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Michael A. Repka
Nigel Langley *Editors*

3D Printing

Emerging Technologies and Functionality of Polymeric Excipients in Drug Product Development

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Preface

3D printing has emerged as a transformative technology within the pharmaceutical space, revolutionizing drug development, personalized medicine, and drug delivery systems. With its ability to precisely create complex structures and customized formulations, 3D printing offers unprecedented advantages in pharmaceutical manufacturing. The technology allows for the rapid prototyping of drug prototypes, accelerating the drug development process and reducing costs associated with traditional manufacturing. Moreover, 3D printing enables the production of personalized medications tailored to individual patients, enhancing treatment efficacy and patient compliance. This customization extends to the fabrication of drug delivery devices, such as implants or oral tablets with specific release profiles. As the field continues to advance, 3D printing is poised to reshape pharmaceutical research, production, and patient care, fostering innovation and improving therapeutic outcomes.

Furthermore, 3D printing has opened new avenues for enhancing drug solubility and bioavailability, addressing challenges that have long plagued certain medications. By utilizing innovative printing techniques and materials, pharmaceutical companies can now create drug formulations with improved absorption rates and reduced side effects. This breakthrough has the potential to transform the treatment landscape for various medical conditions, especially those that previously had limited treatment options.

In addition to drug development, 3D printing has streamlined the production of medical devices and equipment used in the pharmaceutical industry. Custom-made equipment, such as specialized lab tools and unique drug delivery systems, can be rapidly fabricated, promoting efficiency and precision in research and manufacturing processes.

Although there has only been one US FDA approved pharmaceutical product fabricated via 3D printing so far, interest in the process is clearly demonstrated by a wealth of publications. Within this space, *3D Printing: Emerging Technologies and Functionality of Polymeric Excipients in Drug Product Development* has been developed to provide a unique source on 3D printing in the pharmaceutical arena. This text provides insights of the various types of 3D printing, from fused deposition modeling (FDM) to stereolithography (SLA). It also provides a clinical

perspective and the regulatory landscape while investigating polymeric functionalities from different industrial perspectives. The viewpoints expressed by the authors and their respective organizations highlight the technologies and future trends for 3D printing technology. The editors wish to thank and acknowledge the authors of this work. Without their contributions and valuable insights, this text would not have been possible. It is through the authors' collective endeavours that such a comprehensive and valuable body of work was created. It is hoped that this text will facilitate the continued growth of pharmaceutical 3D printing.

3D printing has ushered in a new era in the pharmaceutical industry, offering unprecedented opportunities for innovation, customization, and improved patient care. As researchers, manufacturers, and regulators continue to collaborate and overcome existing barriers, the full potential of 3D printing in the pharmaceutical space is set to transform medicine and revolutionize healthcare on a global scale.

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….To my wife Staci, for her unwavering devotion and love for our family. My brother, for his loyalty and uncompromising principles. My children, Michael, Jonathan, Andrew, Jordyn, and Walker, and my grandchildren, James and Henry, for making everything worthwhile.

Michael A. Repka

….To my wife Tomoko for all her love and support and to my children Tom, Sean and Leo.

Nigel Langley

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Michael A. Repka is the Distinguished Professor of the Department of Pharmaceutics at The University of Mississippi. He is also Founder and Director of the Pii Center for Pharmaceutical Technology. His research interests include the solubilization and delivery of poorly soluble bioactives via Hot Melt Extrusion (HME) technology, while coupling HME techniques with 3D printing to produce patient-centric delivery systems. Dr. Repka has established himself as an expert in this major pharmaceutical processing field through his numerous peer-reviewed publications, presentations and scientific talks.

Nigel Langley is currently the Global Technical Director, Life Sciences at Gaylord Chemical LLC. He has a strong interest in excipient innovation, solubilization, hot melt extrusion and 3D printing. Dr. Langley has also worked at BASF and Croda International PLC and is the current Chair of IPEC-Americas.

Part I
Introduction, Clinical, and Regulatory Landscape

Overview of Pharmaceutical 3D Printing Technologies

Daniel Jacobi and Sung Min Pyo

Contents

Abstract This chapter provides a comprehensive overview of the diverse landscape of pharmaceutical 3D printing technologies. Covering a range of approaches including powder-based, extrusion-based and photopolymerisation methods, this review highlights the distinctive attributes, advantages and challenges associated with each technique. It delves into their applications in drug formulation, personalised medicine and dosage form customisation. As can be seen in this chapter, every 3DP technique has its own advantages and disadvantages. The properties of the drug can influence the choice of the technique. However, the technique chosen influences the properties of the formulation needed to be printable and additionally determines the dosage forms that are possible. By synthesising these insights, Chap. 1 offers a holistic perspective on the evolving field of pharmaceutical 3D printing technologies, showcasing their potential to reshape drug manufacturing and patient-centric healthcare approaches.

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1 Advantages and Opportunities

3D printing (3DP) is an additive manufacturing technique that is becoming increasingly popular in many areas of research. The American Society for Testing and Materials classifies 3DP into seven main categories, [1] of which five are represented in pharma: binder jetting, vat photopolymerisation, powder bed fusion, material jetting and material extrusion [2]. All of these different techniques have in common that they are computer-aided design (CAD) software based. In the software, a model of the dosage form is created and then digitally sliced into layers which subsequently will be printed accordingly layer by layer.

3DP has several advantages over the conventional way of manufacturing pharmaceutical dosage forms. The most prominent advantage is its high flexibility in terms of dose strength and tablet shape, for which a wide variety of dies and punches would be necessary in conventional tablet press. This makes the whole process cost-, time- and labour-intensive [3]. In 3DP, dose is a function of the amount printed. Therefore, the dose strength can be easily adjusted through the infill percentage and/or the overall size of the printlet (depending on the technique used). And this basically is done by one click on the software [4]. The same applies for other important tablet characteristics, e.g. geometrical shapes directly influencing the release kinetics [3]. This feature makes the 3DP technology very promising for tailored tablets, specifically for the use in paediatrics, as the body weight and thus the dose vary the most in this area of medicine.

