatico-Vangosa, M. Uboldi, F. Parietti, M. Turchi, D. von Zeppelin, A. Maroni, L. Zema, A. Gazzaniga, A. Zidan, Quality considerations on the pharmaceutical applications of fused deposition modeling 3D printing, *Int. J. Pharm.* 592 (2021) 119901.
- [91] F. Peng, B.D. Vogt, M. Cakmak, Complex flow and temperature history during melt extrusion in material extrusion additive manufacturing, *Addit. Manuf.* 22 (2018) 197–206.
- [92] F.A. Osorio, E. Bilbao, R. Bustos, F. Alvarez, Effects of Concentration, Bloom Degree, and pH on Gelatin Melting and Gelling Temperatures Using Small Amplitude Oscillatory Rheology, *Int. J. Food Prop.* 10 (2007) 841–851.
- [93] K. Buch, M. Penning, E. Wachtersbach, M. Maskos, P. Languth, Investigation of various shellac grades: additional analysis for identity, *Drug Dev. Ind. Pharm.* 35 (2009) 694–703.
- [94] T.J. Coogan, D.O. Kazmer, In-line rheological monitoring of fused deposition modeling, *J. Rheol.* 63 (2019) 141–155.
- [95] M. Elbadawi, J.L. Rivera-Armenta, B.A.S. Cruz, Polymeric additive manufacturing: the necessity and utility of rheology, *Polymer Rheol.* 10 (2018) 43.
- [96] A. Goyanes, N. Allahham, S.J. Trenfield, E. Stoyanov, S. Gaisford, A.W. Basit, Direct powder extrusion 3D printing: Fabrication of drug products using a novel single-step process, *Int. J. Pharm.* 567 (2019) 118471.
- [97] M. Fanous, S. Gold, S. Muller, S. Hirsch, J. Ogorka, G. Imanidis, Simplification of fused deposition modeling 3D-printing paradigm: Feasibility of 1-step direct powder printing for immediate release dosage form production, *Int. J. Pharm.* 578 (2020) 119124.
- [98] I. El Aita, J. Rahman, J. Breikreutz, J. Quodbach, 3D-Printing with precise layer-wise dose adjustments for paediatric use via pressure-assisted microsyringe printing, *Eur. J. Pharm. Biopharm.* 157 (2020) 59–65.
- [99] I. Seoane-Viano, P. Januskaite, C. Alvarez-Lorenzo, A.W. Basit, A. Goyanes, Semi-solid extrusion 3D printing in drug delivery and biomedicine: Personalised solutions for healthcare challenges, *J. Control. Release* 332 (2021) 367–389.
- [100] M. Alomari, F.H. Mohamed, A.W. Basit, S. Gaisford, Personalised dosing: Printing a dose of one's own medicine, *Int. J. Pharm.* 494 (2015) 568–577.
- [101] D. Mezi, G. Ausias, Y. Grohens, J. Férec, Numerical simulation and modeling of the die swell for fiber suspension flows, *J. Nonnewton. Fluid Mech.* 274 (2019).
- [102] S. Mania, J. Ryl, J.R. Jinn, Y.J. Wang, A. Michalowska, R. Tylingo, The Production Possibility of the Antimicrobial Filaments by Co-Extrusion of the PLA Pellet with Chitosan Powder for FDM 3D Printing Technology, *Polymers* (Basel) 11 (2019).
- [103] A. Melocchi, F. Parietti, A. Maroni, A. Foppoli, A. Gazzaniga, L. Zema, Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling, *Int. J. Pharm.* 509 (2016) 255–263.
- [104] M.G. Buehler, Z.J. Campbell, B.P. Carter, Single-frequency dielectric relaxation used to characterize the glass transition time of polydextrose, *Meas. Sci. Technol.* 28 (2017), 024005/024001–024005/024006.
- [105] T.K. Vidal-Urquiza, A. Blagg, O. Perales-Perez, Structural and thermo-mechanical characterization of calcium and barium alginate films, *TechConnect* (2012) 357–360.
- [106] T. Onishi, H. Hatakeyama, T. Hatakeyama, Differential scanning calorimetric studies on chemically crosslinked sodium carboxymethyl cellulose hydrogels, *Kobunshi Ronbunshu* 65 (2008) 477–482.
- [107] E. Carlier, S. Marquette, C. Peerboom, L. Denis, S. Benali, J.M. Raquez, K. Amighi, J. Goole, Investigation of the parameters used in fused deposition modeling of poly(lactic acid) to optimize 3D printing sessions, *Int. J. Pharm.* 565 (2019) 367–377.
- [108] L. Hirshfield, A. Giridhar, L.S. Taylor, M.T. Harris, G.V. Reklaitis, Dropwise additive manufacturing of pharmaceutical products for solvent-based dosage forms, *J. Pharm. Sci.* 103 (2014) 496–506.
- [109] R. Daly, T.S. Harrington, G.D. Martin, I.M. Hutchings, Inkjet printing for pharmaceutics – A review of research and manufacturing, *Int. J. Pharm.* 494 (2015) 554–567.
- [110] M. Edinger, J. Jacobsen, D. Bar-Shalom, J. Rantanen, N. Genina, Analytical aspects of printed oral dosage forms, *Int. J. Pharm.* 553 (2018) 97–108.
- [111] E.A. Clark, M.R. Alexander, D.J. Irvine, C.J. Roberts, M.J. Wallace, S. Sharpe, J. Yoo, R.J.M. Hague, C.J. Tuck, R.D. Wildman, 3D printing of tablets using inkjet with UV photoinitiation, *Int. J. Pharm.* 529 (2017) 523–530.
- [112] A. Awad, F. Fina, A. Goyanes, S. Gaisford, A.W. Basit, 3D printing: Principles and pharmaceutical applications of selective laser sintering, *Int. J. Pharm.* 586 (2020) 119594.
