



3D printing: Innovative solutions for patients and pharmaceutical industry

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ABSTRACT

Three-dimensional (3D) printing is an emerging technology with great potential in pharmaceutical applications, providing innovative solutions for both patients and pharmaceutical industry. This technology offers precise construction of the structure of dosage forms and can benefit drug product design by providing versatile release modes to meet clinical needs and facilitating patient-centric treatment, such as personalized dosing, accommodate treatment of specific disease states or patient populations. Utilization of 3D printing also facilitates digital drug product development and manufacturing. Development of 3D printing at early clinical stages and commercial scale pharmaceutical manufacturing has substantially advanced in recent years. In this review, we discuss how 3D printing accelerates early-stage drug development, including pre-clinical research and early phase human studies, and facilitates late-stage product manufacturing as well as how the technology can benefit patients. The advantages, current status, and challenges of employing 3D printing in large scale manufacturing and personalized dosing are introduced respectively. The considerations and efforts of regulatory agencies to address 3D printing technology are also discussed.

1. Introduction

First applied to the development of pharmaceuticals in 1996 (Wu et al., 1996), 3D printing of pharmaceuticals has been the source of much research and considerable advancement. Though much of the research conducted since then has centered on exploring and refining 3D printing technology for the pharmaceutical applications, development of commercial scale capabilities has advanced substantially in recent years. FDA approval of the first 3D printed pharmaceutical, Spritam®, coupled with its commercial scale manufacturing, demonstrated the feasibility of using 3D printing methods in large-scale manufacturing of pharmaceuticals. With respect to the 3D printing techniques used in the formulation of pharmaceutical dosage forms, these techniques can be broadly assigned to four categories: extrusion-based, powder-based, liquid-based, and sheet lamination-based systems. Table 1 lists these categories, the various techniques within the categories that have been utilized and some advantages and disadvantages of each technique.

Various reviews have been published regarding the use of 3D printing for pharmaceutical applications (Awad et al., 2021; Sen et al., 2021; Seoane-Viaño et al., 2021; Trenfield et al., 2019; Wang et al., 2022). 3D printing technology is very versatile in that a wide range of

release profiles can be created by controlling tablet structure. Customized appearance, size, dose, and other characteristics of the dosage forms can be achieved by 3D printing, resulting in patient centric designs. In early-stage development, 3D printing technology can accelerate formulation development for pre-clinical studies and allows the production of small batches, including flexible dose-adjustment, to facilitate pilot clinical studies. This review will focus on those applications that are intended for or capable of producing products for early clinical trials as well as commercial applications, including large scale manufacturing and personalized dosing.

2. 3D printing in drug product design

2.1. Complex geometric structures fabricated by 3D printing

3D printing of pharmaceuticals has the advantage of producing sophisticated external shapes and complex geometric internal structures that can be employed to control the rate of drug release, where in the GI tract the drug is released, the time of onset of release and the mode of release. The internal structures range from homogeneous highly porous structures to heterogeneous layered and compartmental structures

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produced using multiple materials. In addition, the distribution of API in these structures can be asymmetric or non-uniform, if desired. These unique capabilities allow for unprecedented control of drug release and the potential to positively impact a drug's pharmacokinetic profile to meet a variety of clinical and commercial purposes. Fig. 1 provides examples of tablet designs that can be employed to achieve each of these release characteristics. All the examples can be applied to not only single component drugs, but also fixed dose combinations (Awad et al., 2019; Goh et al., 2021). There are vast opportunities for using these structures that were not possible using the conventional dosage forms to address clinical unmet needs.

2.2. Versatile drug release achieved by 3D printing

Extended and delayed release products have been marketed for some time but typically involve some types of tablet coating (e.g., enteric coating or slow dissolving coating), osmotic pump systems, etc. 3D printing allows finer control of drug release rate through mechanisms like release control layers and modulating surface area available for drug release without requiring any kind of particle coating and the accompanying complexities (Patel et al., 2021; Zheng et al., 2021). Controlling the location of release has proven difficult to date but 3D printed products have demonstrated the capability of delaying release even to as low in the GI tract as the colon (Melocchi et al., 2021b), opening new opportunities for treating inflammatory bowel diseases. Though the site of drug absorption is typically thought of as occurring in the small intestine, for some drugs it may be advantageous to have the tablet be retained in the stomach if the drug is either better dissolved or

better absorbed in the acidic environment or if the site of action is in the stomach. Using air pockets to create buoyancy or expandable arms/extensions, 3D printing allows for the production of dosage forms that can be gastroretentive and facilitate drug release almost exclusively in the stomach (Charoenying et al., 2020; Jeong et al., 2020). One particularly novel application is the combination of both immediate release and extended release drugs in a single dosage form or the ability to easily incorporate two or more drugs with greatly varying pharmacokinetics and design them to be delivered in a single, once a day dosage form (Khaled et al., 2015). These are just a few examples of the myriad of possibilities in dosage form design and drug release that can be achieved by 3D printing. Table 2 summarizes examples of release kinetics and modes that can be achieved with 3D printed dosage forms.

2.3. Patient-centric drug product design with 3D printing

Formulators are constantly trying to achieve dosage form designs that are patient-centric, to not only enhance the patient experience but also optimize the therapeutic outcome. Patient-centric strategies include enhancing palatability and swallowability, reducing pill burden, increasing dose accuracy, etc. 3D printing technology can increase the versatility of appearance, size, and structure of dosage forms, which contributes to customized personalized dosing. For example, for pediatric treatment, external tablet shapes can be easily adjusted by 3D printing technology to promote ease of swallowing. In addition, researchers have explored the application of 3D printed dosages forms for personalized dosing. This can allow for customization of dosing for an individual patient and allow titration to the individual patient's specific

Table 1
Comparison of Representative 3D Printing Technologies in Pharmaceutical Application.

Category		Technique	Concept/Rationale	Advantage	Limitation
Extrusion-Based Systems	Material Extrusion	Fused Deposition Modeling (FDM)	Drug-loaded filaments are heated to a critical state, making them a semifluid state, and then extruded from the printing nozzle according to the model parameters.	<ul style="list-style-type: none"> High equipment diversity (multiple nozzles) Low equipment price Good mechanical properties of printed dosage forms 	<ul style="list-style-type: none"> Difficult to scale up Low drug loading
		Semi-Solid Extrusion (SSE)	SSE extrudes the paste evenly via a syringe-based print head under pressure or screw gear rotation and deposits layer by layer on the platform for printing.	<ul style="list-style-type: none"> High drug loading Mild printing process/condition Broad range of excipients 	<ul style="list-style-type: none"> Post-processing Low resolution Low efficiency
		Melt Extrusion Deposition (MED®)	MED® converts powder feedstocks into softened/molten states followed by precise layer-by-layer deposition to produce objects with desired structures.	<ul style="list-style-type: none"> No post-processing Easy to scale up High equipment diversity (multiple nozzles) 	<ul style="list-style-type: none"> Low drug loading
Powder-Based Systems	Binder Jetting (BJ)	Ink-Jet 3D printing	BJ assembles 3D objects by first preparing a 2D powder-based layer and then ejecting a binder solution to pattern and solidify specific regions in the powder bed.	<ul style="list-style-type: none"> Easy to scale up High volume High drug loading High resolution No need for support materials 	<ul style="list-style-type: none"> Post-processing Inefficient powder usage Risk of drug degradation
	Powder Bed Fusion (PBF)	Selected Laser Sintering (SLS)	PBF uses a focused power source (e.g., laser or electron beam) to selectively consolidate powder particles into solid objects.	<ul style="list-style-type: none"> High resolution and accuracy Ability to print micro-sized structure 	<ul style="list-style-type: none"> Post-processing Potential material toxicity Limited photosensitive resin
Liquid-Based Systems	Vat Photo-polymerization (VP)	Stereolithography (SLA), Digital Light Processing (DLP)	VP is based on the selective photopolymerization of liquid photosensitive resins using ultraviolet laser source.	<ul style="list-style-type: none"> High resolution High quality surface of printed tablets 	<ul style="list-style-type: none"> Post-processing Limited excipients
		Material Jetting (MJ)	Continuous or Drop on Demand (DOD)	Material droplets are being deposited through a print head building and dried by solvent evaporation or by solidification under ultraviolet light and the object is built layer by layer.	<ul style="list-style-type: none"> Easy to scale up High printing speed
Sheet Lamination-Based Systems	Sheet Lamination (SL)	Screen Printing Innovational Drug Technology (SPID®)	3D screen printing is based on the transfer of the printing paste through distinct openings of the printing screen onto a given substrate.	<ul style="list-style-type: none"> Easy to scale up High printing speed 	<ul style="list-style-type: none"> Post-processing

References: Cui et al., 2021; Mohammed et al., 2020; Moldenhauer et al., 2021; Ragelle et al., 2021.