Not only for OTC products but also in the development phase of new products, this flexibility can be of great advantage. In clinical trials, for example, different dosage strengths can be produced easily and on demand. Moreover, in pre-clinical studies, very small dosage forms suitable for rodents can be produced. In fact, miniprintlets with a diameter of 0.5 mm printed via selective laser sintering 3DP have been reported [2, 5].

Also very interesting is the possibility to print Braille on tablet surfaces to improve the safety for visually impaired persons (Fig. 1) [6].

Furthermore, dosage forms with complex geometries have been described in the literature, such as donut-shaped and torus-shaped printlets and printlets with complex gyroid lattice structures, which can be produced easily with the 3DP but with greater difficulty using conventional methods [7–9].

Besides the higher acceptance by patients, the release profiles can be modified since the geometrical form defines important parameters such as the surface-to-volume ratio [10]. Not only by the shape but also by printing, a thick shell and porous core release profiles can be fine-tuned.

Another advantage of 3D printed pharmaceuticals over conventionally manufactured pharmaceuticals is the potential high drug load. Since no compression is performed to create a printlet unlike a tablet, there is no need for excipients, e.g. filler,

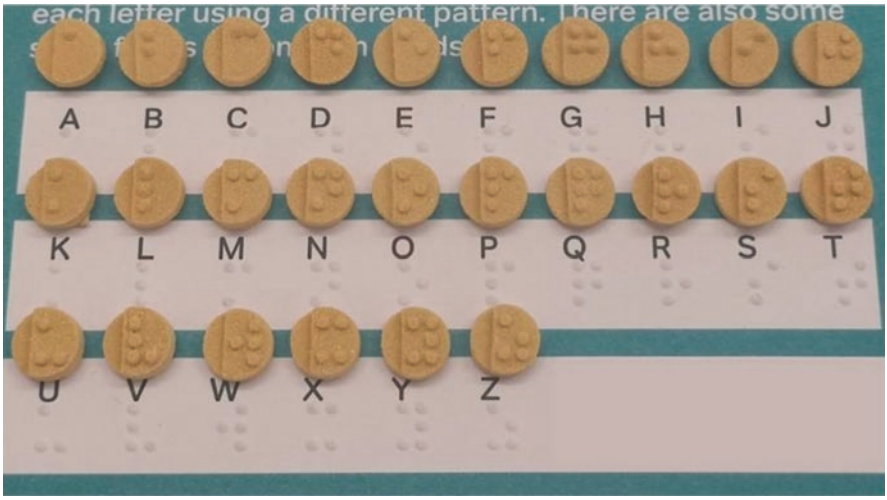

Fig. 1 Image of cylindrical printlets containing the 26 Braille alphabets. (Reprinted with permission from Ref. Atheer Awad et al. [6], pharmaceutics, MDPI [6])

binder and disintegrant, to exhibit good compressibility. In a best-case scenario, only the drug and a suitable polymer are used. In the literature, drug loads as high as 80% are reported [11].

2 Limitations and Challenges

However, to date, there are also some limitations and challenges that need to be overcome in 3DP, mainly attributed to the fact that 3DP has only been used in the pharmaceutical industry for a short time and is therefore not fully explored.

The first point is the speed of the printers. For material jetting technologies, a time span of 2–3 min per printlet is reported [12]. Although this time range may be generally acceptable for tailored tablets or small batches, e.g. for pre-clinical and clinical studies, as mentioned above, it is a major disadvantage for frequently used, non-tailored tablets. A common rotary tablet press can produce up to 500,000 tablets in 1 h [13]. This is more than 16,000 times faster, despite the fact that material jetting technology is already one of the fastest methods among the 3DP technologies [3].

Although it is highly likely that even faster printers will be available in the future as the technology evolves, some physicochemical properties may limit the speed. For example, highly viscous melts always require a certain amount of time to be extruded through a nozzle and adhere to the building platform, which therefore limits printing speed. Plus, many 3DP techniques require additional post-treatment, which will also consume some time. Therefore, while 3DP will definitely become faster in the near future, it will probably never be as fast as a conventional tablet press.

Another challenge to overcome is the small number of approved excipients for 3DP. Moreover, the excipients that can be used differ greatly from the 3DP technique used. For example, selective laser sintering (SLS) requires sinterable polymers and stereolithography (SLA) needs photocurable resins. Unfortunately, these materials are not on the FDA's Inactive Ingredients Database (IID). Material jetting techniques such as hot melt extrusion-coupled fused deposition modelling (FDM) are based on thermoplastic polymers that are commercially available in pharmaceutical grades. However, if the melting point is too high, the polymers, even with plasticisers, may not be suitable for thermosensitive APIs. In other techniques, such as semisolid extrusion or binder jetting, organic solvents are often used. Here, the challenge is to ensure residue-free removal of the solvent from the final product [11].

The last major challenge is regulatory. So far 3D printers are not recognised as GMP-compliant. Furthermore, no tailored tablets have ever been approved. To date, the only 3D printed tablet approved by the FDA is Spritam® [11], which is available in four fixed doses and has been viewed as a door opener for other 3D printed tablets. FabRx, for example, developed the M3DIMAKER™, which claims to be the world's first 3D printer for personalised medicine [14]. Additionally, Triastek, Inc. developed the MED®, another 3D printer for pharmaceutical use, which was accepted to the Emerging Technology Program by the FDA Emerging Technology Team in April 2020 [15]. Also, some pre-clinical studies have been accomplished with printlets already [11].

Concerning the lack of excipients for 3D printing, further research is needed to broaden the knowledge. With advances in new technologies, it is likely that novel polymers will be developed that address the exact needs of a particular 3DP process.