- [113] A. Kjar, Y. Huang, Application of Micro-Scale 3D Printing in Pharmaceutics, *Pharmaceutics* 11 (2019).
- [114] P. Robles-Martinez, X. Xu, S.J. Trenfield, A. Awad, A. Goyanes, R. Telford, A.W. Basit, S. Gaisford, 3D printing of a multi-layered polypill containing six drugs using a novel stereolithographic method, *Pharmaceutics* 11 (2019).
- [115] J. Wang, A. Goyanes, S. Gaisford, A.W. Basit, Stereolithographic (SLA) 3D printing of oral modified-release dosage forms, *Int. J. Pharm.* 503 (2016) 207–212.
- [116] X. Xu, P. Robles-Martinez, C.M. Madla, F. Joubert, A. Goyanes, A.W. Basit, S. Gaisford, Stereolithography (SLA) 3D printing of an antihypertensive polypill: Case study of an unexpected photopolymer-drug reaction, *Addit. Manuf.* 33 (2020).
- [117] C. Curti, D.J. Kirby, C.A. Russell, Stereolithography Apparatus Evolution: Enhancing Throughput and Efficiency of Pharmaceutical Formulation Development, *Pharmaceutics* 13 (2021).
- [118] L. Vaut, J.J. Juszczyk, K. Kamguyan, K.E. Jensen, G. Tosello, A. Boisen, 3D Printing of Reservoir Devices for Oral Drug Delivery: From Concept to Functionality through Design Improvement for Enhanced Mucoadhesion, *ACS Biomater. Sci. Eng.* 6 (2020) 2478–2486.
- [119] Y. Teramoto, Functional thermoplastic materials from derivatives of cellulose and related structural polysaccharides, *Molecules* 20 (2015) 5487–5527.
- [120] W.G. Glasser, G. Samaranyake, M. Dumay, V. Dave, Novel Cellulose Derivatives. 111. Thermal Analysis of Mixed Esters with Butyric and Hexanoic Acid, *J. Polym. Sci.* 33 (1995) 2045–2054.
- [121] T. Ahlfeld, G. Cidonio, D. Kilian, S. Duin, A.R. Akkineni, J.I. Dawson, S. Yang, A. Lode, R.O.C. Oreffo, M. Gelinsky, Development of a clay based bioink for 3D cell printing for skeletal application, *Biofabrication* 9 (2017), 034103/034101–034103/034116.

- [122] J. Long, A.E. Etxeberria, A.V. Nand, C.R. Bunt, S. Ray, A. Seyfoddin, A 3D printed chitosan-pectin hydrogel wound dressing for lidocaine hydrochloride delivery, *Mater. Sci. Eng., C* 104 (2019).
- [123] C. Schneider, R. Langer, D. Loveday, D. Hair, Applications of ethylene vinyl acetate copolymers (EVA) in drug delivery systems, *J. Control. Release* 262 (2017) 284–295.
- [124] M. Monschke, K. Kayser, K.G. Wagner, Processing of Polyvinyl Acetate Phthalate in Hot-Melt Extrusion-Preparation of Amorphous Solid Dispersions, *Pharmaceutics* 12 (2020) 337.
- [125] S. Kolhe, P.D. Chaudhari, D. More, In-Vitro In-Vivo Studies of Lamotrigine Tablets Prepared by Hot Melt Extrusion Technique, *Int. J. Pharm. Pharm. Sci.* 6 (2014) 65.
- [126] J. Maly, A. Jaros, X.I.V. Tablets, Evaluation of properties of some water-soluble lubricants for tablets, *Pharmazeutische Industrie* 29 (1967) 399–404.
- [127] J. Siepmann, A. Faham, S.D. Clas, B.J. Boyd, V. Jannin, A. Bernkop-Schnurch, H. Zhao, S. Lecommandoux, J.C. Evans, C. Allen, O.M. Merkel, G. Costabile, M.R. Alexander, R.D. Wildman, C.J. Roberts, J.C. Leroux, Lipids and polymers in pharmaceutical technology: Lifelong companions, *Int. J. Pharm.* 558 (2019) 128–142.
- [128] G. Van den Mooter, The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate, *Drug Discov Today Technol* 9 (2012) e71–e174.
- [129] R. Laitinen, P.A. Priemel, S. Surwase, K. Graeser, C.J. Strachan, H. Grohgan, T. Rades, Theoretical Considerations in Developing Amorphous Solid Dispersions, in: N. Shah, H. Sandhu, D.S. Choi, H. Chokshi, A.W. Malick (Eds.), *Amorphous Solid Dispersions*, Springer, New York, New York, NY, 2014, pp. 35–90.
- [130] Eric Ofosu Kissi, Nilsson Robin, Liebert Parreiras Nogueiras, Anette Larsson, Ingunn Tho, Influence of Drug Load on the Printability and Solid-State Properties of 3D-Printed Naproxen-Based Amorphous Solid Dispersion, *Molecules* 26 (2021) 4492, <https://doi.org/10.3390/molecules26154492>.
- [131] S.R.K. Vaka, M.M. Bommana, D. Desai, J. Djordjevic, W. Phuapradit, N. Shah, Excipients for Amorphous Solid Dispersions, in: N. Shah, H. Sandhu, D.S. Choi, H. Chokshi, A.W. Malick (Eds.), *Amorphous Solid Dispersions: Theory and Practice*, Springer, New York, New York, NY, 2014, pp. 123–161.
- [132] M. Rams-Baron, R. Jachowicz, E. Boldyreva, D. Zhou, W. Jamroz, M. Paluch, Physical Instability: A Key Problem of Amorphous Drugs, in: M. Rams-Baron, R. Jachowicz, E. Boldyreva, D. Zhou, W. Jamroz, M. Paluch (Eds.), *Amorphous Drugs*, Springer International Publishing, Cham, 2018, pp. 107–157.