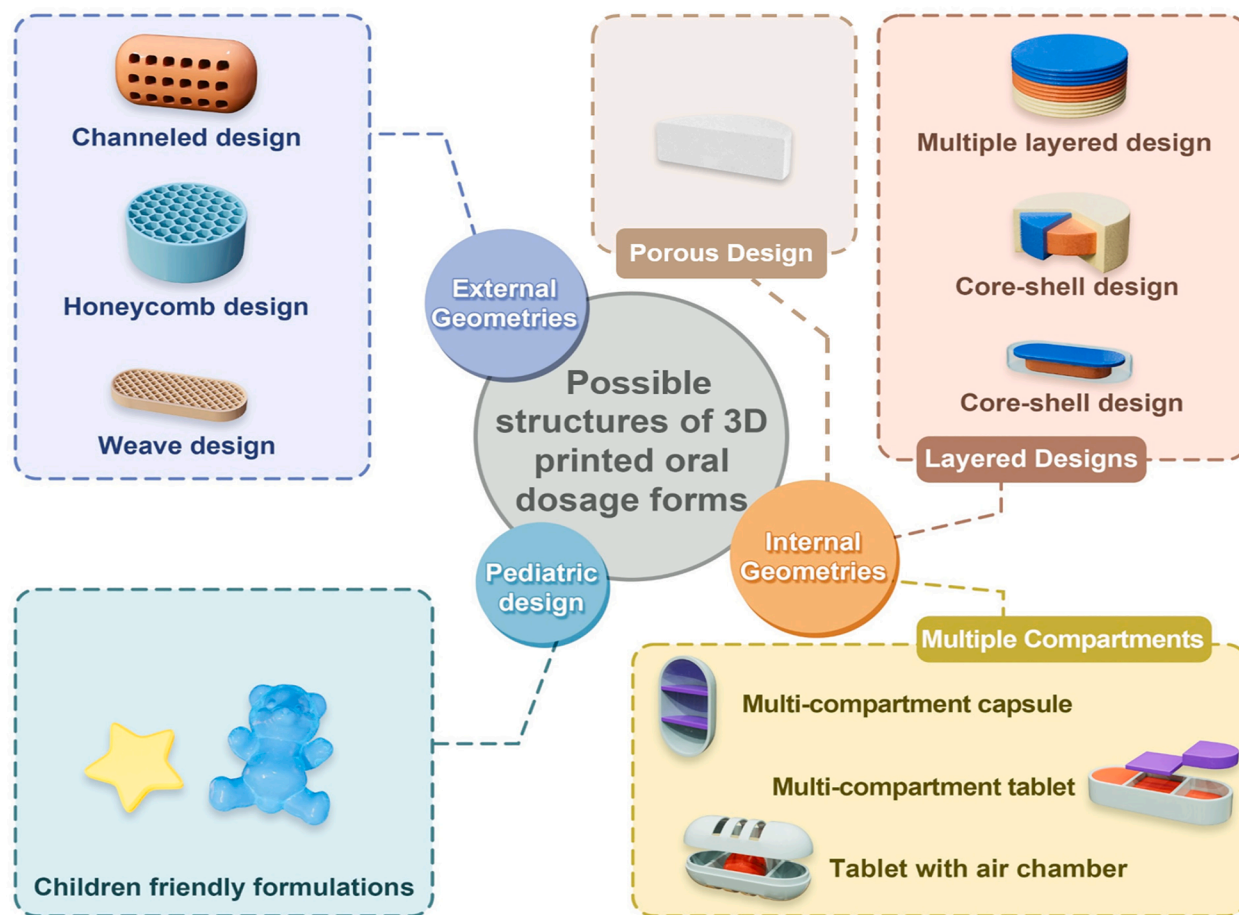


Fig. 1. Possible Structures of 3D Printed Oral Dosage Forms.

therapeutic needs. Advancing this idea of personalized dosing, 3D printers for personalized dosing have been developed by several companies, including FabRx, DiHeSys and Craft Health. Some of the drug products have been used in early clinical trials, which will be introduced in Section 4.5.

2.3.1. Patient preferences

Several surveys have been conducted to evaluate patient acceptability and preference for 3D printed tablets. For example, Goyanes et al. (Goyanes et al., 2017) examined patient preferences of ten different shapes of 3D printed tablets (Printlets™), produced in four different sizes and nine different colors. With respect to size, not surprisingly the smaller the tablet the higher patient acceptance. Though there was a substantial variation in patient response to the range of colors, the darker colors in general received less favorable reviews. With respect to tablet shape, familiar designs such as a caplet shape or shapes with more rounded edges generally scored higher pre- and post-swallowing. Tablets with sharper edges or non-conventional shapes, e.g., cube-shaped, received lower scores. These findings were confirmed in a similar study (Fastø et al., 2019), where patients tended to prefer more traditional shapes, again possibly due to a familiarity factor and color desirability varied greatly. Preferences of pediatric subjects have also been evaluated, but in this case with the same shape of tablet (Printlets™) but made by four different printing methods: digital light processing (DLP), selective laser sintering (SLS), semi-solid extrusion (SSE) and fused deposition modeling (FDM) (Januskaite et al., 2020). The majority of pediatric subjects preferred tablets prepared by DLP methods, mostly likely due to the well-defined and smooth edges, as well as deeper color. However, when the children learned that the tablets produced by SSE methods were chewable, they changed their primary

preference, even though the SSE tablets were originally rated least preferred.

2.3.2. Geriatric patients and pediatric patients

In general, elderly patients tend to take more medications, which can result in lesser adherence rates and less than optimal therapeutic outcomes. Combination products can help reduce the number of tablets a patient must take and thus, simplify the dosing regimen. In addition to the ability to easily combine multiple medications in a single tablet, 3D printing also offers the opportunity to combine medications with dramatically different pharmacokinetic profiles within a single tablet. This advantage was clearly demonstrated in the work by Khaled and colleagues (Khaled et al., 2015), who produced a five-in-one polypill for treating cardiovascular disease containing aspirin, hydrochlorothiazide for immediate release and three sustained release compartments containing pravastatin, atenolol, and ramipril.

For adult patients who experience difficulty swallowing (dysphagia) such as the elderly, or Parkinson's disease patients, beyond altering tablet shape, orodispersible tablets produced by 3D printing can rapidly disperse in the mouth with a minimum of water to allow for easy swallowing. These orodispersible dosage forms, along with chewable dosage forms, can also be applied to pediatric formulations. In one other example of pediatric-centric formulations, 3D printing has been applied to the breakfast setting by using cereal-based materials. 3D printed drug-containing cereal "flakes" are then mixed with milk and the drug releases into the milk solution and the stomach fluids for absorption. This administration method improves patient acceptance (Karavasilis et al., 2022). These, along with the examples discussed later regarding formulations to aid visually impaired patients are just a few examples of how 3D printing of pharmaceuticals can be of benefit to special

Table 2
Examples of Release Kinetics and Modes Achieved by 3D Printing Technologies.

Kinetics/ Mode	Technique	Structure	Description	Reference
Immediate release	FDM	Capsule-shaped tablets	The tablets fabricated possessed excellent mechanical strength and released more than 85 % of its drug content within 30 min.	(Sadia et al., 2016)
	DDP	Tablets with varying infill densities	DPP with incorporation of in-built porosity providing higher surface area enables manufacture of rapid release dosage forms.	(Fanous et al., 2020)
	BJ	Tablets with highly porous microstructure	BJ can produce fast disintegrating, highly porous tablets containing either large doses of hydrophobic drug or small doses of hydrophilic drug. Specific extended-release profiles were achieved by modulating the percentage of crosslinkable polymers in tablets.	(Kozakiewicz-Latala et al., 2022)
Extended release	SLA	Torus-shaped tablets	The multi-compartment tablets containing three model drugs showed over 90 % release from the outer layer, over 70 % release from the middle layer and only 40 % from the core after 4 h.	(Wang et al., 2016)
Varying release rates	BJ and DoD	Modular tablets with outer layer, middle layer and core	Extended release API 1 and immediate release API 2 with two pulses were constructed in separate compartments. In vitro and in vivo evaluations demonstrated the release profiles and absorption patterns as design.	(Lu et al., 2022)
	MED®	Multi-compartment tablet		(Zheng et al., 2021)
Zero order release	FDM	Tablets with core-shell structure	Tablets with drug core and lateral insoluble shells achieved tunable, zero-	(Fina et al., 2020)

Table 2 (continued)

Kinetics/ Mode	Technique	Structure	Description	Reference
Delayed release	FDM	Tablets with core-shell structure	order release kinetics.	(Melocchi et al., 2021b)
			Drug core with the gastroresistant coat and soluble/erodible coat showed delayed release onset in vitro, which has potential for colon-targeted delivery.	
Pulsatile release	FDM	Tablets with drug-free loop in the middle	In vitro and in vivo evaluations demonstrated the pulsatile release and absorption pattern of the printed tablets.	(Kadry et al., 2018)

FDM: fused deposition modelling; DDP: direct powder printing; BJ: binder jetting; SLA: stereolithography; DoD: drop-on-demand; MED: melt extrusion deposition; API: active pharmaceutical ingredient.

populations.

The ability to adjust doses not only for pediatric patients in general, but to customize the dose for an individual pediatric patient can result in improved therapeutic outcomes. The ability of 3D printing to produce customized doses for individual pediatric patients with a rare disease (Maple Syrup Urine Disease) was recently demonstrated, with improved management of the patient condition as compared to more traditional compounding techniques (Goyanes et al., 2019).

2.3.3. Additional special applications of 3D printing

One can imagine a myriad of special applications of dosage forms produced by 3D printing that can improve delivery, patient acceptance, patient usability and outcomes. One example is wearable personalized oral delivery devices that are fit to an individual. Liang and colleagues developed a “mouthguard” produced by 3D printing that serves as a tunable release drug eluting device (Liang et al., 2018). As another example, patients with vision loss can be challenged in assuring they have selected the correct medication for administration. Using 3D printing methods, researchers have developed Braille imprinted, drug impregnated intraoral films to assist patients in identifying the correct drug dosage form (Awad et al., 2020; Eleftheriadis and Fatouros, 2021). These are just a few examples of innovative drug dosage forms that can be produced by 3D printing to either aid patient acceptance and usage, while improving therapeutic outcomes.

3D printing techniques, including photopolymerization and extrusion methods, have also been utilized to produce microneedle systems for transdermal drug delivery (Economidou and Douroumis, 2021, Li et al., 2022). Transdermal microneedles potentially allow for the administration of poor oral bioavailability molecules, such as macromolecules, proteins and DNA, as well as vaccines through permitting compound access to the dermal microcirculation. These microneedles can be either drug-loaded or non-drug-loaded. In the case of drug-loaded microneedles, they can be solid with a drug coating, hollow wherein the drug is in the supporting structure and passes through the hollow needle to the skin or the needle can be drug-containing but dissolvable. Non-drug loaded microneedles can be used to pierce the skin and followed by administration of a drug-containing patch. Photopolymerization techniques, including SLA and DLP, are able to produce the necessary resolution for the development of sharp enough microneedles but can be slow and expensive. These techniques may also have challenges in removing unreacted substance and side reactions with API. Extrusion

methods result in a lower resolution but can be less expensive and more efficient for production. Both methods have been shown to be effective in drug delivery but mass production will require development of more cost-effective and higher capacity methods. Much research continues in this promising application of 3D printing.

3. Accelerating Early-Stage drug development with 3D printing

3D printing technology can accelerate early-stage drug development through simplification of formulation development and facilitation of early clinical studies. With respect to formulation development, 3D printing can be combined with modeling and prediction tools, such as machine learning and artificial intelligence. Furthermore, an efficient 3D printing-based Formulation by Design approach has been developed as a reliable tool for formulation development. These features enable fast prototyping as well as a high degree of flexibility in changing doses. With respect to early clinical studies, 3D printing flexibility and scalability makes it convenient to produce small batches of varying formulations/doses supporting rapid and efficient conduct of clinical trials.