In conclusion, 3DP has the potential to revolutionise not only drug development and manufacturing but also the way to treat patients, especially when it comes to small patient populations and/or drugs with high interpersonal pharmacokinetic variability. Nevertheless, each technique used for 3DP in pharmacy has its own unique advantages, disadvantages and parameters, which will be highlighted in the next section.

3 Fact Sheets of 3DP Methods for Pharmaceutical Application

3.1 Binder Jetting Technology/Drop-On Powder (DOP) Technology

Binder jetting, also known under the name "drop-on powder" (DOP) technique belongs to the powder bed-based 3DP technologies and has become popular in 2015 through the product Spritam®, the first and so far the only tablet approved by the FDA in 2015 using 3DP technology [16].

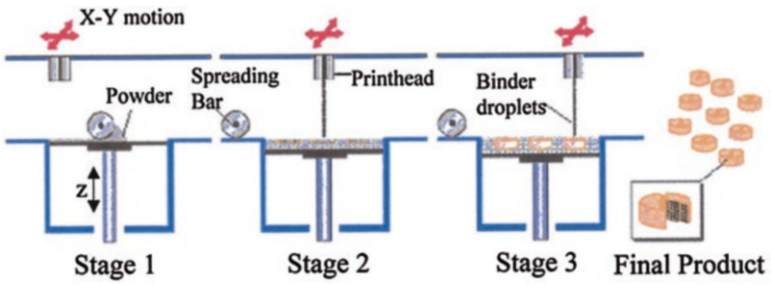

Fig. 2 The schematic illustration of the DOP printing process. (Reprinted with permission from Ref. Katstra et al. [17])

As visualised in Fig. 2, a binder jetting printer generally consists of a print head, a building platform, a feed reservoir and a roller. For the printing of the first layer, the building platform is lifted to the uppermost position, and the roller spreads a layer of powder (commonly containing the drug) onto the building platform. The print head then ejects ink droplets onto the powder bed and binds the powder particles together like an adhesive. The binder that creates this adhesive effect can either be dissolved in the ink or blended with the API in dry powder form.

Next, the building platform is lowered, and the roller spreads a new layer of powder from the reservoir onto the building platform. These steps are repeated until all layers are printed, and the product has the desired height [17]. Since the result is a powder bed with printlets in it, the binder jetting technology requires a post-treatment involving recirculation of unused powder, brushing of adhering powder from the printlets and evaporating of the remaining solvent.

There are several types of print heads available for the system. The two most used types are thermal and piezoelectrical print heads (Fig. 3a, b, respectively) [18]. Thermal print heads use a resistor to heat the ink to 200–300 °C [19]. During heating, bubbles form in the print head. When the bubbles collapse, the resulting pressure waves eject parts of the ink through the nozzle, creating droplets.

What needs to be highlighted on this technique is that 0.5% of the ink is heated for a few microseconds [20]. This ensures that there is no substantial degradation of proteins, allowing the printing of human growth hormone and insulin [21]. It is more the solvent used in the ink that limits the field of application. Since the ejection depends on the gas phase transition, only solvents with a relatively high vapor pressure can be used [11].

The more commonly used print head for DOP is the piezoelectrical print head. Here, electrical pulses cause the deformation of a piezoelectric crystal, which compresses a capillary to dose the ink [22]. This actuation technique is advantageous over the thermal technique, because it allows more control over the droplet formation. The crystal can be cycled on and off quickly, whereas a hot resistor needs time to cool. In addition, piezoelectrical print heads can be used with a wider range of solvents, since the volatility of the solvent is not a concern.

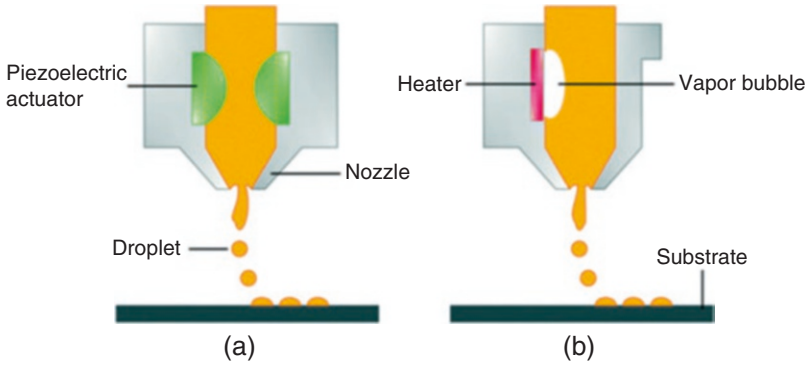

Fig. 3 Schematic illustration showing the principles of operation of a drop-on-demand inkjet printing system. (Reprinted with permission from Muhammad Arif Mahmood et al. [25], Compounds, MDPI [25])

Parameters for adjusting the droplet size and by this the accuracy and resolution of the DOP technique are the nozzle diameter and the surface tension of the ink. Likewise, the print head speed and the frequency of droplet ejection are important as both parameters will influence the concentration of the binder in the ink and thereby the hardness or porosity of the printlet [23].

The porosity can also be adjusted by the droplet spacing (distance between two droplets) and line spacing (distance between two lines). The layer thickness normally lies in the range of 50–200 μm. Therefore, droplet size must be smaller, normally ranging between 50 and 150 μm to ensure the homogeneity of the layer thickness [24]. Finally, the standoff distance (distance between print head and powder bed) must also be considered. The distance must be large enough to allow the formation of droplets but at the same time be kept as small as possible to reduce environmental airflow. For a piezoelectrical print head, the standoff distance is typically between 2 and 3 mm. However, since each powder formulation behaves differently and the spread of droplets on the powder depends on characteristics such as droplet volume, equilibrium contact angle and infiltration into the porous powder bed, the ideal parameters must be determined anew for each formulation [25, 26].