- [133] A. Basit, S. Gaisford, 3D Printing of Pharmaceuticals, *AAPS Press*, Springer, 2018.
- [134] Y. Wang, Y. Miao, J. Zhang, J.P. Wu, T.B. Kirk, J. Xu, D. Ma, W. Xue, Three-dimensional printing of shape memory hydrogels with internal structure for drug delivery, *Mater Sci Eng C Mater Biol Appl* 84 (2018) 44–51.
- [135] A. Melocchi, M. Uboldi, N. Inverardi, F. Briatico-Vangosa, F. Baldi, S. Pandini, G. Scalet, F. Auricchio, M. Cerea, A. Foppoli, A. Maroni, L. Zema, A. Gazzaniga, Expandable drug delivery system for gastric retention based on shape memory polymers: Development via 4D printing and extrusion, *Int. J. Pharm.* 571 (2019) 118700.
- [136] A. Melocchi, N. Inverardi, M. Uboldi, F. Baldi, A. Maroni, S. Pandini, F. Briatico-Vangosa, L. Zema, A. Gazzaniga, Retentive device for intravesical drug delivery based on water-induced shape memory response of poly(vinyl alcohol): design concept and 4D printing feasibility, *Int. J. Pharm.* 559 (2019) 299–311.
- [137] A. Melocchi, M. Uboldi, M. Cerea, A. Foppoli, A. Maroni, S. Moutaharrik, L. Palugan, L. Zema, A. Gazzaniga, Shape memory materials and 4D printing in pharmaceuticals, *Adv. Drug Deliv. Rev.* 173 (2021) 216–237.
- [138] J. Wang, Y. Zhang, N.H. Aghda, A.R. Pillai, R. Thakkar, A. Nokhodchi, M. Maniruzzaman, Emerging 3D printing technologies for drug delivery devices: Current status and future perspective, *Adv. Drug Deliv. Rev.* 174 (2021) 294–316.
- [139] M. Elbadawi, T. Gustafsson, S. Gaisford, A.W. Basit, 3D printing tablets: Predicting printability and drug dissolution from rheological data, *Int. J. Pharm.* 590 (2020) 119868.
- [140] T.J. Coogan, D.O. Kazmer, Prediction of interlayer strength in material extrusion additive manufacturing, *Addit. Manuf.* 35 (2020) 101368.
- [141] A. Isreb, K. Baj, M. Wojsz, M. Isreb, M. Peak, M.A. Alhnan, 3D printed oral theophylline doses with innovative 'radiator-like' design: Impact of polyethylene oxide (PEO) molecular weight, *Int. J. Pharm.* 564 (2019) 98–105.
- [142] A. Samaro, P. Janssens, V. Vanhoorne, J. Van Renterghem, M. Eeckhout, L. Cardon, T. De Beer, C. Vervae, Screening of pharmaceutical polymers for extrusion-based Additive Manufacturing of patient-tailored tablets, *Int. J. Pharm.* 586 (2020) 119591.
- [143] L.K. Prasad, H. Smyth, 3D Printing technologies for drug delivery: a review, *Drug Dev. Ind. Pharm.* 42 (2016) 1019–1031.
- [144] C. Korte, J. Quodbach, 3D-printed network structures as controlled-release drug delivery systems: dose adjustment, API release analysis and prediction, *AAPS PharmSciTech* (2018) 3333, <https://doi.org/10.1208/s12249-018-1017-0>.
- [145] A. Maroni, A. Melocchi, F. Parietti, A. Foppoli, L. Zema, A. Gazzaniga, 3D printed multi-compartment capsular devices for two-pulse oral drug delivery, *J. Control. Release* 268 (2017) 10–18.
- [146] A. Melocchi, F. Parietti, G. Loreti, A. Maroni, A. Gazzaniga, L. Zema, 3D Printing by Fused Deposition Modeling (FDM) of a Swellable/Erodible Capsular Device for Oral Pulsatile Release of Drugs, *J. Drug Delivery Sci. Technol.* 30 (2015) 360.
- [147] J. Boetker, J.J. Water, J. Aho, L. Arnfast, A. Bohr, J. Rantanen, Modifying release characteristics from 3D printed drug-eluting products, *Eur. J. Pharm. Sci.* 90 (2016) 47–52.
- [148] K. Ilyés, N.K. Kovács, A. Balogh, E. Borbás, B. Farkas, T. Casian, G. Marosi, I. Tomuș, Z.K. Nagy, The applicability of pharmaceutical polymeric blends for the fused deposition modelling (FDM) 3D technique: Material considerations-printability-process modulation, with consecutive effects on in vitro release, stability and degradation, *Eur. J. Pharm. Sci.* 129 (2019) 110–123.
- [149] J. Zhang, R. Thakkar, Y. Zhang, M. Maniruzzaman, Structure-function correlation and personalized 3D printed tablets using a quality by design (QbD) approach, *Int. J. Pharm.* 590 (2020) 119945.
- [150] A. Goyanes, A. Fernandez-Ferreiro, A. Majeed, N. Gomez-Lado, A. Awad, A. Luaces-Rodriguez, S. Gaisford, P. Aguiar, A.W. Basit, PET/CT imaging of 3D printed devices in the gastrointestinal tract of rodents, *Int. J. Pharm.* 536 (2018) 158–164.
- [151] A. Goyanes, A.B. Buanz, G.B. Hatton, S. Gaisford, A.W. Basit, 3D printing of modified-release aminosalicilate (4-ASA and 5-ASA) tablets, *Eur. J. Pharm. Biopharm.* 89 (2015) 157–162.
