A Review of State-of-The-Art on Enabling Manufacturing Processes for Precision Medicine

Atheer Awad
UCL School of Pharmacy, University College London, UK
atheer.awad.15@ucl.ac.uk

Alvaro Goyanes
UCL School of Pharmacy, University College London, UK
a.goyanes@ucl.ac.uk

Abdul W. Basit
UCL School of Pharmacy, University College London, UK
a.basit@ucl.ac.uk

Ahmed S Zidan
Food and Drug Administration, US
Ahmed.Zidan@fda.hhs.gov

Changxue Xu
Department of Industrial Engineering, Texas Tech University, US
changxue.xu@ttu.edu
ASME Member

Wei Li
Walker Department of Mechanical Engineering, University of Texas, US
weiwli@austin.utexas.edu
ASME Fellow

Roger J. Narayan
Department of Materials Science and Engineering, North Carolina State University, US
roger_narayan@ncsu.edu
ASME Fellow

Roland K. Chen[1]
School of Mechanical and Materials Engineering, Washington State University, US
roland.chen@wsu.edu
ASME Member

[1] Corresponding author

ABSTRACT

Precision medicine is an emerging healthcare delivery approach that considers variability between patients, such as genetic makeups, in contrast to the current one-size-fits-all approach that is designed to treat the average patient. The White House launched the Precision Medicine Initiative in 2015, starting an endeavor to reshape healthcare delivery. To translate the concept of precision medicine from the bench to practice, advanced manufacturing will play an integral part, including fabrication of personalized drugs and drug delivery devices, and drug screening platforms. These products are highly customized and require robust yet flexible manufacturing systems. The advanced manufacturing field has rapidly evolved in the past five years. In this state-of-the-art review, products manufactured for precision medicine will be introduced, followed by a brief review on processing materials and their characteristics. A review on different manufacturing processes applicable to those aforementioned products is provided. The current status of the development of regulatory submission and quality control considerations are also discussed. Finally, this paper presents a future outlook on manufacturing processes used for precision medicine.

Keywords: Precision medicine, personalized medicine, 3D printing, additive manufacturing, drug delivery

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1. INTRODUCTION

Precision medicine (PM) is a novel healthcare approach that considers variability between patients' genetic makeups, behaviors, and lifestyles; all of which affect their pharmacokinetic and pharmacodynamic responses to medications. Due to that, the PM model involves the personalization of healthcare interventions and treatments to meet the individual requirements, needs and preferences of each patient [1]. This concept has

gained considerable attention following the implementation of the Precision Medicines Initiative in the U.S. in 2015, wherein an increased movement of treatments away from a 'one-size-fits-all' approach towards customization has been observed [2]. Although solid oral dosage forms, such as tablets and capsules, are traditionally mass-produced in a limited number of dose strengths, forms, and sizes [3], these dosages are not suitable for use in all patient groups. This is mainly due differences in the genetic profile, disease state, gender, age and weight of each patient, which together determine their individual therapeutic needs [4,5].

Three-dimensional (3D) printing is an additive manufacturing technique that has recently reinvigorated several industries, including automation, aviation, engineering, and medicine [6–10]. Within pharmacy, 3D printing is set to streamline a new generation of personalized medicine, wherein small batches of customized 3D printed tablets, patches and devices are design using computer-aided design (CAD) software and produced on-demand at the point-of-care. The adoption of such healthcare model will likely be advantageous for multiple purposes on the front-line patient care. This includes providing benefits to certain patient groups with strict therapeutic needs (*e.g.*, requiring particular dosing regimen, dosage forms or sizes). As an example, owing to their unique physical and pharmacokinetic properties, both pediatric and geriatric patients have specific dosing needs that could significantly vary from those of typical adult patients [11]. Moreover, both patient subgroups are usually known for being incapable or reluctant to swallow medications.

Normally to obtain optimal doses, patients and carers often tend to crush or split tablets with higher dose strengths. However, these drug manipulations could have negative impacts related to inaccurate dosing [12,13] or could potentially lead to dose dumping in the case of modified-release formulations [14,15]. In this regard, printing pharmaceutical dosage forms could offer a suitable alternative to overcome the associated issues. In particular, tailored formulations could be designed with precise drug content and specifications that meet the individual needs and preferences of each patient [16]. These tailored drugs could involve 3D printed tablets with different shapes, sizes and colors [17] or in the form of various patient-friendly formulations, such as chewable formulations [18], fast-dissolving tablets [19–22] or orodispersible films [23]. Thus, healthcare professionals would be able to dispense medications safely and potentially improve patient adherence to treatment plans whilst minimizing unwanted adverse events [3].

With geriatric patients, printing pharmaceuticals could offer additional benefits to those suffering from multiple chronic diseases and are on a polypharmacy (i.e., the usage of five or more different medications concurrently) [24]. This is because such a complex medical regime could affect patient adherence to medicines or lead to medication errors [25]. As 3D printing has the ability to precisely deposit substances in predetermined positions based on the 3D designs of the dosage form, it can be used to create polypills containing numerous drugs and/or doses, which in turn can be administered to concurrently treat the same condition [26] or combined as a treatment for multiple illnesses [27].