One characteristic of printlets prepared by DOP is their high porosity, making this technique ideal for orodispersible tablets. As an analogy, DOP printing is like wet granulation without any compression [27]. The particles are only forming a solid printlet because of weak interparticle forces, e.g. capillary effects and solid bridges, creating micron-scale interconnected pores in the printlet [11].

And this is indeed the reason why DOP was chosen for Spritam®. It was also favourable that high drug loads can be achieved, since this technique requires only an active ingredient, a polymeric excipient and a suitable solvent, which is later evaporated and removed. In case of Spritam®, the drug load is up to 1000 mg, and the printlets will disintegrate with a sip of water almost immediately with a mean disintegration time of 11 s and a range of 2–27 s [28].

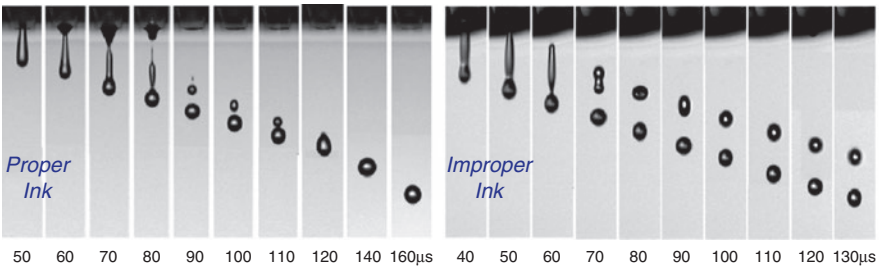

Fig. 4 Representative photo sequences of drop formation for fluids and a constant driving voltage of 25 V. (Reprinted with permission from Daehwan Jang et al. [29])

What is considered a disadvantage of DOP is the necessity of using a solvent. In any case, an additional evaporation time is required. Depending on the solvent used, the process can take considerable time. And if an organic solvent is used, it must be proven that the drying process ensures a residue-free product.

Further, depending on the viscosity of the formulation, satellite droplets or even clogging of the nozzle may occur. The achievable resolution of DOP is also a limiting factor and is especially declining when satellite droplets appear. Satellite droplets are droplets that are not spherical and therefore reduce drastically the resolution of DOP (Fig. 4) [29]. However, both can be prevented by optimising the ink formulation and are therefore not a criterion for exclusion.

3.2 Ink Jetting/Inkjet Printing

Basically, ink jetting is very similar to the DOP technique. The main difference is that ink jetting does not deposit droplets to a powder bed but to various other surfaces, e.g. polymer films, microneedles for transdermal drug delivery or stents, just to name a few [30–32]. But ink jetting is not limited to these 2D applications. Additionally, 3D printlets produced by ink jetting have been reported. The ink formulations used were based on hot melts, e.g. beeswax, and photocurable polymer solutions. Depending on the formulations, printlet could be just printed on a building platform or had to be printed into a blank preform tablet [33–35].

For ink jetting, two main approaches are reported: continuous ink jet (CIJ, Fig. 5) and drop on demand (DOD). In CIJ, a high-pressure pump pushes the ink mechanically through a single nozzle with a diameter of 40–80 µm, creating a continuous stream. The resulting droplets are charged and can therefore be deflected at a defined angle from the main path to deposit on substrates' surface [36, 37]. Depending on the used printer model, typical droplet volumes of 420–1550 pL can be created [38].

In contrast, DOD print heads can create significantly smaller droplets with volumes in the range of 1–70 pL, allowing a higher resolution and therefore often is preferred over CIJ [22].

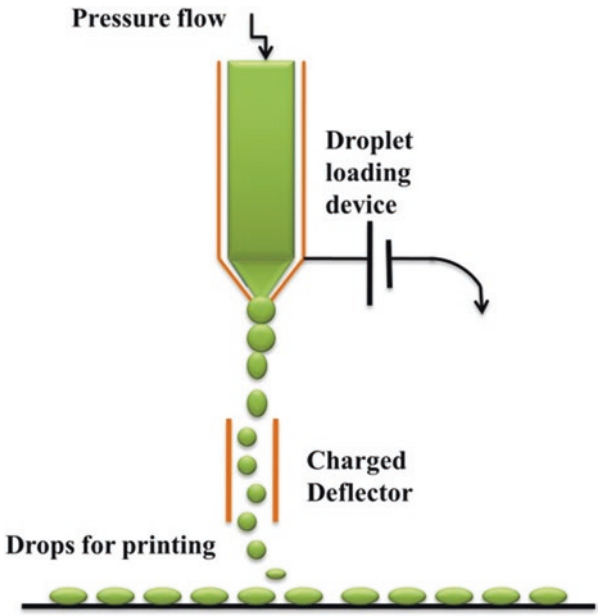

Fig. 5 Schematic illustration showing the principles of operation of a continuous inkjet printer. (Reprinted with permission from Ref. Andrea Alice Konta et al. [94], bioengineering, MDPI [94])

Print heads for ink jetting can use the same actuation techniques as mentioned above for drop-on powder. Additionally, the use of acoustic and electrostatic print heads is reported. Acoustic print heads use acoustic lenses to focus an ultrasound beam directly on the ink's surface to eject droplets [37]. Electrostatic print heads apply an electrostatic field to the nozzle, originating the name. This field attracts ions to the nozzle. As a result, the concentration of charged molecules at the nozzle increases. Coulombic repulsion is then causing the meniscus at the nozzle end to form what is known as Taylor cone. When the charge repulsion exceeds the surface tension of the liquid, droplets are ejected though the nozzle [39].

Since ink jetting mainly involves the deposition of ink on a given surface, all parameters that can be optimised are related to the ink. Above all, the viscosity, overall fluidity and surface tension of the ink must be taken into account. Depending on the solvent system used, an appropriate evaporation step must be carried out for the post-treatment of the printlets.