- [152] D.E. Moseson, M.A. Jordan, D.D. Shah, I.D. Corum, B.R. Alvarenga Jr., L.S. Taylor, Application and limitations of thermogravimetric analysis to delineate the hot melt extrusion chemical stability processing window, *Int. J. Pharm.* 590 (2020) 119916.
- [153] C.I. Gioumouxouzis, A.T. Chatzitaki, C. Karavasili, O.L. Katsamenis, D. Tzetzis, E. Mystiridou, N. Bouropoulos, D.G. Fatouros, Controlled Release of 5-Fluorouracil from Alginate Beads Encapsulated in 3D Printed pH-Responsive Solid Dosage Forms, *AAPS PharmSciTech* 19 (2018) 3362–3375.
- [154] J. Zhang, X. Feng, H. Patil, R.V. Tiwari, M.A. Repka, Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets, *Int. J. Pharm.* 519 (2017) 186–197.
- [155] R. Govender, S. Abrahamsen-Alami, S. Folestad, M. Olsson, A. Larsson, Enabling modular dosage form concepts for individualized multidrug therapy: expanding the design window for poorly water-soluble drugs, *Int. J. Pharm.* (2021) 120625.
- [156] T.C. Okwuosa, C. Soares, V. Gollwitzer, R. Habashy, P. Timmins, M.A. Alhnan, On demand manufacturing of patient-specific liquid capsules via co-ordinated 3D printing and liquid dispensing, *Eur. J. Pharm. Sci.* 118 (2018) 134–143.
- [157] A. Goyanes, U. Det-Amornrat, J. Wang, A.W. Basit, S. Gaisford, 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems, *J. Control. Release* 234 (2016) 41–48.
- [158] J.M. Nasereddin, N. Wellner, M. Alhijaj, P. Belton, S. Qi, Development of a Simple Mechanical Screening Method for Predicting the Feedability of a Pharmaceutical FDM 3D Printing Filament, *Pharm. Res.* 35 (2018) 151.
- [159] L. Viidik, J. Vesala, R. Laitinen, O. Korhonen, J. Ketolainen, J. Aruvali, K. Kirsima, K. Kogermann, J. Heinamäki, I. Laidmae, T. Ervasti, Preparation and characterization of hot-melt extruded polycaprolactone-based filaments intended for 3D-printing of tablets, *Eur. J. Pharm. Sci.* 158 (2021) 105619.
- [160] K. Vithani, A. Goyanes, V. Jannin, A.W. Basit, S. Gaisford, B.J. Boyd, A Proof of Concept for 3D Printing of Solid Lipid-Based Formulations of Poorly Water-Soluble Drugs to Control Formulation Dispersion Kinetics, *Pharm. Res.* 36 (2019) 102.
- [161] M. Kyobula, A. Adediji, M.R. Alexander, E. Saleh, R. Wildman, I. Ashcroft, P.R. Gellert, C.J. Roberts, 3D inkjet printing of tablets exploiting bespoke complex geometries for controlled and tuneable drug release, *J. Control. Release* 261 (2017) 207–215.
- [162] E. Fuenmayor, M. Forde, A.V. Healy, D.M. Devine, J.G. Lyons, C. McConville, I. Major, Comparison of fused-filament fabrication to direct compression and injection molding in the manufacture of oral tablets, *Int. J. Pharm.* 558 (2019) 328–340.
- [163] S.A. Khaled, M.R. Alexander, R.D. Wildman, M.J. Wallace, S. Sharpe, J. Yoo, C.J. Roberts, 3D extrusion printing of high drug loading immediate release paracetamol tablets, *Int. J. Pharm.* 538 (2018) 223–230.
- [164] S.A. Khaled, J.C. Burley, M.R. Alexander, C.J. Roberts, Desktop 3D printing of controlled release pharmaceutical bilayer tablets, *Int. J. Pharm.* 461 (2014) 105–111.
- [165] Y. Yang, H. Wang, H. Li, Z. Ou, G. Yang, 3D printed tablets with internal scaffold structure using ethyl cellulose to achieve sustained ibuprofen release, *Eur. J. Pharm. Sci.* 115 (2018) 11–18.
- [166] C. Korte, J. Quodbach, Formulation development and process analysis of drug-loaded filaments manufactured via hot-melt extrusion for 3D-printing of medicines, *Pharm. Dev. Technol.* 23 (2018) 1117–1127.
- [167] G.D. Goh, V. Dikshit, A.P. Nagalingam, G.L. Goh, S. Agarwala, S.L. Sing, J. Wei, W.Y. Yeong, Characterization of mechanical properties and fracture mode of additively manufactured carbon fiber and glass fiber reinforced thermoplastics, *Mater. Des.* 137 (2018) 79–89.
- [168] J.M. Mercado-Colmenero, C. Martin-Doñate, V. Moramarco, M.A. Attolico, G. Renna, M. Rodriguez-Santiago, C. Casavola, Mechanical Characterization of the Plastic Material GF-PA6 Manufactured Using FDM Technology for a Compression Uniaxial Stress Field via an Experimental and Numerical Analysis, *Polymers* 12 (2020) 246.
- [169] Y. Cheng, H. Qin, N.C. Acevedo, X. Jiang, X. Shi, 3D printing of extended-release tablets of theophylline using hydroxypropyl methylcellulose (HPMC) hydrogels, *Int. J. Pharm.* 591 (2020) 119983.
- [170] H.M. Heidemann, M.E.R. Dotto, J.B. Laurindo, B.A.M. Carciofi, C. Costa, Cold plasma treatment to improve the adhesion of cassava starch films onto PCL and PLA surface, *Colloids Surf. A* 580 (2019) 123739.