3.1. Predictive formulation development for 3D printed dosage forms using modeling, machine learning and artificial intelligence techniques

Due to the digital design and construction of 3D printing, modeling and predictive work have been performed to accelerate formulation development. Since 3D printing technology enables precise construction of structure of dosage forms, it is possible to rapidly achieve the desired target release profile with the aid of mathematical modeling. Zheng et al. have constructed a series of compartment-containing tablets with a water-insoluble shell and hydroxypropyl cellulose based metoprolol loaded core using MED® 3D printing technology (Zheng et al., 2021). With the supporting structure of the shell, the drug core dissolved layer-by-layer via a surface erosion mechanism. The surface area of the drug core was the key factor determining the drug release profile. When the surface area remained constant for each core layer, metoprolol release followed zero-order release kinetics and the rate was consistent with the theoretical predictions. Furthermore, the tablets designed with stepwise changes in surface area exhibited a stepwise change in release rate. Eight models with different changes in surface area, including stepwise decreasing, continuous decreasing, increasing-decreasing, etc., were proved to match the predicted target release. A linear relationship ($R^2 = 0.9832$) was observed, demonstrating that actual metoprolol release rate was directly proportional to the surface area of the exposed layer from which metoprolol can be released. Therefore, it is feasible to achieve challenging release profiles with 3D printed multilayered tablets using mathematical modeling, which enables fast prototyping and accelerates the formulation development.

Determining the optimal combination of excipients that are not only compatible with the API but result in the desired release characteristics can be a time-consuming and many times, empiric process. Until recently, this was especially true for 3D printed formulations, since formulators had less experience with these newer techniques and the matrix was, in many cases, different. For example, creating drug-loaded filaments for FDM printing is very different than creating a traditional tablet or capsule formulation. Likewise, creating pastes for extrusion printing brings new challenges not typically encountered in powders for compression tableting. Fortunately, several innovations in recent years have taken a substantial portion of the guesswork out of this process and greatly expanded the opportunity for a broader range of users making the 3D printing formulation process less dependent on individual subject matter experts in each laboratory and increasing the possibility of personalized medicine formulations to be accomplished in clinics and hospitals by trained technical personnel.

One of the resources providing formulation information and advice that can be utilized in 3D printing formulation development is the BASF Zoomlab ("BASF Zoomlab"). Using an advanced algorithm, the Virtual

Pharma Assistant Zoomlab™ helps formulators select the optimal excipients for a given API. By inputting the properties of the API and the desired target profile the algorithms suggest the optimal excipients for API compatibility and performance in achieving the desired target profile. One can also input chemistries of excipients to help guide the algorithms in excipient selection or virtually make tweaks to the formulation and see the predicted results of those changes in excipient selection or percentage of the composition. This process allows for testing many combinations virtually, reducing the need for numerous laboratory tests and purchase of expensive excipients. This software algorithm was originally developed for conventional formulations but also has applicability in 3D printing applications.

More specific to 3D printed formulations, several methodologies have been developed to assess the compatibility and performance of excipient-API combinations, predict release profiles, assess printability, and predict internal tablet structures that would result in the desired release profile. A substantial body of this work has involved application of artificial intelligence (AI) and machine learning (ML) methods to the assessment of potential 3D printing formulations and predicting optimal formulation composition. Comprehensive reviews of the application of AI/ML to 3D printing of pharmaceuticals have recently been published (Elbadawi et al., 2021a, 2021b), so a few selected examples of the application of these methodologies and their utility will be highlighted here.

Recently, a ML methodology was developed to predict filament performance and printability, printing conditions, as well as the expected dissolution profile based on 968 formulations mined from 114 publications using FDM techniques (Muñiz Castro et al., 2021). Input parameters for forming the filament from the hot melt extrusion process included extruder type, extrusion speed, extrusion temperature, extrusion torque and filament mechanical characteristics. For the actual FDM printing, the printer brand and type, nozzle diameter, printing speed, printing temperature, platform temperature and whether the formulation was printable or not, were input. Finally, the components of the formulation were input, including their percent composition. Information about the object printed, shape of the object, dimensions of the object (Length × Width × Height), weight, layer thickness, the type of shell, thickness of the shell, and percentage infill were mined from the articles and input, as well. Drug solubility in water was either obtained from the article or from literature values. Finally, any available information about dissolution testing and the accompanying results were included in the model. Using ML with an artificial neural network, important parameters for printing and dissolution characteristics were predicted with good accuracy. Filament mechanical characteristics and printability were predicted with an accuracy of 94 %. Extrusion temperatures were predicted within ± 5 °C and printing temperature within ± 6.87 °C. Finally, and impressively, the T20, T50 and T80 dissolution times were predicted within ± 24.29 min. At least for FDM processes, this methodology demonstrates great potential to speed the formulation development process by reducing trial and error testing of different configurations of process and composition.

These same investigators have also developed a web-based software program (Elbadawi et al., 2020), M3DISEEN, that allows formulators to select a molecule or input their molecule, select from a broad list of excipients and predict the FDM printability and filament characteristics and the hot melt extrusion and FDM printing temperatures for the API-excipients combination. This software uses AI and ML techniques to analyze and monitor a large set of data related to the APIs, excipients and printing parameters. To populate the dataset, 614 drug-loaded formulations were designed, printed and assessed in house using 145 different pharmaceutical excipients. Information from 75 % of the formulations were used as the training set and the remaining 25 % used as the testing set. The AI generated model predicted printability with an accuracy of 76 % and filament characteristics with an accuracy of 67 %. The hot melt extrusion temperature was predicted with a mean absolute error of 8.9 °C and the FDM processing temperature was predicted with

an absolute error of 8.3 °C. This user-friendly software can produce accurate results by inputting only the trade names of the excipients, in addition to the API, including an estimate of the dissolution profile. By altering the composition of the components, one can readily observe any predicted changes in the dissolution profile. Again, for FDM users producing pharmaceuticals, this software has the potential to greatly reduce the number of iterations and testing necessary to achieve the desired performance characteristics.

Most of this predictive work has focused on optimizing the excipient-API combinations for performance and printability or predicting the API release profile from a given set of excipients and a pre-determined tablet structure. However, more recently researchers have developed AI methods for predicting the internal tablet structure, or in some cases multiple structures, that should result in the desired release profile (Grof and Štěpánek, 2021). These investigators used an Evolutionary Algorithm method for predicting tablet structure(s). Even though 3D printing methods can produce an almost limitless number of tablet structures, patient preferences and acceptability were considered. Limitations were placed on the algorithm with respect to external tablet shape (cylindrical) and tablet size (compact within typical patient preferences). When considering two-dimensional configurations, the tablets were designed to only release from the sides of the tablet and not from the top or bottom. In the case of three-dimensional designs, the tablets were also constrained to release from the top and sides. Using combinations of fast- and slow-dissolving sections and sections with and without API, this methodology was able to predict tablet configurations expected to produce different release profiles, including immediate release, delayed release and stepwise release of API. Though these predictions were not tested in actual tablet preparations to assess performance of the algorithm predictions, the methodology may provide a useful tool for designing tablet internal structures to achieve desired release profiles. Recently, Ong et al., reported increased performance in predicting optimal formulation characteristics using both in-house and literature-mined data from HME and FDM 3D printed formulations (Ong et al.,

2022). The dataset contained 1594 formulations with a more heterogeneous set of HME outcomes (i.e., both positive and negative results). The optimized ML models predicted the printability (i.e., whether filaments could be extruded through nozzles) and filament characteristics resulting in positive outcomes with higher accuracy than previously reported. These results demonstrated the importance of having a data rich and balanced outcome dataset for optimal ML performance.

3.2. Accelerating formulation development using formulation by design

Choosing the right excipients and a tablet structural design can be a challenging process that requires extensive formulation knowledge. Excipients should provide the desired performance characteristics (e.g., easily tableted, provide the desired disintegration rate, compatibility with the API, etc.). Tablet structure can affect achievement of the desired PK profile. This is true for both conventional tablet formulations, as well the formulation of 3D printed tablets. To address this challenge, a novel process, 3D Printing Formulation by Design (3DPfD®), has been developed by incorporating physicochemical and biopharmaceutical properties of API and excipients and tablet structural information to determine the optimal formulation (Zheng et al., 2021). Because 3D printing is capable of creating structures to control the release rate, duration and mode, formulation variables can be defined to reduce the uncertainty common in traditional formulation processes. Therefore, the Formulation by Design process has shifted the traditional empirical based approach to a rational design process. This process is graphically depicted in Fig. 2. The approach begins by establishing the desired in vivo target pharmacokinetic profile and then working backwards to determine the tablet in vitro release profile that would be required to achieve this PK profile. Physiological parameters, such as GI transit time, location of absorption, etc., are then used to determine the release mode required, the onset of release and the rate of release, and relatedly, the amount of drug required to be released at different time intervals over the course of absorption. From a database of known tablet

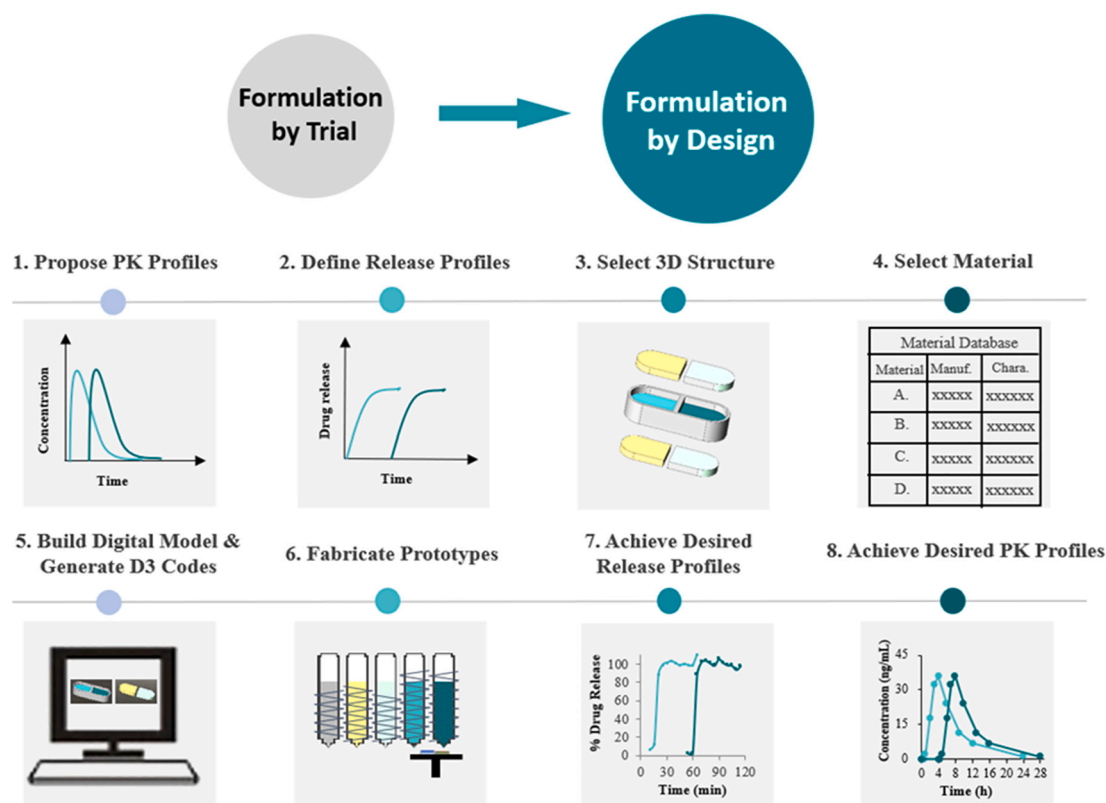


Fig. 2. Schematic Diagram of 3D Printing Formulation by design (3DPfD®) Approach. Reproduced with permission from Zheng et al., 2021.