Advantages of ink jetting technologies lay in the ease of use and low processing costs since ink jet printers are basically commonly used office printers [30]. Additionally, numerous excipients used for ink jetting are available in pharmaceutical grades. Furthermore, ink jet printing can be done under ambient environments, thus is a suitable technique for thermal-sensitive drugs [21].

Disadvantages include the need to use solvents, which can be considered problematic for environmental and health reasons, especially in the case of organic

solvents. Particularly interesting is that 3D ink jetting can be used to create *d*ata-*e*nriched *e*dible *p*harmaceuticals (DEEP). Via ink jetting, a drug with QR code can be printed on an edible film. This film serves as a dosage form and can be scanned before administration. It encodes relevant information about the drug, the dosage form and the patient, which can be accessed using devices such as smartphone [40].

3.3 Material Extrusion/Extrusion Moulding Printing

Material extrusion, also known as extrusion moulding printing, is one of the most commonly used 3DP techniques, the reasons for which we will explain in the following section. Among the known material extrusion techniques, fused deposition modelling (FDM) is by far the best known. There are numerous reports on other processes in the literature. In the following section, semi-solid extrusion (SSE) and direct powder extrusion (DPE) will also be addressed in addition to the FDM process.

3.3.1 Fused Deposition Modelling (FDM)

FDM is a very promising 3DP approach. Generally, FDM is coupled with hot melt extrusion (HME). The extruder creates filaments for the FDM by melting drugs with polymers. These filaments are then pulled into the printer with gears, heated to form a viscous melt and subsequently printed (Fig. 6).

The advantages of this technology interplay are numerous. Since HME is a well-established technology in pharma itself, some excipients are already available, and the equipment price is relatively low. Furthermore, HME can produce the optimal formulation for the FDM 3DP, therefore widening the spectrum of excipients, that can be used for FDM printing. For example, polymethacrylate filaments cannot be used for FDM because of their brittleness. However, melting and mixing it with a plasticiser and a filler in HME produces FDM printable filaments [41]. Additionally, because drug-containing filaments can be an amorphous solid dispersion, FDM printing can be used as an enabling technology for poorly soluble drugs [42].

In general, HME-FDM printed dosage forms exhibit excellent mechanical properties and high drug uniformity. Dose strength and release can be adjusted by the infill percentage of the printlet. It can be used for taste masking, coating and manufacturing of hollow objects (Fig.7) and for polypills [43–45]. It is also an environmentally friendly technique since no solvents are used [46].

But like every technology, FDM has its drawbacks. FDM is not easy to scale up, and compared with other 3DP technologies like drop-on powder, drug loading is not as high [11]. Compared with conventional methods for the production of tablets, FDM printlets exhibit a slower dissolution rate since the material used for creating the tablet is a dense solid dispersion and not a compressed granulate. However, formulations that release the drug in 10 min have been reported [47]. This example

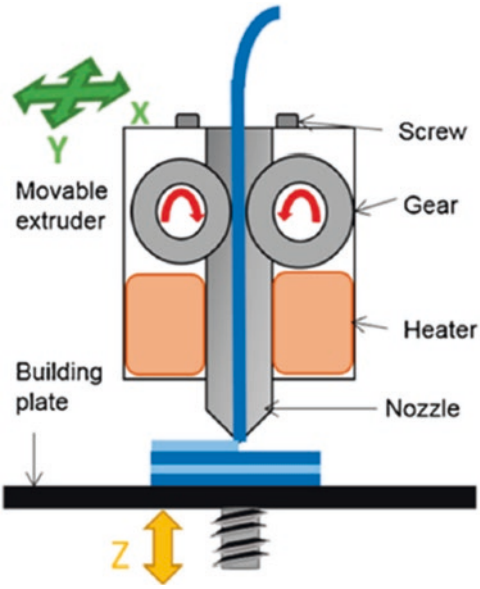

Fig. 6 Mechanism of a fused deposition modelling (FDM) 3D printer. (Reprinted with permission from Ref. Deck Khong Tan et al. [42], pharmaceutics, MDPI [42])

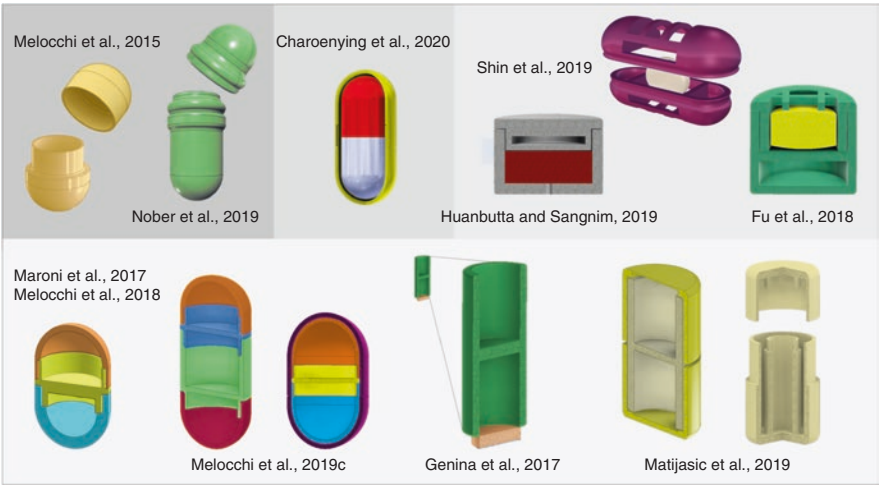

Fig. 7 Various hollow systems assembled after production. (Reprinted with permission from Ref. Alice Melocchi et al. [45])

shows that FDM can create suitable printlets but it is also evident that a lot of formulation development is needed.