- [171] J. Aho, J.P. Boetker, S. Baldursdottir, J. Rantanen, Rheology as a tool for evaluation of melt processability of innovative dosage forms, *Int. J. Pharm.* 494 (2015) 623–642.
- [172] J. Johannesson, J. Khan, M. Hubert, A. Teleki, C.A.S. Bergstrom, 3D-printing of solid lipid tablets from emulsion gels, *Int. J. Pharm.* 597 (2021) 120304.
- [173] N. Sandler, I. Salmela, A. Fallarero, A. Rosling, M. Khajeheian, R. Kolakovic, N. Genina, J. Nymän, P. Vuorela, Towards fabrication of 3D printed medical devices to prevent biofilm formation, *Int. J. Pharm.* 459 (2014) 62–64.
- [174] T. Jungst, W. Smolan, K. Schacht, T. Scheibel, J. Groll, Strategies and Molecular Design Criteria for 3D Printable Hydrogels, *Chem. Rev.* 116 (2016) 1496–1539.
- [175] M. Khorasani, M. Edinger, D. Rajjada, J. Botker, J. Aho, J. Rantanen, Near-infrared chemical imaging (NIR-CI) of 3D printed pharmaceuticals, *Int. J. Pharm.* 515 (2016) 324–330.
- [176] S.J. Trenfield, A. Goyanes, R. Telford, D. Wilsdon, M. Rowland, S. Gaisford, A.W. Basit, 3D printed drug products: Non-destructive dose verification using a rapid point-and-shoot approach, *Int. J. Pharm.* 549 (2018) 283–292.
- [177] H. Vakili, R. Kolakovic, N. Genina, M. Marmion, H. Salo, P. Ihalainen, J. Peltonen, N. Sandler, Hyperspectral imaging in quality control of inkjet printed personalised dosage forms, *Int. J. Pharm.* 483 (2015) 244–249.
- [178] N. Scutaris, S.A. Ross, D. Douroumis, 3D Printed “Starmix” Drug Loaded Dosage Forms for Paediatric Applications, *Pharm. Res.* 35 (2018) 34.
- [179] S. Lamichhane, J.B. Park, D.H. Sohn, S. Lee, Customized Novel Design of 3D Printed Pregabalin Tablets for Intra-Gastric Floating and Controlled Release Using Fused Deposition Modeling, *Pharmaceutics* 11 (2019).
- [180] M. Fanous, M. Bitar, S. Gold, A. Sobczuk, S. Hirsch, J. Ogorka, G. Imanidis, Development of immediate release 3D-printed dosage forms for a poorly water-soluble drug by fused deposition modeling: Study of morphology, solid state and dissolution, *Int. J. Pharm.* 599 (2021) 120417.
- [181] B.C. Pereira, A. Isreb, M. Isreb, R.T. Forbes, E.F. Oga, M.A. Alhnan, Additive Manufacturing of a Point-of-Care “Polypill”: Fabrication of Concept Capsules of Complex Geometry with Bespoke Release against Cardiovascular Disease, *Adv. Healthc. Mater.* 9 (2020) e2000236.
- [182] M. Alhijaj, J. Nasereddin, P. Belton, S. Qi, Impact of Processing Parameters on the Quality of Pharmaceutical Solid Dosage Forms Produced by Fused Deposition Modeling (FDM), *Pharmaceutics* 11 (2019) 633.
- [183] J. Skowrya, K. Pietrzak, M.A. Alhnan, Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing, *Eur. J. Pharm. Sci.* 68 (2015) 11–17.
- [184] E. Icten, H.S. Purohit, C. Wallace, A. Giridhar, L.S. Taylor, Z.K. Nagy, G.V. Reklaitis, Dropwise additive manufacturing of pharmaceutical products for amorphous and self-emulsifying drug delivery systems, *Int. J. Pharm.* 524 (2017) 424–432.
- [185] T.H. Kang, B.G. Compton, W.T. Heller, S. Qian, G.S. Smith, V.S. Urban, C.E. Duty, C. Do, Potentials with small-angle neutron scattering technique for understanding structure-property relation of 3D-printed materials, *Polym. Eng. Sci.* 59 (2019) E65–E70.
- [186] D. Markl, J.A. Zeitler, C. Rasch, M.H. Michaelsen, A. Mullertz, J. Rantanen, T. Rades, J. Botker, Analysis of 3D Prints by X-ray Computed Microtomography and Terahertz Pulsed Imaging, *Pharm. Res.* 34 (2017) 1037–1052.
- [187] M. Tiddia, I. Mihara, M.P. Seah, G.F. Trindade, F. Kollmer, C.J. Roberts, R. Hague, G. Mula, I.S. Gilmore, R. Havelund, Chemical Imaging of Buried Interfaces in Organic-Inorganic Devices Using Focused Ion Beam-Time-of-Flight-Secondary-Ion Mass Spectrometry, *ACS Appl. Mater. Interfaces* 11 (2019) 4500–4506.
- [188] N. Sandler, A. Maattanen, P. Ihalainen, L. Kronberg, A. Meierjohann, T. Viitala, J. Peltonen, Inkjet printing of drug substances and use of porous substrates-towards individualized dosing, *J. Pharm. Sci.* 100 (2011) 3386–3395.
- [189] M. Elbadawi, B. Muniz Castro, F.K.H. Gavins, J.J. Ong, S. Gaisford, G. Perez, A. W. Basit, P. Cabalar, A. Goyanes, M3DISEEN: A novel machine learning approach for predicting the 3D printability of medicines, *Int. J. Pharm.* 590 (2020) 119837.
- [190] S. Qi, Thermal Analysis of Pharmaceuticals, in: A. Müller, Y. Perrie, T. Rades (Eds.), *Analytical Techniques in the Pharmaceutical Sciences*, Advances in Delivery Science and Technology, New York, USA, 2016.