structures that produce the desired modes, rates and onset times of release, the tablet structure is selected. In the case of 3D printing, the construction of the tablet structure is aided through a “stackable approach” to including tablet elements, much like stacking Legos to build a structure. In this way, tablet structures that produce complex release profiles can be constructed with relative ease. Once the tablet structure is selected, excipients with the required physicochemical characteristics to facilitate tablet construction and performance as well as API compatibility are chosen from a database of pharmaceutical excipients and Generally Recognized as Safe (GRAS) materials. Once the tablet structure and excipients are selected, the appropriate software code can be generated to print prototypes of the formulation, allowing rapid testing, both in vitro and in vivo, for evaluation of its performance. Even if small tweaks are required, because of the flexibility and small batch capabilities of 3D printing, these changes can be made in hours, rather than days or weeks. In application of these methods, Zheng et al. used 3DFBD® and 3D printing to achieve the desired in vitro dissolution profile and target in vivo PK results (Zheng et al., 2021). This approach is particularly powerful when used with 3D printing techniques, since release profiles can be tuned to a much greater degree and with more precision and accuracy than with conventional tablet formulation techniques.

3.3. Increasing efficiency of early Phase human studies with 3D printing technology

In early phase (e.g., Phases I and II) human studies, generally small batches of drug product are required. However, even with smaller volume traditional tableting equipment, a substantial amount of active pharmaceutical ingredient (API) may be required due to the inherent capacity of the equipment that requires a minimum quantity to operate. In addition, runs of several hundred tablets may be necessary given these capacity issues and inherent fill capacities. This can result in significantly more drug product to be made than the required number of units for the trial, being both very labor and material intensive. For instance, a first-in-human Phase I trial of 20 subjects might only require preparation of 30 or so tablets of a given strength. Since these studies are typically single ascending dose trials, then another 30 tablets of each additional dosage strength are then required. If the minimum production batch size is a few hundred tablets (conventional equipment), then a significant amount of API is required and excess drug product is produced, increasing both cost and waste.

However, 3D printing technologies offer unique advantages that can be leveraged to address these shortcomings (Kipping et al., 2022). Smaller, low capacity, low volume 3D printers are commonplace and can produce from a single tablet from very small drug substance batch sizes and because of their flexibility can then be employed to produce only the number of tablets required. Also, because of the additive nature of 3D printing, tablet size and/or amount of API added can be rapidly adjusted, even from tablet to tablet, therefore, tablets of different strengths can be easily produced. Thus, one can readily prepare small batches (e.g., 20–30 tablets) of differing dosage strengths for clinical testing. Because this process is on-demand production lead time is reduced, thus shortening the development cycle. This flexibility and small volume production can greatly reduce the amount of API required and therefore greatly reduced cost and waste. To facilitate multiple dose Phase I trials, or even larger Phase II trials, these printers can readily make several hundred to a thousand tablets a day, providing ample drug product for conducting the trials. Furthermore, the flexibility of 3D printers allows for rapid assessment of potential commercial formulations in Phase II trials. In demonstration of the potential utility of producing clinical trial material by 3D printing, it has been estimated that companies may be able to save as much as 70 % of the cost for tablet production in early clinical trials, including API savings of up to 50 % and a 60 % savings in time (Huls, 2021).

This concept may be further advanced through achieving even

greater efficiency in facilitating the conduct of adaptive clinical trials. In adaptive trials, a drug in development is administered to 3–4 subjects at a given dose and plasma samples are collected, which are then rapidly (sometimes overnight) analyzed for drug concentrations. Then, the next dose to be given is based on a pre-determined algorithm wherein based on the observed plasma concentrations, the subsequent dose may be increased beyond the next planned dose level if the drug is not detectable or below the threshold concentration. This process is repeated, with subsequent dose levels again determined based on the algorithm and the measured plasma concentrations. Once the target concentrations are achieved, a larger cohort of subjects is then given the dose level of the drug and the dose escalated from that point to the pre-determined maximum dose or concentration. Using this design, one may reduce the number of dose levels required and the number of subjects who must be exposed to the drug without meaningful results. Given the above-mentioned advantages of 3D printing (on-demand, flexible dosage strength production, small batches), this technology can greatly facilitate the conduct of adaptive clinical trials, saving even more resources and time.

Finally, the value of 3D printing techniques in accelerating clinical trials has been demonstrated through formulations that can be rapidly and easily formulated to control drug release onset and thus, assess the region of GI absorption for modified release products (Smith et al., 2018). Though oral formulations, such as “powder in a bottle” have been used extensively to test first in human dosing, these immediate release formulations are not as useful if the final product does not possess ideal biopharmaceutical properties or is expected to be modified release. Even if one uses them for the first in human trial for expected modified formulations, it is frequently necessary to study the regional absorption of the modified release form for achievement of the desired pharmacokinetic profile. To make multiple modified release formulations and test each individually with conventional methods is both time consuming and expensive. To address this bottleneck, a process has been developed wherein a hollow “capsule” is 3D printed via FDM with varying wall thicknesses to achieve varying levels of delay of drug release (Smith et al., 2018). The capsule is partially constructed leaving a hollow center, through the opening the hollow center is filled with either dry API powder or the API in liquid form and the capsule then completed. In the case of inclusion of API in powder form, the filling is conducted manually, whereas for liquid filling, the liquid API is simply extruded through a print nozzle. Apart from the value of being able to easily control release onset, this methodology also solves the potential issue of formulating the drug substance into the filament, which can require several iterations and be time consuming. Instead, the same filament can be used for the construction of all capsules and the API in either solid or liquid form is included within, obviating any need to formulate the API into the filament for extrusion substantially shortening the development time and effort. Using this design, in vitro and in vivo (animal) studies were conducted and a good in vitro – in vivo correlation was observed. A similar concept has recently been reported by Aprexia Pharmaceuticals, ZipCup™, wherein the top and bottom (cup) of the tablet are formed, the API can then be inserted into the bottom and the two components sealed to provide a complete dosage form (Smith, 2021; Yoo, 2021).

4. Progress in 3D printing technologies and their potential in pharmaceutical large-scale manufacturing and personalized dosing

4.1. Advantages of 3D printing in large-scale manufacturing

Though the benefits of 3D printing in the production of small-scale batches and prototyping of pharmaceutical formulations or the production of personalized medicine for individuals is readily recognized, there are many advantages of 3D printing in large-scale manufacturing, particularly with recent advances in 3D printing technology. A graphical representation of the advantages described below is presented in Fig. 3.

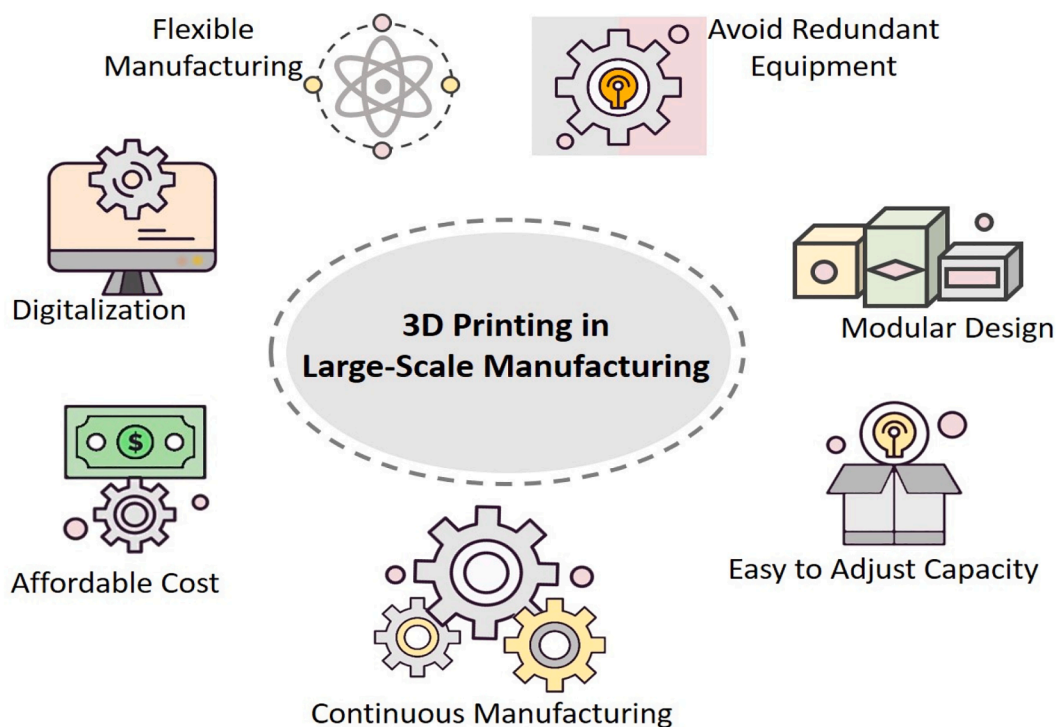


Fig. 3. Advantages of 3D Printing in Large-Scale Manufacturing.