Additionally, the limited choice of thermoplastic polymers with good melt viscosity properties for extrusion is still a challenge in the development of a FDM formulation. With regard to tailored medicine, FDM is theoretically very suitable since dose strength is a function of infill percentage and/or size. However, HME

needs a certain amount of raw material to work properly. Therefore, the process is not applicable for the manufacturing of very small batches, e.g. the preparation of printlets for a single person. Finally, thermal-sensitive drugs might be problematic since thermal degradation can occur in the melting process. Nonetheless, studies reported FDM printing with temperatures below 100 °C, [48] showing again that HME-FDM suitable polymers and formulation development are needed to widen the uses of FDM.

Since FDM uses a melt to print, the viscosity of the melt is of great importance and, therefore, the temperature. If the temperature is too low, the nozzle might become clogged due to the high viscosity of the melt. If it is too high, uncontrolled spreading of the melt can occur due to low viscosity. Additionally, the drug might degrade [49–51]. The nozzle size is influencing the resolution. However, the narrowest diameter possible is again depending on the viscosity of the formulation. Another important parameter is the temperature of the building platform since the first basal layer has to adhere there. The temperature must be optimal, so that the first layer adheres strongly to the platform and is stabilised, but does not adhere too strongly because otherwise, the printlet could be damaged when it is taken off the platform [52]. For the same reason, printing speed is an important parameter as well. The faster the printing, the less time is needed for a printlet to be completed. However, the faster the printing, the more vibration occurs, which lead not only to a weaker adherence of the printlet to the building platform but also to weaker bonding between printed layers. Therefore, the overall quality of the printlet decreases [53, 54]. The standoff distance is to be considered as well. Since FDM uses viscous melts, a too small distance leads to the clogging of the nozzle. A too large distance, however, leads to clumping of the melt at the tip of the nozzle. A too large distance, however, leads to clumping of the melt at the tip of the nozzle. Therefore, a proper standoff distance fitting the formulation and the environmental settings is needed [55]. Regarding the printlet, infill percentage, layer thickness and shell thickness are of importance for the mechanical properties and the release rate. Infill percentage adjusts the dose strength but also the porosity of the manufactured object, therefore influencing the dissolution profile. Infill percentages in the range of 0% (a hollow shell) and 100% (a dense printlet) are possible.

The layer thickness is the most important parameter determining the resolution and therefore the surface roughness. It should not be below 100 μm [56]. Lastly, the shell thickness is an important parameter for controlled-release dosage forms. If the shell is too thin, release is not controllable, since gastric fluid will be able to penetrate the dosage form [57].

To date, a wide range of dosage forms have been reported for FDM, e.g. immediate- and controlled-release dosage forms, polypills and intragastric floating drug delivery systems, [3] showing the wide variety of dosage forms printable with FDM (Fig. 7).

3.3.2 Direct Powder Extrusion (DPE)

Very closely related to FDM, direct powder extrusion (DPE) is a novel 3DP technique based on material extrusion. The print head consists of a hopper for the powder, a screw for mixing and transportation of the material downwards, heating elements and a nozzle [58]. Basically, DPE is a very small HME in a print head [2]. Thus, the overall process of the DPE resembles the one in a FDM and is not described here.

DPE is advantageous over FDM for small batch-sized medicines. Since the production of filaments via HME is skipped, the process is faster. Also, DPE is more efficient when small batches are manufactured because the "small HME" in the print head does not need as much material feed as a normal-sized HME. In a study by Goyanes et al., 8 g was printed via this technique. This makes DPE especially useful for the application of 3DP in hospital pharmacies and/or in (pre-)clinical studies, in which the available amount of the drug is commonly limited [58, 59].

However, it must be noted that solid formulation development is still necessary for the 3DP of qualitative printlets via DPE. Not every powder can be printed. Powders (e.g. or other material like pellets) need to exhibit good flowability properties, and a mixture of materials needs to be capable of providing homogeneity. For powders, also electrostatic forces need to be considered. These can cause variation in the feeding while printing, thus making it impossible to have a continuous and homogenous flow through the nozzle [60] (Fig. 8).

Rather interestingly and showing the progress of this 3DP technology, the Chinese company Triastek, Inc. developed a 3D printer called MED® (short for melt

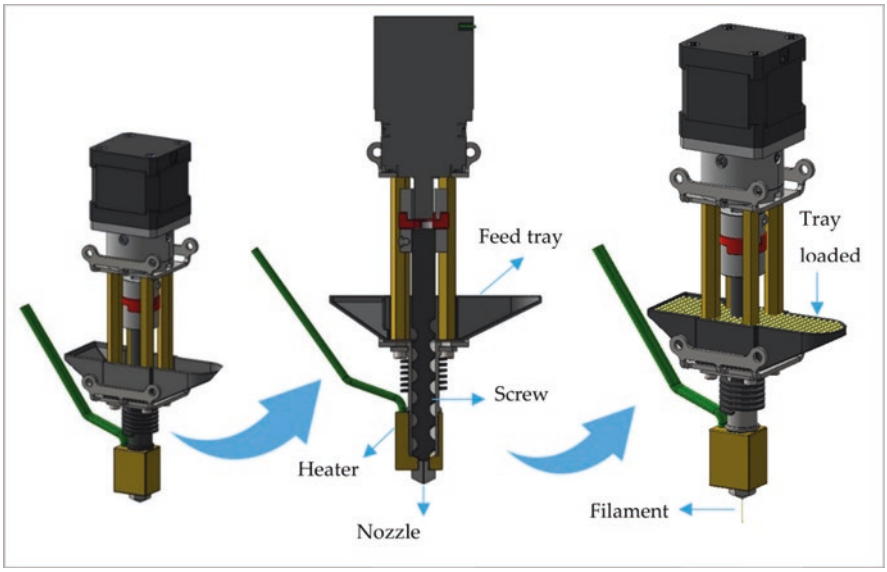

Fig. 8 Design of the single-screw direct powder extruder FabRx 3D printer, M3DIMAKER™. (Reprinted with permission from Ref. Boniatti et al. [60]. Pharmaceutics. MDPI [60])

extrusion deposition) that could be considered a type of DPE [15]. In April 2020, MED® was accepted to the Emerging Technology Program by the FDA Emerging Technology Team [61].