- [191] K. Xu, A.P. Milanov, A. Devi, Tuning the thermal properties of hafnium precursors by tailoring the ligands, *ECS Trans.* 25 (2009) 625–631.
- [192] J.E.K. Schawe, S. Ziegelmeier, Determination of the thermal short time stability of polymers by fast scanning calorimetry, *Thermochim. Acta* 623 (2016) 80–85.
- [193] M.M. Knopp, K. Löbmann, D.P. Elder, T. Rades, R. Holm, Recent advances and potential applications of modulated differential scanning calorimetry (mDSC) in drug development, *Eur. J. Pharm. Sci.* 87 (2016) 164–173.
- [194] E. Verdonck, K. Schaap, L.C. Thomas, A discussion of the principles and applications of Modulated Temperature DSC (MTDSC), *Int. J. Pharm.* 192 (1999) 3–20.
- [195] S. Ali, K. Kolter, M. Karl, Evaluation of different polymers in 3D printing technologies, *Am. Pharm. Rev.* 22 (2019) 166–175. <https://www.americanpharmaceuticalreview.com/Featured-Articles/518798-Evaluation-of-Different-Polymers-in-3D-Printing-Technologies/>.
- [196] M.M. Knopp, N.E. Olesen, P. Holm, K. Löbmann, R. Holm, P. Langguth, T. Rades, Evaluation of drug-polymer solubility curves through formal statistical analysis: comparison of preparation techniques, *J. Pharm. Sci.* 104 (2015) 44–51.
- [197] M.M. Knopp, N. Gannon, I. Porsch, M.B. Rask, N.E. Olesen, P. Langguth, R. Holm, T. Rades, A Promising New Method to Estimate Drug-Polymer Solubility at Room Temperature, *J. Pharm. Sci.* 105 (2016) 2621–2624.
- [198] D.S. Jones, Y. Tian, O. Abu-Diak, G.P. Andrews, Pharmaceutical applications of dynamic mechanical thermal analysis, *Adv. Drug Deliv. Rev.* 64 (2012) 440–448.
- [199] E.O. Kissi, H. Grohgan, K. Lobmann, M.T. Ruggiero, J.A. Zeitler, T. Rades, Glass-Transition Temperature of the beta-Relaxation as the Major Predictive Parameter for Recrystallization of Neat Amorphous Drugs, *J. Phys. Chem. B* 122 (2018) 2803–2808.
- [200] E.O. Kissi, G. Kasten, K. Löbmann, T. Rades, H. Grohgan, The Role of Glass Transition Temperatures in Coamorphous Drug-Amino Acid Formulations, *Mol. Pharm.* 15 (2018) 4247–4256.
- [201] E.O. Kissi, M.T. Ruggiero, N.J. Hempel, Z. Song, H. Grohgan, T. Rades, K. Lobmann, Characterising glass transition temperatures and glass dynamics in mesoporous silica-based amorphous drugs, *PCCP* 21 (2019) 19686–19694.
- [202] P.O. Okeyo, P.E. Larsen, E.O. Kissi, F. Ajallouiean, T. Rades, J. Rantanen, A. Boisen, Single particles as resonators for thermomechanical analysis, *Nat. Commun.* 11 (2020) 1235.
- [203] S.N. Cassu, M.I. Felisberti, Poly(vinyl alcohol) and poly(vinylpyrrolidone) blends: 2. Study of relaxations by dynamic mechanical analysis, *Polymer* 40 (1999) 4845–4851.
- [204] K. Grzybowska, S. Capaccioli, M. Paluch, Recent developments in the experimental investigations of relaxations in pharmaceuticals by dielectric techniques at ambient and elevated pressure, *Adv. Drug Deliv. Rev.* 100 (2016) 158–182.
- [205] J. Brady, T. Dürig, P.I. Lee, J.X. Li, Polymer Properties and Characterization, in: Y. Qiu, Y. Chen, G.G.Z. Zhang, L. Yu, R.V. Mantri (Eds.), *Developing Solid Oral Dosage Forms*, Academic Press, Boston, 2017, pp. 181–223.
- [206] Council of Europe, European Pharmacopoeia, 2.9.7. Friability of Uncoated Tablets, Council of Europe, Strasbourg, 2005, pp. 234.
- [207] Council of Europe, European Pharmacopoeia, 2.9.8. Resistance to crushing of tablets, Council of Europe, Strasbourg, 2005, pp. 235.
- [208] R. Govender, S. Abrahamsen-Alami, S. Folestad, A. Larsson, High Content Solid Dispersions for Dose Window Extension: A Basis for Design Flexibility in Fused Deposition Modelling, *Pharm. Res.* 37 (2019) 9.
- [209] Council of Europe, European Pharmacopoeia, 2.9.36 Powder flow, Council of Europe, Strasbourg, 2007, pp. 320.
- [210] M. Elbadawi, Rheological and Mechanical Investigation into the Effect of Different Molecular Weight Poly(ethylene glycol)s on Polycaprolactone-Ciprofloxacin Filaments, *ACS Omega* 4 (2019) 5412–5423.
- [211] J. Aho, J. Van Renterghem, L. Arnfast, T. De Beer, J. Rantanen, The flow properties and presence of crystals in drug-polymer mixtures: Rheological investigation combined with light microscopy, *Int. J. Pharm.* 528 (2017) 383–394.
- [212] D.B. Braun, M.R. Rosen (Eds.), *Rheology Modifiers Handbook*, William Andrew Publishing, 2000.
- [213] J. Aho, N. Genina, M. Edinger, J.P. Botker, S. Baldursdottir, J. Rantanen, Drug-loaded poly(ϵ -caprolactone) for 3D printing of personalized medicine: a rheological study, *Annu. Trans. - Nord. Rheol. Soc.* 24 (2016) 97–100.