The enhanced flexibility of 3D printing machines allows for a reduced need of redundant equipment, equipment with differing capacities or even some specialized formulation/tableting equipment. Equally important to pharmaceutical production is the ability to construct tablets or other dosage forms that conventional manufacturing processes cannot. When moving from very small prototype batches to small clinical trial batches, to large clinical trial batches to full-scale commercial manufacturing, at least three and sometimes four different pieces of tableting equipment with different capacities are required. Furthermore, mixing and blending machines of different capacities are required to produce batch sizes appropriate for each tableting machine's capacity. This creates significant redundancies, especially if each piece of equipment is not in continuous use. Because of the capacity range of 3D printing equipment, one can use as few as two 3D printers to cover this entire range of formulation batch sizes. A small-scale machine can readily produce batches of only a few tablets for early formulation testing but be easily scaled to produce several thousand tablets for larger clinical trials without requiring equipment modification or changeover. A second commercial scale machine can then produce millions of tablets a year to meet commercial demand. In addition to batch size issues, the flexibility of 3D printing equipment in being able to produce tablets of different shapes, sizes and release profiles all through software control of the final product, reduces the need for multiple and sometimes custom tablet dies and punches, which are sometimes unique to each tableting machine.

3D printing equipment can be developed in a modular design, allowing for several benefits. Multiple modules can readily be "daisy-chained" to increase capacity quickly and easily, or to produce multiple smaller batches and reduce space requirements. Furthermore, a modular design facilitates rapid equipment substitution in the case of need for repairs or even cleaning, with a module easily swapped in without requiring complete equipment shutdown or overhaul.

With the increasing focus on digitalization of the pharmaceutical manufacturing process, 3D printing is ideally suited for these efforts. With the entire production process software-controlled, the ability to have real-time Process Analytical Technology (PAT) and the application of Supervisory Control and Data Acquisition (SCADA) enabling real-

time, traceable data for each individual tablet, 3D printing manufacturing can greatly facilitate these digitalization efforts.

Admittedly, early 3D printing efforts were expensive on a per tablet basis making commercialization challenging. However, recent advances in capacity and throughput, new printing techniques, the ability to implement continuous manufacturing and streamlining of the production process have greatly reduced the per tablet cost of goods sold (cost of tablet production minus the API cost). To this end, the cost of 3D printing manufacturing has now become affordable on a per tablet basis and is comparable to more conventional tableting techniques. One must take a holistic view and compare all processes between the tablet compression step and printing step. Comparison of the two processes should start from the weighing of raw materials all the way to the finished product. Using MED® 3D printing technology, the production rate has been shown to be equivalent to or potentially higher than the production rate of coated tablets for a 150 kg batch over 72 h of production. Using Screen Printing Innovative Drug (SPID®) Technology, a reported production capacity of up to 1,500,000 units per day can be achieved.

Pharmaceutical manufacturers have been somewhat hesitant to implement continuous manufacturing techniques due to uncertainty regarding potential issues that might arise during the regulatory review process. However, a recent FDA audit of timeline to approval for drugs produced by continuous manufacturing as compared to conventional production processes reported that there were no apparent regulatory barriers associated with drugs produced with continuous manufacturing methods and that the mean and median times to approval were eight and three months shorter, respectively, as compared to drugs manufactured with conventional methods (Fisher et al., 2022). The 3D printing process and equipment is well-suited to take advantage of continuous manufacturing processes. In-line mixing/blending is easily accomplished with 3D printing with a direct transfer of material to the formulation deposition orifice. Product is then formed either directly in the packaging or onto a build plate where it can be seamlessly packaged online. In addition, the use of individual blister packs for packaging provides an ideal unit wherein a bar code or QR code can be affixed, again within the continuous process, allowing for traceable data to be

included with each individual tablet. This traceable data can include real-time PAT derived information, providing data on key quality information such as tablet weight, API content, etc. This real-time data can facilitate real-time release testing (RTRT), except for dissolution testing. This integrated, real-time manufacturing process has the potential to provide not only equivalent, but potentially improved product quality, real-time tracking and monitoring of the production process and the manufacturing product, thereby increasing real-time quality assessment and oversight. This automation of the process requires minimal intervention by operators, reducing personnel costs and the potential human error. Finally, continuous manufacturing can also reduce ingredient waste, for excipients as well as the much more costly API, which with the reduction in personnel costs can have a substantial, positive impact on overall product cost.

4.2. Current status of large-scale manufacturing with 3D printing technologies

4.2.1. Powder-based methods

Powder-binding 3D printing was the first process design that produced tablets on a commercial scale. This process was used to produce the first FDA approved and commercially marketed 3D printed pharmaceutical, Spritam®, produced by Aprelia Pharmaceuticals. Besides allowing sufficient production capacity to meet commercial needs, the technique allows full control over external tablet geometry and some control over internal tablet geometry. One can include the API in the powder bed, or if the dose is low enough and the API soluble in the printing fluid, then the API can be deposited within the binding fluid. This latter advantage, inclusion of the API in the print fluid, is particularly beneficial for very low dose APIs, obviating the need for trying to assure homogeneous mixing of a small amount of API with a large amount of powder.

This process is “powder-intensive” and any API-containing powder that was not “printed” with the binding fluid must either be recycled or discarded, resulting in reduced efficiency and potentially wastage of API. A recent advancement has been reported wherein the tablet is printed directly within the blister cavity, potentially reducing powder waste. For orodispersible tablets, such as Spritam®, these tablets must be packaged in individual blisters to avoid tablet breakage as they are more friable than typical tablets. These orodispersible characteristics also can reduce the pharmaceutical elegance of the tablets, since the minimum amount of binding fluid is added producing tablets that resulted in a less smooth surface. Finally, tablets produced by powder-binding methods require both drying, since many layers of printing fluid are deposited, and frequently require some form of de-dusting to remove excess powder. This step of removing excess powder can be an issue for reproducibility of drug content, particularly for very potent APIs. Aprelia also developed the second generation of orodispersible drug delivery platform ZipCup™. This technology accepts more diverse payloads, which may have different drug release kinetics, while maintaining high drug loading capacity and rapid disintegration (Smith, 2021; Yoo, 2021).

Merck KGaA has also evaluated laser sintering/powder bed fusion 3D printing methods for large scale commercialization, reporting a potential daily production volume of 100,000 tablets per day (Huls, 2021) using this method. Laser sintering can produce tablets with very fine structures, allowing for enhanced tablet appearance. Their work demonstrated the utility for production of clinical trial batches and the associated cost and time savings, but also the capability of production levels suitable for commercial scale manufacturing. Since no solvent is involved in the production, the need for post-processing is eliminated, however, the issue of excess powder and whether to recycle the powder (containing API) or send it to waste remains. The compatibility of photocurable resins and drugs should be ensured to avoid unwanted chemical reactions between the drugs and the resins.

4.2.2. Extrusion-based methods

Though extrusion deposition methods (including filament deposition) have garnered the most research focus, as demonstrated by the number of publications, they have traditionally been seen as more applicable to the production of small batches, such as clinical trial supplies, or for personalized medicine due to the slow print speed and limited daily production. However, recent advances in equipment design and process improvements have made it possible to achieve commercial scale production with these methods. Typically, extrusion methods have utilized a single nozzle for deposition of material resulting in production of one tablet at a time. However, using a nozzle array design and a melt extrusion methodology (MED®) Triastek has reported the capability of a daily output of 150–200,000 tablets per day (Li, 2022) overcoming the limitations of a single nozzle design. Though theoretically achievable, these levels of production volume have not yet been reported with FDM equipment. An advantage of extrusion methods is the obviation of the need for post-formation processing since there is no liquid solvent to require drying and no dusting of excess powder. This allows for direct handling of the tablets immediately after formation for PAT analysis and packaging. However, with extrusion methods, since they are usually conducted at elevated temperatures the thermostability of the API must be considered. To address this issue, TNO (The Netherlands Organization) has begun to explore scale up manufacturing of low temperature melt extrusion printing (Aulbers, 2021), resulting in two patents (Rijfers et al., 2021a, 2021b).

4.2.3. Screen printing methods

More recently, Laxxon Medical has reported on the use of Screen Printing Innovative Drug (SPID®) Technology with the capability of producing tablets, film, implants, transdermal patches with novel drug formulations, galenic and novel geometric structures (Moldenhauer et al., 2021; Schneeberger et al., 2018). The company reports a very high production capacity of up to 1,500,000 units per day, approaching the capacity of traditional tableting methods. In 3D screen printing a mesh screen with open areas in the shape of the desired tablet/formulation is laid down and a semi-solid paste containing the API is applied. In this way, material is only retained in the designated areas where tablets are to be formed. The deposited layer is dried, the screen removed, and the process repeated. The process does involve drying of each layer before depositing another layer of material. However, the size and dimensions of the screen allow thousands of tablets to be produced at a time resulting in a very high potential production volume, despite this need for drying. Because no heat is required, the thermostability of the API is not of concern. Laxxon has also reported the ability to integrate QR codes directly on each dosage form, permitting the tracking of information on each tablet (Enke et al., 2022).

4.3. Key considerations in large-scale manufacturing

Though significant advances have been made to demonstrate the utility of 3D printing for large scale drug manufacturing, some potential issues will need to be addressed for adoption throughout the industry. Certainly, production volume will remain a key issue since drug companies will want to be assured they can produce enough of a given product and that enough redundancy in capacity exists in case of mechanical breakdown or other factors disrupting production. This may necessitate 3D printing manufacturers to have multiple machines or machines in multiple locations to assure no interruption of production. The cost-of-goods-sold (cost of producing the tablet minus the API cost) will also be a concern and in many ways is directly related to production capacity. Even with the ability to achieve drug release and pharmacokinetic profiles not possible with conventional technology, companies will desire the lowest possible cost production of each tablet to maximize profitability.

The 3D printing of commercial products will also require tight control over the quality and consistency of the product, particularly since

the product may involve complex tablet structures that could be challenging to produce with quality and consistency. This puts great emphasis on the results of validation batches, development of key quality attributes, monitoring of these attributes and the processes that may affect the attributes. A recent paper from 3D printing experts in academia, industry and regulatory agencies has highlighted the critical technical aspects of FDM that can affect the quality of drug products (Melocchi et al., 2021a). Additional published work (Macedo et al., 2022) has also described this kind of work as applied to FDM production of drug product, measuring the production of batches of 30 tablets with two different printers containing either a 0.4 mm or 0.7 mm nozzle. These authors evaluated tablet mass, drug content, density and dissolution properties, as well as thermal (differential scanning calorimetry) and spectroscopic (near IR and FT-IR) properties. They observed no significant differences in most of the parameters, except for tablet mass which was hypothesized to be due to deviations in filament diameter. In general, the tablets produced with the 0.4 mm nozzle exhibited less variability for the parameters measured. More studies of this type will be required to demonstrate quality and consistency of 3D printing at the point-of-care.