3.3.3 Semi-Solid Extrusion (SSE)

Semi-solid extrusion (SSE) is another material extrusion technique. As the name suggest, the extruded and therefore printed material is in a semi-solid state, being a viscous melt or a gel or paste. For printing a melt, thermoplastic polymers with a relatively low melting point are used as excipients, so that the feed consists of a semi-molten material. For printing a gel or a paste, drug and other excipients are mixed with a solvent or a more complex solvent system [61]. The great advantage of printing a semi-solid like a gel or a paste over other material extrusion techniques is the low temperature during the process, which is especially relevant for thermal-sensitive drugs but is also the reason SSE is used for bioprinting approaches [63]. The printing process is rather simple. The feed material is located in a syringe. When the material is in a semi-solid state, either by warming it up or because of the solvents, the material is extruded through the nozzle. Solidification occurs either through cooling or through evaporation of the solvent. Additionally, other mechanisms have been reported as well, e.g. solidification via ionic cross-linking as a $CaCl_2$ solution was applied on a 3DP object made of alginate [64].

There are two main extrusion mechanisms used in pharma: firstly, extrusion via a pneumatic-based system in which pressurised air is used to compress and extrude the material (Fig. 9) [63]. Its advantages include high precision due to the rapid response time and suitability even for highly viscous material [63].

Secondly, a mechanical-based system can be chosen. This system can either be piston-driven or screw-driven. The piston-driven system allows for better control of the extrusion flow. However, the screw-driven approach is more suitable for viscous material [65]. In general, mechanical-based systems are simpler, more affordable and easier to transport than the pneumatic-based system since they lack the need of an air compressor [63].

Furthermore, the mechanical-based systems allow the easy and quick exchange of the syringes; thus, the overall printing process can be faster. In general, the optimal formulation for SSE should exhibit shear thinning behaviour without thixotropy, meaning a rapid recovery of the initial consistency of the formulation after pressure or sheering is stopped. This makes the extrusion controllable since no formulation can drop out of the nozzle when there is no force applied [62]. Because of the syringe-based feedstock, SSE qualifies perfectly for future “Nespresso” style system in which a pharmaceutical manufacturer could provide ready-to-use SSE formulations in syringes to caregivers like community and hospital pharmacies [3]. The printlets could then be printed on demand and without formulation development being necessary for the pharmacies. This concept makes SSE a promising tool for the decentralised manufacturing of medicine via 3DP [62].

Disadvantages of this technology lay in the lower resolution compared to other material extrusion techniques [66]. A higher resolution can be achieved by the use

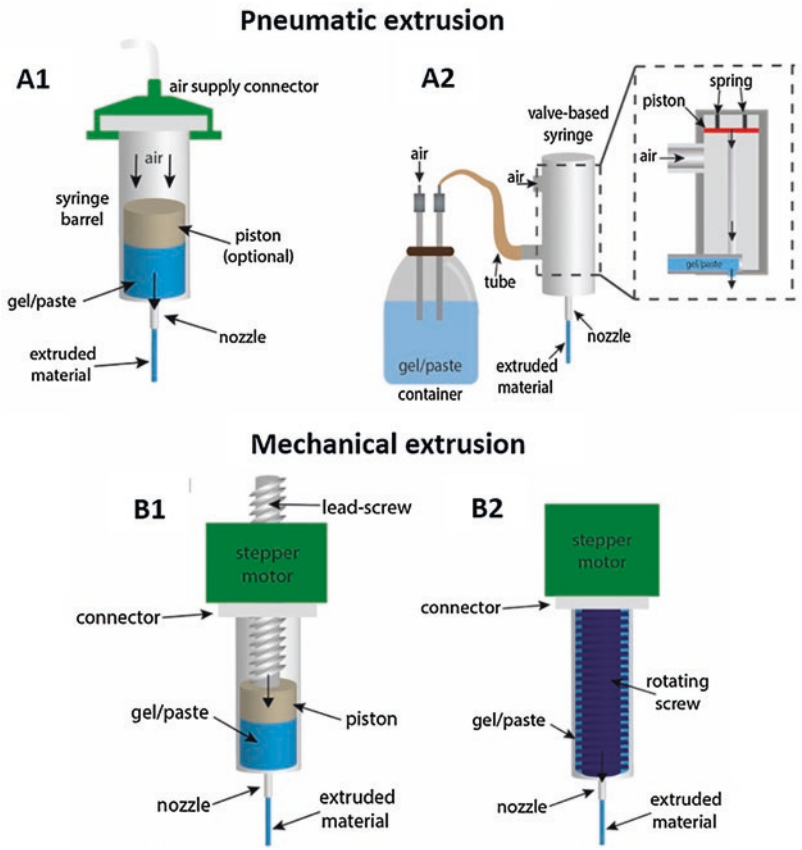

Fig. 9 Semi-solid extrusion (SSE) mechanisms: Pneumatic extrusion including (A1) valve-free and (A2) valve-based and mechanical extrusion including (B1) piston- or (B2) screw-driven extrusion. (Reprinted with permission from Ref. Seoane-Viaño et al. [62])

of a nozzle with narrower orifices; however, this option is limited by the viscosity of the printed formulation, since high viscous materials need a wider nozzle to flow properly [62].

In case of a gel or a paste created with solvents, evaporation is needed. Furthermore, the use of organic solvents is not considered environmental-friendly.

So far, a variety of dosage forms printed via SSE has been reported, e.g. immediate-release tablets, gastro-floating tablets and polypills. Additionally, SSE is capable of manufacturing chewable dosage forms which is an asset for paediatric medicine. Also, due to the printing of semi-solid materials, lipid-based dosage forms like suppositories have been reported as well (Fig. 10) [67–69].