- [214] N.G. Solanki, M. Tahsin, A.V. Shah, A.T.M. Serajuddin, 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.* 107 (2018) 390–401.
- [215] N.G. Solanki, S.G. Gumaste, A.V. Shah, A.T.M. Serajuddin, Effects of Surfactants on Itraconazole-Hydroxypropyl Methylcellulose Acetate Succinate Solid Dispersion Prepared by Hot Melt Extrusion. II: Rheological Analysis and Extrudability Testing, *J. Pharm. Sci.* 108 (2019) 3063–3073.
- [216] Q. Li, H. Wen, D. Jia, X. Guan, H. Pan, Y. Yang, S. Yu, Z. Zhu, R. Xiang, W. Pan, Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing, *Int. J. Pharm.* 525 (2017) 5–11.
- [217] J. Norman, R.D. Madurawe, C.M. Moore, M.A. Khan, A. Khairuzzaman, A new chapter in pharmaceutical manufacturing: 3D-printed drug products, *Adv. Drug Deliv. Rev.* 108 (2017) 39–50.
- [218] G.F. Acosta-Velez, C.S. Linsley, T.Z. Zhu, W. Wu, B.M. Wu, Photocurable Bioinks for the 3D Pharming of Combination Therapies, *Polymers (Basel)* 10 (2018).
- [219] T. De Beer, A. Burggraef, M. Fonteyne, L. Saerens, J.P. Remon, C. Vervaet, Near infrared and Raman spectroscopy for the in-process monitoring of pharmaceutical production processes, *Int. J. Pharm.* 417 (2011) 32–47.
- [220] G. Reich, Near-infrared spectroscopy and imaging: basic principles and pharmaceutical applications, *Adv. Drug Deliv. Rev.* 57 (2005) 1109–1143.
- [221] Q. Gao, Y. Liu, H. Li, H. Chen, Y. Chai, F. Lu, Comparison of several chemometric methods of libraries and classifiers for the analysis of expired drugs based on Raman spectra, *J. Pharm. Biomed. Anal.* 94 (2014) 58–64.
- [222] Council of Europe, European Pharmacopoeia, 2.2.40. Near-infrared spectroscopy, Council of Europe, Strasbourg, 2014.
- [223] A.A. Bunaciu, H.Y. Aboul-Enein, S. Fleschin, Application of Fourier Transform Infrared Spectrophotometry in Pharmaceutical Drugs Analysis, *Appl. Spectrosc. Rev.* 45 (2010) 206–219.
- [224] A. Paudel, D. Rajjada, J. Rantanen, Raman spectroscopy in pharmaceutical product design, *Adv. Drug Deliv. Rev.* 89 (2015) 3–20.
- [225] Y.S. Li, J.S. Church, Raman spectroscopy in the analysis of food and pharmaceutical nanomaterials, *J. Food Drug Anal.* 22 (2014) 29–48.

- [226] C.J. Strachan, T. Rades, K.C. Gordon, J. Rantanen, Raman spectroscopy for quantitative analysis of pharmaceutical solids, *J. Pharm. Pharmacol.* 59 (2007) 179–192.
- [227] Council of Europe, European Pharmacopoeia, 2.2.48. Raman spectroscopy, Council of Europe, Strasbourg, 2021.
- [228] S.M. Dadou, Z. Senta-Loys, A. Almajaan, S. Li, D.S. Jones, A.M. Healy, Y. Tian, G. P. Andrews, The development and validation of a quality by design based process analytical tool for the inline quantification of Ramipril during hot-melt extrusion, *Int. J. Pharm.* 584 (2020) 119382.
- [229] G.P. Andrews, D.S. Jones, Z. Senta-Loys, A. Almajaan, S. Li, O. Chevallier, C. Elliot, A.M. Healy, J.F. Kelleher, A.M. Madi, G.C. Gilvary, Y. Tian, The development of an inline Raman spectroscopic analysis method as a quality control tool for hot melt extruded ramipril fixed-dose combination products, *Int. J. Pharm.* 566 (2019) 476–487.
- [230] N.K. Thakral, R.L. Zanon, R.C. Kelly, S. Thakral, Applications of Powder X-Ray Diffraction in Small Molecule Pharmaceuticals: Achievements and Aspirations, *J. Pharm. Sci.* 107 (2018) 2969–2982.
- [231] S. Datta, D.J. Grant, Crystal structures of drugs: advances in determination, prediction and engineering, *Nat Rev Drug Discov* 3 (2004) 42–57.
- [232] R. Suryanarayanan, S. Rastogi, X-Ray Powder Diffractometry, in: J. Swarbrick (Ed.), *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare USA, New York, 2007.
- [233] I. El Aita, J. Breitkreutz, J. Quodbach, On-demand manufacturing of immediate release levetiracetam tablets using pressure-assisted microsyringe printing, *Eur. J. Pharm. Biopharm.* 134 (2019) 29–36.
- [234] T. Ehtezazi, M. Algellay, Y. Islam, M. Roberts, N.M. Dempster, S.D. Sarker, The Application of 3D Printing in the Formulation of Multilayered Fast Dissolving Oral Films, *J. Pharm. Sci.* 107 (2018) 1076–1085.
- [235] A. Goyanes, F. Fina, A. Martorana, D. Sedough, S. Gaisford, A.W. Basit, Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing, *Int. J. Pharm.* 527 (2017) 21–30.
- [236] A. Hodzic, M. Llusa, S.D. Fraser, O. Scheibelhofer, D.M. Koller, F. Reiter, P. Laggner, J.G. Khinast, Small- and wide-angle X-ray scattering (SWAXS) for quantification of aspirin content in a binary powder mixture, *Int. J. Pharm.* 428 (2012) 91–95.