4.4. Advantages of 3D printing in personalized dosing

While the advent of 3D printing of pharmaceuticals has the potential to revolutionize large-scale manufacturing, an equally, if not more meaningful impact may be in the opportunities to produce small but personalized batches for truly personalized dosing. Because small-scale 3D printers are portable and can be made relatively easy to operate, they can be placed in pharmacies, hospitals, long-term care facilities, military field hospitals, rural areas or isolated regions or even patient's homes to provide point-of-care manufacturing. This distributed manufacturing model could allow medications to be custom-made for individual patients and doses adjusted as necessary beyond the traditionally limited dosage range provided by large-scale manufacturing. For instance, a patient being treated for deep vein thrombosis with warfarin therapy and who experiences substantial changes in INR (international normalized ratio; a measure of clotting) with small dosage changes could be adjusted to receive for instance, 4.3 mg of warfarin instead of the commercially available 5 mg tablet based on the patient's body weight, liver and renal function as well as associated genotypes. This fine-tuning of dose is especially critical for narrow therapeutic index drugs, like warfarin (Rettie and Tai, 2006). One can think of several drugs for which this kind of dose personalization could be beneficial, even more so for certain patient populations, such as pediatric patients, geriatric patients or patients with rare diseases.

AI also can play a significant role in personalized medicine (Fig. 4). One can imagine the use of AI to coalesce and analyze patient-specific clinical data for therapeutic drug monitoring and to suggest the optimal dose, to choose the optimal formulation based on patient needs (e.g., chewable vs solid oral tablet, modified release vs immediate release, etc.), to choose a formulation that allows multiple medications

within the same tablet to simplify dosing and to interface with diagnostic and clinical information specific to the individual patient. In this way, a sort of continuous feedback loop can be created to constantly adjust and optimize drug therapy based on a patient's characteristics over time.

4.5. Current status of 3D printing for personalized dosing

FabRx has developed the M3DIMAKER™ 3D printer for the production of personalized medicines ("M3DIMAKER Pharmaceutical 3D Printer", 2022) and more recently announced a next generation machine, Mark II M3DIMAKER with multi-nozzle, higher throughput and greater automation. The extrusion-based printer (can be equipped with either FDM, SSE or Direct Powder Extrusion) has a footprint sufficiently small to permit placing the device in a clinic, hospital, pharmacy, etc. for on-demand, point-of-care manufacturing of pharmaceuticals. In-line quality control is provided to allow real-time monitoring and product release, including a camera to detect tablet defects. To assure that only authorized users can operate the system, fingerprint access control and a data matrix reader provide security against unauthorized use. The developers have reported that tablets (Printlets™) can be produced in ~7–17 s depending on the formulation and the extrusion technique (Goyanes, 2022; Rodríguez-Pombo et al., 2022). In a further advancement of point-of-care manufacturing, FabRx has developed a printer, operating on SLA principles, which uses the light from the smartphone's screen to photopolymerise liquid resins from which solid tablet structures are formed (Xu et al., 2021). A custom app on the phone is used to determine the shape of the tablets to be printed. More recently, DiHeSys has announced the development of a 3D printer, the FlexDosePrinter, which can digitally print personalized medications in hospitals and pharmacies (Franken, 2022). In this instance, the APIs can be contained in either the filament or the inks.

Several recent announcements of either completed or planned clinical trials have been made to demonstrate the utility of point-of-care 3D printing of pharmaceuticals. The team from FabRx completed the first clinical study using personalized 3D printed dosage forms to treat children with Maple Syrup Urine Disease, a rare metabolic disorder (Goyanes et al., 2019). This study demonstrated good patient acceptance and equal, if not better, control of key parameters associated with the disease. This same group recently announced an agreement with Gustave Roussy to develop personalized, multi-drug dosage forms for the treatment of early-stage breast cancer ("FabRx and Gustave Roussy Enter into an Agreement" 2021). These efforts will not only include creating new 3D printed dosage forms but will also involve conducting clinical trials to compare the effectiveness and acceptability of these new dosage forms to conventional drug therapy. Finally, TNO (The Netherlands Organization) has announced a collaboration with clinicians at the Erasmus MC Sophia Children's Hospital in Rotterdam to explore the application of 3D printed tailored dosages for children ("Making customised medication", 2021). These examples demonstrate acceleration of the application of 3D printing in point-of-care applications and the increasing utility of the technology.

4.6. Challenges of 3D printing in personalized dosing

Despite the great potential of 3D printing in personalized medicine, the path to widespread adoption will require that several important issues be addressed. When the production of personalized medicines by 3D printing is carried out in a distributed manner in non-cGMP facilities, the issue of quality control arises. These issues include but are not limited to assuring that the right drug substance is being printed, assuring that the right amount of drug substance is printed, physical integrity of the drug product and assuring the right amount of tablets is printed, particularly if the drug product were to be printed at the patient's private home. Because there is no formal process for assuring these key quality attributes are achieved, as occurs in cGMP bulk

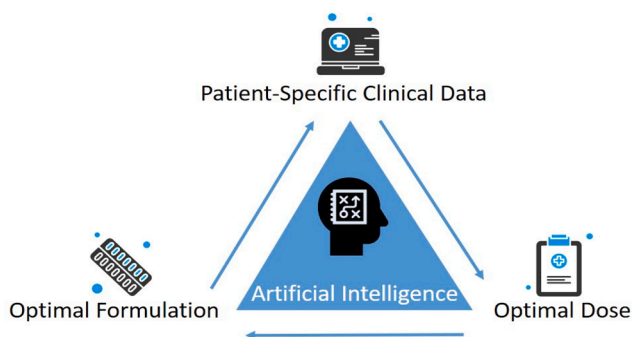


Fig. 4. Potential Application of AI in Personalized Medicine.

manufacturing, these issues take on great importance. Equipment will need to have robust, real-time PAT for monitoring these and other key quality attributes. Furthermore, depending on the location of the equipment, professional remote monitoring may be necessary to avoid misuse or abuse of the printing process and subsequent products produced. As discussed briefly below in the section of regulatory issues, regulatory agencies are working on a framework for guidance in these areas that can help to address some of the needs and solutions.

5. Regulatory aspects of 3D printed drug products

5.1. Requirements of safety, efficacy and quality for 3D printed drug products

Though the techniques for producing tablets may differ with 3D printing technology, the approval of Spritam®, as well as recent presentations by regulatory officials (Zidan and O'Connor, 2022), demonstrated that the regulatory and expected quality framework is the same regardless of the method of manufacture. Thus, sponsors bringing forth 3D printed products for regulatory approval may need to clearly demonstrate to agencies any unique processes or testing requirements, e.g., differences in friability and hardness testing for orodispersible tablets, but the overall regulatory framework within which the sponsor will be evaluated and thus, should prepare its submission package remain the same as with other oral dosage forms.

5.2. Innovative regulatory agency teams to address emerging technologies

The FDA has formed the Emerging Technology Team (ETT), as a cross-functional group with representation from all relevant quality assessment and inspection programs of the agency. The ETT has developed a framework and clear objectives for how it will operate, what services it will provide to sponsors accepted into the program and goals for facilitating interaction of the sponsor and the agency as a whole (Zidan and O'Connor, 2022).

This ETT framework and accompanying objectives can be extremely beneficial to sponsors developing new technologies, such as 3D printing, in helping navigate the regulatory process and provide valuable information to the agency for evaluating new products produced by 3D printing. Over the course of the engagement with the ETT, activities may include: Early engagement and discussions on the technology and proposed product, Emerging Technology site visits, Integrated quality assessments or Pre-approval inspections. In this way, a constant and consistent dialogue is achieved leading to more and better information for both the applicant and the agency. A similar organization has been developed by the European Medicines Agency (EMA), entitled the Innovation Task Force (ITF), which is similarly structured and likewise, assists sponsors with new technology very early in the development process. 3D printing is also included as a type of advanced manufacturing technologies included within ITF's interests.

To assist sponsors who are implementing new technology in the development of pharmaceutical products, in 2017, FDA published Guidance for Industry – Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization (FDA/CDER, 2017). This guidance document describes the ETT and its role but also gives sponsors insights into the agency's preferences for engaging and interacting with sponsors. For a more complete description of the innovative drug manufacturing processes, such as 3D printing, including technical challenges and regulatory issues the reader is directed to a recent publication by the National Academies of Sciences, Engineering, and Medicine (NASEM), produced upon request of the Center for Drug Evaluation and Research of FDA entitled "Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations" (National Academies of Sciences, Engineering, and Medicine, 2021).

With respect to personalized medicine and point-of-care

manufacturing, in the United States this likely falls within the Food and Drug Administration's 503A and 503B sections of the Food, Drug and Cosmetic Act (FDA, 2020). If an extemporaneously compounded formulation is prepared, for instance by 3D printing, pursuant to a prescription written for a specific patient, it is likely that this would not fall under the cGMP manufacturing requirements and thus, personalized doses and dosage forms could be printed and dispensed for an individual patient. The option of applying section 503B also exists, wherein an "outsourcing facility" could either compound (e.g., 3D print) a formulation pursuant to a health care facility's request a specially formulated or unique dose of a medication under cGMP requirements or produce a formulation specific to an individual patient and pursuant to a valid prescription without being required to follow cGMP. Similarly, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK has embarked on a project of "innovation regulation" and launched consultation on point of care manufacturing which could facilitate the decentralized application of 3D printing ("Consultation on Point of Care manufacturing", 2021).

6. Summary

A significant body of work has been developed to advance the use of 3D printing techniques to produce pharmaceuticals. As these efforts have advanced, additive manufacturing technology has demonstrated not only the potential of producing personalized/individualized products for specific patients but has also become a new manufacturing option for the large-scale production. Because 3D printing can produce dosage form designs with performance characteristics difficult to create with conventional methods, the ability to now bring these unique advantages to the mass-produced products has the potential to improve drug efficacy and/or reduce adverse events, which should lead to improved patient outcomes. The continued advances within 3D printing research community will lead to new solutions for both patients and pharmaceutical industry.