Since SSE is a material extrusion technique, process parameters like nozzle diameter and travel speed, extrusion rate, standoff distance and temperature are important to consider. They are similar to the parameters of FDM and can be seen there.

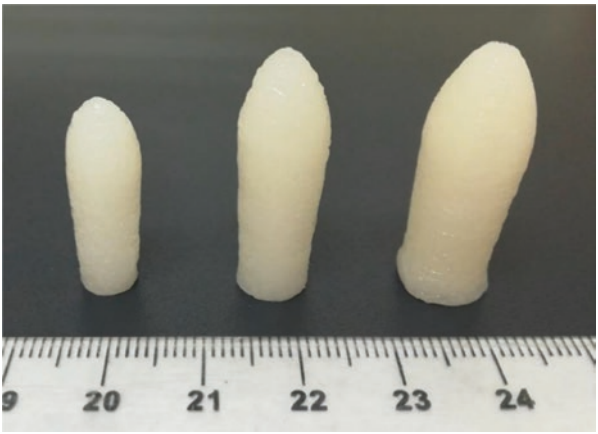

Fig. 10 Lipid-based suppositories with self-emulsifying properties intended for human administration, printed in three different sizes as an example of personalisation. (Reprinted with permission from Ref. Seoane-Viaño et al. [62])

3.4 Powder Bed Fusion Techniques

Several techniques are associated with the term powder bed fusion, all having in common that a laser is used to melt powder particles to form a 3D object [70]. Out of these different techniques, selective laser sintering (SLS) is the most prominent and widely used method in pharma. Therefore, we are going to focus on this technique.

3.4.1 Selective Laser Sintering

A selective laser sintering (SLS) 3D printer consists of six components: most prominent the laser to sinter the powder and Galvano mirrors to project and direct the laser beam onto the correct spot, a building platform, a powder reservoir to hold and dispense fresh powder onto the building platform, a mechanical roller to spread the fresh powder evenly on the platform and finally a material vat to recover unsintered and therefore unused material (Fig. 11).

For the whole printing process, the printing chamber experiences an inflow of inert gas (like nitrogen or argon) to remove condensates produced during printing. This is done to prevent oxidation of the powder and the printed object [71]. For the printing of the first layer, the building platform is lifted to the uppermost position. Subsequently, a fresh layer of powder is spread from the reservoir onto the building platform by the roller [72]. Through the whole printing process, the printer is heating the powder bed so that only a small energy input by the laser is required for sintering. The laser is focused via Galvano mirrors onto the correct position of the

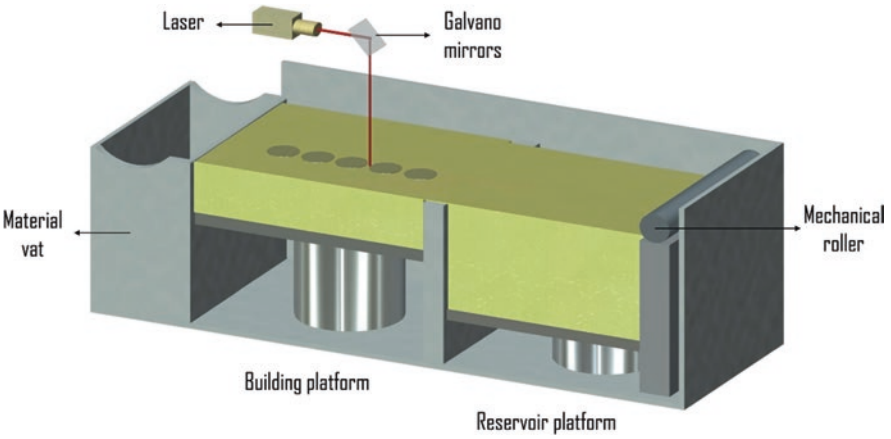

Fig. 11 Graphical illustration of a selective laser sintering (SLS) 3D printer, highlighting its major components. (Reprinted with permission from Ref. Atheer Awad et al. [71])

powder bed and is melting the surface of the powder particles, fusing them together. After a short cooling time to assure solidification of the melted and fused particles, the building platform is lowered on step (= one layer). Afterwards a new layer of powder is spread onto the first one. These steps repeat until the 3D object is completed and all layers have been printed [73].

Then, the printer needs to cool down and post-process steps are necessary, including picking the solid printlets out of the powder bed and sieving and brushing them to get rid of the adherend powder [74]. Also polishing or coating the printlets to improve their appearance or mechanical properties can be an option [76].

Since the laser is the instrument manufacturing the 3D object, the parameters directly and indirectly influencing the energy transfer from the beam to the powder are of great importance. Thus, we are going to elucidate these in greater detail now.

To date, there are four different lasers mentioned in the literature, of which the CO_2 laser is the most prominent. This is mainly because of its low cost and sufficient power. Since the wavelength emitted by a gas laser is dependent on the gas used, the CO_2 laser exhibits a wavelength of 10.6 μm. This is the longest wavelength of all lasers used in SLS, and it is a profound advantage since mainly thermoplastic polymers are used as excipients for SLS in pharma. These polymers usually show a higher absorptance of radiation with higher wavelength.

Normally the power of industrial CO_2 SLS lasers ranges between 50 and 200 W and resolutions between 30 and 60 μm can be achieved [11, 71].

A very modern laser used in SLS is the CO laser which is capable of a higher printing resolution and therefore, the fabrication of finer objects due to the finer spot size (the diameter of the laser beam), which is only half that of an CO_2 laser [71].

Additionally, diode and fibre lasers are available. Diode lasers do not have a fixed wavelength. Fibre lasers, on the other hand, have a fixed wavelength of 1.064 μm (approximately ten times shorter than the wavelength of a CO_2 laser). Like the CO