- [237] V. Klang, C. Valenta, N.B. Matsko, Electron microscopy of pharmaceutical systems, *Micron* 44 (2013) 45–74.
- [238] H. Bunjes, J. Kuntsche, *Light and electron microscopy, Analytical Techniques in the Pharmaceutical Sciences*, Springer, 2016, pp. 491–522.
- [239] M. Ibrahim, M. Barnes, R. McMillin, D.W. Cook, S. Smith, M. Halquist, D. Wijesinghe, T.D. Roper, 3D Printing of Metformin HCl PVA Tablets by Fused Deposition Modeling: Drug Loading, Tablet Design, and Dissolution Studies, *AAPS PharmSciTech* 20 (2019) 195.
- [240] M. Farzan, R. Roth, G. Quebatte, J. Schoelkopf, J. Huwyler, M. Puchkov, Loading of Porous Functionalized Calcium Carbonate Microparticles: Distribution Analysis with Focused Ion Beam Electron Microscopy and Mercury Porosimetry, *Pharmaceutics* 11 (2019) 32.
- [241] K. Kajula, J. Hyrylainen, A. Koistinen, J.T.T. Leskinen, O. Korhonen, Detection of amorphous-amorphous phase separation in small molecular co-amorphous mixtures with SEM-EDS, *Eur. J. Pharm. Biopharm.* 150 (2020) 43–49.
- [242] D. Markl, A. Strobel, R. Schlossnickl, J. Botker, P. Bawuah, C. Ridgway, J. Rantanen, T. Rades, P. Kane, K.E. Peiponen, J.A. Zeitler, Characterisation of pore structures of pharmaceutical tablets: A review, *Int. J. Pharm.* 538 (2018) 188–214.
- [243] N. Scoutaris, A.L. Hook, P.R. Gellert, C.J. Roberts, M.R. Alexander, D.J. Scurr, ToF-SIMS analysis of chemical heterogeneities in inkjet micro-array printed drug/polymer formulations, *J. Mater. Sci. - Mater. Med.* 23 (2012) 385–391.
- [244] M. Haaser, K.C. Gordon, C.J. Strachan, T. Rades, Terahertz pulsed imaging as an advanced characterisation tool for film coatings—a review, *Int. J. Pharm.* 457 (2013) 510–520.
- [245] H. Lin, Y. Dong, Y. Shen, J. Axel Zeitler, Quantifying Pharmaceutical Film Coating with Optical Coherence Tomography and Terahertz Pulsed Imaging: An Evaluation, *J. Pharm. Sci.* 104 (2015) 3377–3385.
- [246] P. Hitzer, T. Bauerle, T. Drieschner, E. Ostertag, K. Paulsen, H. van Lishaut, G. Lorenz, K. Rebner, Process analytical techniques for hot-melt extrusion and their application to amorphous solid dispersions, *Anal. Bioanal. Chem.* 409 (2017) 4321–4333.
- [247] Council of Europe, European Pharmacopoeia, 5.25. Process analytical technology, Council of Europe, Strasbourg, 2021.
- [248] J. Rantanen, J. Khinast, The Future of Pharmaceutical Manufacturing Sciences, *J. Pharm. Sci.* 104 (2015) 3612–3638.
- [249] Y. Tlegenov, W.F. Lu, G.S. Hong, A dynamic model for current-based nozzle condition monitoring in fused deposition modelling, *Progress Additive Manuf.* 4 (2019) 211–223.
- [250] D.A. Anderegg, H.A. Bryant, D.C. Ruffin, S.M. Skrip, J.J. Fallon, E.L. Gilmer, M.J. Bortner, In-situ monitoring of polymer flow temperature and pressure in extrusion based additive manufacturing, *Addit. Manuf.* 26 (2019) 76–83.
- [251] M. Elbadawi, L.E. McCoubrey, F.K.H. Gavins, J.J. Ong, A. Goyanes, S. Gaisford, A. W. Basit, Harnessing artificial intelligence for the next generation of 3D printed medicines, *Adv. Drug Deliv. Rev.* 175 (2021) 113805.
- [252] H.D. Özeren, R.T. Olsson, F. Nilsson, M.S. Hedenqvist, Prediction of plasticization in a real biopolymer system (starch) using molecular dynamics simulations, *Mater. Des.* 187 (2020) 108387.
- [253] M. Maus, K.G. Wagner, A. Kornherr, G. Zifferer, Molecular dynamics simulations for drug dosage form development: thermal and solubility characteristics for hot-melt extrusion, *Mol. Simul.* 34 (2008) 1197–1207.
- [254] Y. Yuan, C. Abeykoon, W. Mirihanage, A. Fernando, Y.-C. Kao, J.A.W. Harings, Prediction of temperature and crystal growth evolution during 3D printing of polymeric materials via extrusion, *Mater. Des.* 196 (2020) 109121.
- [255] M. Grieves, J. Vickers, Digital Twin: Mitigating Unpredictable, Undesirable Emergent Behavior in Complex Systems, in: F.-J. Kahlen, S. Flumerfelt, A. Alves (Eds.), *Transdisciplinary Perspectives on Complex Systems*, Springer International Publishing, Cham, 2017, pp. 85–113.
- [256] Y. Chen, O. Yang, C. Sampat, P. Bhalode, R. Ramachandran, M. Ierapetritou, Digital Twins in Pharmaceutical and Biopharmaceutical Manufacturing: A Literature Review, *Processes* 8 (2020).
- [257] L. Zhang, X. Chen, W. Zhou, T. Cheng, L. Chen, Z. Guo, B. Han, L. Lu, Digital Twins for Additive Manufacturing: A State-of-the-Art Review, *Appl. Sci.* 10 (2020).