CRedit authorship contribution statement

Timothy Tracy: Writing – original draft, Writing – review & editing. **Lei Wu:** Writing – original draft, Writing – review & editing. **Xin Liu:** Project administration, Writing – review & editing. **Senping Cheng:** Funding acquisition, Writing – review & editing. **Xiaoling Li:** Conceptualization, Writing – review & editing.

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.

Data availability

Data will be made available on request.

References

- National Academies of Sciences, Engineering, and Medicine; Division on Earth and Life Studies; Board on Chemical Sciences and Technology; Committee to Identify Innovative Technologies to Advance Pharmaceutical Manufacturing, 2021. Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations. National Academies Press (US), Washington (DC).
- Aulbers, A., 2021. Digital Drug Manufacturing: Tomorrow's Medicine Enabled Through 3D Printing. Presented at the 3DP Pharma Tech Forum. Virtual Conference.
- Awad, A., Fina, F., Trenfield, S.J., Patel, P., Goyanes, A., Gaisford, S., Basit, A.W., 2019. 3D Printed Pellets (Miniprintlets): A Novel, Multi-Drug, Controlled Release Platform Technology. *Pharmaceutics* 11, E148. <https://doi.org/10.3390/pharmaceutics11040148>.

- Awad, A., Yao, A., Trenfield, S.J., Goyanes, A., Gaisford, S., Basit, A.W., 2020. 3D printed tablets (printlets) with braille and moon patterns for visually impaired patients. *Pharmaceutics* 12 (2), 172. <https://doi.org/10.3390/pharmaceutics1202172>.
- Awad, A., Fina, F., Goyanes, A., Gaisford, S., Basit, A.W., 2021. Advances in powder bed fusion 3D printing in drug delivery and healthcare. *Advanced Drug Delivery Reviews* 174, 406–424. <https://doi.org/10.1016/j.addr.2021.04.025>.
- BASF Zoomlab, <http://www.zoomlab.com> (accessed 8.7.22).
- Charoenying, T., Patrojanasophon, P., Ngawhirunpat, T., Rojanarata, T., Akkaramongkolporn, P., Opanasopit, P., 2020. Fabrication of floating capsule-in-3D-printed devices as gastro-retentive delivery systems of amoxicillin. *J. Drug Deliv. Sci. Technol.* 55, 101393 <https://doi.org/10.1016/j.jddst.2019.101393>.
- Cui, M., Pan, H., Su, Y., Fang, D., Qiao, S., Ding, P., Pan, W., 2021. Opportunities and challenges of three-dimensional printing technology in pharmaceutical formulation development. *Acta Pharm. Sin. B* 11, 2488–2504. <https://doi.org/10.1016/j.apsb.2021.03.015>.
- FabRx And Gustave Roussy Enter Into An Agreement To Develop A Novel, Personalised, Multi-Drug Dosage Form For The Treatment Of Patients With Early-Stage Breast Cancer, 2021. *FabRx*. URL <https://www.fabrx.co.uk/2021/06/25/fabrx-and-gustave-roussy-enter-into-an-agreement-to-develop-a-novel-personalised-multi-drug-dosage-form-for-the-treatment-of-patients-with-early-stage-breast-cancer/> (accessed 8.7.22).
- Economidou, S.N., Douroumis, D., 2021. 3D Printing as a transformative tool for microneedle systems: Recent advances, manufacturing considerations and market potential. *Adv. Drug. Del. Rev.* 173, 60–69. <https://doi.org/10.1016/j.addr.2021.03.007>.
- Elbadawi, M., Muñiz Castro, B., Gavins, F.K.H., Ong, J.J., Gaisford, S., Pérez, G., Basit, A. W., Cabalar, P., Goyanes, A., 2020. M3DISEEN: A novel machine learning approach for predicting the 3D printability of medicines. *Int. J. Pharm.* 590, 119837 <https://doi.org/10.1016/j.ijpharm.2020.119837>.
- Elbadawi, M., McCoubrey, L.E., Gavins, F.K.H., Ong, J.J., Goyanes, A., Gaisford, S., Basit, A.W., 2021a. Harnessing artificial intelligence for the next generation of 3D printed medicines. *Adv. Drug Deliv. Rev.* 175, 113805 <https://doi.org/10.1016/j.addr.2021.05.015>.
- Elbadawi, M., McCoubrey, L.E., Gavins, F.K.H., Ong, J.J., Goyanes, A., Gaisford, S., Basit, A.W., 2021b. Disrupting 3D printing of medicines with machine learning. *Trends Pharmacol. Sci.* 42, 745–757. <https://doi.org/10.1016/j.tips.2021.06.002>.
- Eleftheriadis, G.K., Fatouros, D.G., 2021. Haptic Evaluation of 3D-printed Braille-encoded Intraoral Films. *Eur. J. Pharm. Sci.* 157, 105605 <https://doi.org/10.1016/j.ejps.2020.105605>.
- Enke, M., Kuhne, K., Seyferth, S., Fischer, D., Schneeberger, A., 2022. 3D Screen Printing Enables Application of Integrated QR Codes on Pharmaceutical Dosage Forms in Mass Production – A Game Changer. *Biomed. J. Sci. Tech. Res.* 41 <https://doi.org/10.26717/BJSTR.2022.41.006630>.
- Fanouf, M., Gold, S., Muller, S., Hirsch, S., Ogorka, J., Imanidis, G., 2020. 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, 119124 <https://doi.org/10.1016/j.ijpharm.2020.119124>.
- Fastö, M.M., Genina, N., Kaae, S., Kälveback Sporrang, S., 2019. Perceptions, preferences and acceptability of patient designed 3D printed medicine by polypharmacy patients: a pilot study. *Int. J. Clin. Pharm.* 41, 1290–1298. <https://doi.org/10.1007/s11096-019-00892-6>.
- FDA, 2020. Compounding Laws and Policies.
- FDA/CDER/Purdie, F.P., 2017. Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization.
- Fina, F., Goyanes, A., Rowland, M., Gaisford, S., W. Basit, A., 2020. 3D Printing of Tunable Zero-Order Release Printlets. *Polymers* 12, 1769. <https://doi.org/10.3390/polym12081769>.
- Fisher, A.C., Liu, W., Schick, A., Ramanadham, M., Chatterjee, S., Brykman, R., Lee, S.L., Kozlowski, S., Boam, A.B., Tsiontides, S.C., Kopcha, M., 2022. An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US. *Int. J. Pharm.* 622, 121778 <https://doi.org/10.1016/j.ijpharm.2022.121778>.
- Franken, C., 2022. 3DP - Market Approaches. Presented at the 3DP Tech Forum. Virtual Conference.
- Goh, W.J., Tan, S.X., Pastorin, G., Ho, P.C.L., Hu, J., Lim, S.H., 2021. 3D printing of four-in-one oral poly pill with multiple release profiles for personalized delivery of caffeine and vitamin B analogues. *Int. J. Pharm.* 598, 120360 <https://doi.org/10.1016/j.ijpharm.2021.120360>.
- Consultation on Point of Care manufacturing [WWW Document]. GOV.UK. 2021. URL <https://www.gov.uk/government/consultations/point-of-care-consultation/consultation-on-point-of-care-manufacturing> (accessed 8.7.22).
- Goyanes, A., 2022. Extrusion 3D Printing in a Clinical Setting. Presented at the 3DP Tech Forum, Virtual Conference.
- Goyanes, A., Scarpa, M., Kamlow, M., Gaisford, S., Basit, A.W., Orlu, M., 2017. Patient acceptability of 3D printed medicines. *Int. J. Pharm.* 530, 71–78. <https://doi.org/10.1016/j.ijpharm.2017.07.064>.
- Goyanes, A., Madla, C.M., Umerji, A., Duran Piñeiro, G., Giraldez Montero, J.M., Lamas Diaz, M.J., Gonzalez Barcia, M., Taherali, F., Sánchez-Pintos, P., Couce, M.-L., Gaisford, S., Basit, A.W., 2019. Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: First single-centre, prospective, crossover study in patients. *Int. J. Pharm.* 567, 118497 <https://doi.org/10.1016/j.ijpharm.2019.118497>.
- Grof, Z., Štěpánek, F., 2021. Artificial intelligence based design of 3D-printed tablets for personalised medicine. *Comput. Chem. Eng.* 154, 107492 <https://doi.org/10.1016/j.compchemeng.2021.107492>.
- Huls, C., 2021. Digitalizing the Production of Pills. ONLINE 3D Medical Printing Conference.
- Januskaite, P., Xu, X., Ranmal, S.R., Gaisford, S., Basit, A.W., Tuleu, C., Goyanes, A., 2020. I Spy with My Little Eye: A Paediatric Visual Preferences Survey of 3D Printed Tablets. *Pharmaceutics* 12, E1100. <https://doi.org/10.3390/pharmaceutics12111100>.
- Jeong, H.M., Weon, K.-Y., Shin, B.S., Shin, S., 2020. 3D-Printed Gastroretentive Sustained Release Drug Delivery System by Applying Design of Experiment Approach. *Mol. Basel Switz.* 25, E2330. <https://doi.org/10.3390/molecules25102330>.
- Kadry, H., Al-Hilal, T.A., Keshavarz, A., Alam, F., Xu, C., Joy, A., Ahsan, F., 2018. Multipurpose filaments of HPMC for 3D printing of medications with tailored drug release and timed-absorption. *Int. J. Pharm.* 544, 285–296. <https://doi.org/10.1016/j.ijpharm.2018.04.010>.
- Karavasili, C., Zgouro, P., Manousi, N., Lazaridou, A., Zacharis, C.K., Bouropoulos, N., Moschakis, T., Fatouros, D.G., 2022. Cereal-based 3D printed dosage forms for drug administration during breakfast in pediatric patients within a hospital setting. *Adv. Drug. Del.* 111, 2562–2570. <https://doi.org/10.1016/j.xphs.2022.04.013>.
- Khaled, S.A., Burley, J.C., Alexander, M.R., Yang, J., Roberts, C.J., 2015. 3D printing of five-in-one dose combination poly pill with defined immediate and sustained release profiles. *J. Control. Release.* 217, 308–314. <https://doi.org/10.1016/j.jconrel.2015.09.028>.
- Kipping, T., Price, D., Huls, C., 2022. Innovations in 3D Printing for Solid Dosage Forms. Kozakiewicz-Latała, M., Nartowski, K.P., Dominik, A., Malec, K., Gołkowska, A.M., Złocińska, A., Rusińska, M., Szymczyk-Ziółkowska, P., Ziółkowski, G., Górniak, A., Karolewicz, B., 2022. Binder jetting 3D printing of challenging medicines: From low dose tablets to hydrophobic molecules. *Eur. J. Pharm. Biopharm.* 170, 144–159. <https://doi.org/10.1016/j.ejpb.2021.11.001>.
- Li, R., Zhang, L., Jiang, X., Li, L., Wu, S., Yuan, X., Cheng, H., Jiang, X., Gou, M., 2022. 3D-printed microneedle arrays for drug delivery. *J. Control. Rel.* 350, 933–948. <https://doi.org/10.1016/j.jconrel.2022.08.022>.
- Li, X., 2022. Melt Extrusion Deposition (MED) 3D Printing: An Emerging Technology for Pharmaceutical Applications. Presented at the 3D Printing in Pharmaceutical Development: History, Current Landscape and the Future., Chinese Biopharmaceutical Association. Virtual Conference.
- Liang, K., Carbone, S., Brambilla, D., Leroux, J.-C., 2018. 3D printing of a wearable personalized oral delivery device: A first-in-human study. *Sci. Adv.* 4, eaat2544. <https://doi.org/10.1126/sciadv.aat2544>.
- Lu, A., Zhang, J., Jiang, J., Zhang, Y., Giri, B.R., Kulkarni, V.R., Aghda, N.H., Wang, J., Maniuzzaman, M., 2022. Novel 3D Printed Modular Tablets Containing Multiple Anti-Viral Drugs: A Case of High Precision Drop-on-Demand Drug Deposition. *Pharm. Res.* <https://doi.org/10.1007/s11095-022-03378-9>.
- M3DIMAKER Pharmaceutical 3D Printer. *FabRx*. <https://www.fabrx.co.uk/technologies/> (accessed 8.5.22).
- Macedo, J., da Costa, N.F., Vanhoorne, V., Vervaeke, C., Pinto, J.F., 2022. The Precision and Accuracy of 3D Printing of Tablets by Fused Deposition Modelling. *J. Pharm. Sci.* S0022-3549 (22), 00198–00208. <https://doi.org/10.1016/j.xphs.2022.05.006>.
- Making customised medication with a 3D printer [WWW Document]. TNO. URL <https://www.tno.nl/en/tno-insights/articles/making-customised-medication-with-a-3d-printer/> (accessed 8.7.22).
- Melocchi, A., Briatico-Vangosa, F., Ubaldi, M., Parietti, F., Turchi, M., von Zeppelin, D., Maroni, A., Zema, L., Gazzaniga, A., Zidan, A., 2021a. Quality considerations on the pharmaceutical applications of fused deposition modeling 3D printing. *Int. J. Pharm.* 592, 119901 <https://doi.org/10.1016/j.ijpharm.2020.119901>.
- Melocchi, A., Ubaldi, M., Briatico-Vangosa, F., Moutaharrik, S., Cerea, M., Foppoli, A., Maroni, A., Palugan, L., Zema, L., Gazzaniga, A., 2021b. The Chronotropic™ System for Pulsatile and Colonic Delivery of Active Molecules in the Era of Precision Medicine: Feasibility by 3D Printing via Fused Deposition Modeling (FDM). *Pharmaceutics* 13, 759. <https://doi.org/10.3390/pharmaceutics13050759>.
- Mohammed, A., Elshaer, A., Sareh, P., Elsayed, M., Hassanin, H., 2020. Additive Manufacturing Technologies for Drug Delivery Applications. *Int. J. Pharm.* 580, 119245 <https://doi.org/10.1016/j.ijpharm.2020.119245>.
- Moldenhauer, D., Nguyen, D.C.Y., Jescheck, L., Hack, F., Fischer, D., Schneeberger, A., 2021. 3D screen printing - An innovative technology for large-scale manufacturing of pharmaceutical dosage forms. *Int. J. Pharm.* 592, 120096 <https://doi.org/10.1016/j.ijpharm.2020.120096>.
- Muñiz Castro, B., Elbadawi, M., Ong, J.J., Pollard, T., Song, Z., Gaisford, S., Pérez, G., Basit, A.W., Cabalar, P., Goyanes, A., 2021. Machine learning predicts 3D printing performance of over 900 drug delivery systems. *J. Control. Release.* 337, 530–545. <https://doi.org/10.1016/j.jconrel.2021.07.046>.
- Ong, J.J., Castro, B.M., Gaisford, S., Cabalar, P., Basit, A.W., Pérez, G., Goyanes, A., 2022. Accelerating 3D printing of pharmaceutical products using machine learning. *International Journal of Pharmaceutics: X* 100120. <https://doi.org/10.1016/j.ijpx.2022.100120>.
- Patel, S.K., Khoder, M., Peak, M., Alhnan, M.A., 2021. Controlling drug release with additive manufacturing-based solutions. *Adv. Drug Deliv. Rev.* 174, 369–386. <https://doi.org/10.1016/j.addr.2021.04.020>.
- Ragelle, H., Rahimian, S., Guzzi, E.A., Westenskow, P.D., Tibbitt, M.W., Schwach, G., Langer, R., 2021. Additive manufacturing in drug delivery: Innovative drug product design and opportunities for industrial application. *Adv. Drug Deliv. Rev.* 178, 113990 <https://doi.org/10.1016/j.addr.2021.113990>.
- Rettie, A.E., Tai, G., 2006. The pharmacogenomics of warfarin: closing in on personalized medicine. *Mol. Interv.* 6, 223–227. <https://doi.org/10.1124/mi.6.4.8>.
- Rijfers, A., Brouwers, L., Verhoeven, G., 2021a. An Extrusion Print Head for Printing a Viscous Material. *WO* 2021 (177820), A1.
- Rijfers, A., Brouwers, L., Verhoeven, G., Penbrouwers, M., 2021b. A Print Head Module and Printer. *WO* 2021 (158102), A1.

- Rodríguez-Pombo, L., Xu, X., Seijo-Rabina, A., Ong, J.J., Alvarez-Lorenzo, C., Rial, C., Nieto, D., Gaisford, S., Basit, A.W., Goyanes, A., 2022. Volumetric 3D printing for rapid production of medicines. *Addit. Manuf.* 52, undefined-undefined. <https://doi.org/10.1016/j.addma.2022.102673>.
- Sadia, M., Sośnicka, A., Arafat, B., Isreb, A., Ahmed, W., Kelarakis, A., Alhnan, M.A., 2016. Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets. *Int. J. Pharm.* 513, 659–668. <https://doi.org/10.1016/j.ijpharm.2016.09.050>.
- Schneeberger, A., Seyferth, S., Fischer, D., 2018. Scalable 3D Screen Printing Technology in Pharmaceutical Manufacturing - High Degree of Freedom in Terms of Drug Choice. *Arch. Dent.* 3, 19–21.
- Sen, K., Mehta, T., Sansare, S., Sharifi, L., Ma, A.W.K., Chaudhuri, B., 2021. Pharmaceutical applications of powder-based binder jet 3D printing process - A review. *Adv. Drug Deliv. Rev.* 177, 113943 <https://doi.org/10.1016/j.addr.2021.113943>.
- Seoane-Viaño, I., Trenfield, S.J., Basit, A.W., Goyanes, A., 2021. Translating 3D printed pharmaceuticals: From hype to real-world clinical applications. *Advanced Drug Delivery Reviews* 174, 553–575. <https://doi.org/10.1016/j.addr.2021.05.003>.
- Smith, D., Kapoor, Y., Hermans, A., Nofsinger, R., Kesiosoglou, F., Gustafson, T.P., Procopio, A., 2018. 3D printed capsules for quantitative regional absorption studies in the GI tract. *Int. J. Pharm.* 550, 418–428. <https://doi.org/10.1016/j.ijpharm.2018.08.055>.
- Smith, K., 2021. Material compatibility in 3D printing. Presented at the ONLINE 3DP Pharma Tech Forum, Purdue University, West Lafayette, IN.
- Trenfield, S.J., Awad, A., Madla, C.M., Hatton, G.B., Firth, J., Goyanes, A., Gaisford, S., Basit, A.W., 2019. Shaping the future: recent advances of 3D printing in drug delivery and healthcare. *Expert Opin. Drug Deliv.* 16, 1081–1094. <https://doi.org/10.1080/17425247.2019.1660318>.
- Wang, J., Goyanes, A., Gaisford, S., Basit, A.W., 2016. Stereolithographic (SLA) 3D printing of oral modified-release dosage forms. *Int. J. Pharm.* 503, 207–212. <https://doi.org/10.1016/j.ijpharm.2016.03.016>.
- Wang, N., Shi, H., Yang, S., 2022. 3D printed oral solid dosage form: Modified release and improved solubility. *J. Control. Release.* 351, 407–431. <https://doi.org/10.1016/j.jconrel.2022.09.023>.
- Wu, B.M., Borland, S.W., Giordano, R.A., Cima, L.G., Sachs, E.M., Cima, M.J., 1996. Solid free-form fabrication of drug delivery devices. *J. Control. Release* 40, 77–87. [https://doi.org/10.1016/0168-3659\(95\)00173-5](https://doi.org/10.1016/0168-3659(95)00173-5).
- Xu, X., Seijo-Rabina, A., Awad, A., Rial, C., Gaisford, S., Basit, A.W., Goyanes, A., 2021. Smartphone-enabled 3D printing of medicines. *Int. J. Pharm.* 609, 121199 <https://doi.org/10.1016/j.ijpharm.2021.121199>.
- Yoo, J., 2021. Why 3DP for Pharma today? Patient focused opportunities and challenges. Presented at the ONLINE 3DP Pharma Tech Forum.
- Zheng, Y., Deng, F., Wang, B., Wu, Y., Luo, Q., Zuo, X., Liu, X., Cao, L., Li, M., Lu, H., Cheng, S., Li, X., 2021. Melt extrusion deposition (MED™) 3D printing technology - A paradigm shift in design and development of modified release drug products. *Int. J. Pharm.* 602, 120639 <https://doi.org/10.1016/j.ijpharm.2021.120639>.
- Zidan, A.S., O'Connor, T., 2022. Quality Considerations of 3D Printing of Drug Products: ETT Collaborative Approach for Fostering Innovation. Presented at the 3DP Pharma Tech Forum, Virtual Conference.