3D printing of pharmaceuticals could also safeguard the dispensing of narrow therapeutic index drugs (i.e., drugs that have minute intervals between their minimum effective dose and their minimum toxic dose), which if dosed inaccurately could lead to ineffective therapy or elicit toxic side effects [3]. Therefore, rather than modifying existing dosage forms, it is more convenient and accurate for healthcare professionals to directly design and prepare 3D printed tablets with the specified drug content and release properties [28]. This ensures that the correct dose is being delivered to the patient with the simplest dosing regime and chances of errors or variability in therapeutic effect are reduced. Similarly, 3D printing could be exploited to facilitate the administration of medications that require flexibility in dosing, such as those that need to be quickly titrated at the start or end of the treatment plan (*e.g.*, prednisolone [29] and budesonide [28,30]).

3D printing is foreseen to be seamlessly integrated with other digital health technologies, such as internet of things [31–33], 3D scanning, [34–37], smartphone technologies [38], artificial intelligence (AI) and machine learning (ML) [39–44], permitting the adoption of closed-loop healthcare systems that can remotely communicate and function together. As an example, healthcare professionals can remotely monitor patients' vitals using wireless sensors [45–49], enabling them to adjust treatments based on their real-time disease states [50][1]. Such a modification could be wirelessly sent to the patient in the form of an electronic prescription. With 3D imaging and scanning technologies, tailored implants and devices can be created to fit the specific body measurements of each patient. Elsewhere, AI and ML may be used to aid health care professionals in designing dosage forms that are specific to each patient. With everything

turning digital, perhaps in the future, patients will be empowered to use their own smartphones to operate the 3D printers and obtain their medicines on-demand.

According to the American Society for Testing and Materials (ASTM), there are seven main 3D printing technologies (Figure 1) [51], which depending on the principles underpinning them can be grouped into four different categories; (I) extrusion based, (II) jetting-based, (III) photopolymerization-based, and (IV) powder-based technologies. Although each of these technologies have different starting materials and energy sources, they all share the common feature of creating objects in a layer-by-layer manner. Depending on the nature of the processes and resolution of each printing system, a variety of different pharmaceutical products can be produced. Herein, this review will provide a timely summary of the different products and additive manufacturing technologies commonly used for PM applications. The overall manufacturing system and quality control measures that require implementation are also discussed. In addition, the current regulatory perspective is provided, with a forward-thinking view of the future of this technology being offered.

2. PRODUCTS MANUFACTURED FOR PRECISION MEDICINE

2.1 Solid oral dosage forms

Several studies have evaluated the use of 3D printing for the preparation of various personalized solid oral dosage forms, including tablets [52–55], capsules [56–58] and films [59–61]. Oral 3D printed tablets with diverse drug doses and release properties can be prepared, wherein the modification in the drug release can be attained by fine-tuning

different printing parameters [62]. Furthermore, depending on the 3D printing technology used, 3D printed tablets with different physical and chemical properties can be produced. The end-product's appearance, perceived taste, texture and familiarity could all impact the visual preference and acceptability of patients to medications [63]. As such, when formulating 3D printed tablets, it is not only essential to select the most suitable printing parameters needed to acquire the desired therapeutic effect, but to also consider patients' preferences.

3D printed tablets of different shapes and sizes tend to have different drug release properties, depending on their surface area-to-volume ratios [64]. As an example, when five different shapes, including a cube, a pyramid, a cylinder, a sphere and a torus, were evaluated, *in vitro* dissolution studies have shown that the fastest drug release was obtained from the pyramid 3D printed tablets, whereas, the cylindrical 3D printed tablets exhibited the slowest drug release properties [65]. Additionally, it has been shown that patients have preferences to picking and swallowing tablets of certain shapes and sizes, both of which could affect their compliance to medications (Figure 2A) [17]. Alternatively, the drug release properties can be controlled by modifying the internal structure of the 3D printed tablets. Typically, 3D printed tablets with solid interiors tend to have slower drug release patterns compared to hollow ones [66]. In other cases, 3D printed tablets with modified internal arrangements can be designed to accelerate the drug release. These can be in the form of gyroid lattices (Figure 2B) [67], radiator -like [68] or channelled tablets (Figure 2C) [20]. In other approaches, the drug release characteristics were modified by changing the polymer matrix composition. This enabled obtaining various

drug release properties, including orally disintegrating (Figure 2D), immediate-release [69–71], sustained-release [72–74] and delayed-release (Figure 2E) [75–77] formulations.

Unlike other pharmaceutical production methods, 3D printing allows the precise spatial disposition of materials, facilitating the fabrication of a vast array of polypills in multi-drug or dose combinations [78–81]. This has been demonstrated using multiple 3D printing technology, wherein the number of drugs included in a single polypill ranged between two [82] to six drugs (Figure 3A) [27]. The actives do not have to necessarily release simultaneously and can instead be separated in different compartments when compatibility is an issue [83,84]. Moreover, such a compartmentalization concept is not only applicable to large solid oral dosage forms but can also extend to smaller formulations. As an example, the high precision of the laser-based 3D printing technologies can be exploited for the preparation of small 3D printed pellets containing two spatially separated drugs (Figure 3B) [85]. Such intricate dosage forms are suitable for administration to patients from different age groups, including pediatric and geriatric patients, both of which often have difficulty swallowing large oral dosage forms. As alternative, chewable dosage forms with different shapes, colors and flavors can be designed to contain single [18,86–88] or multiple actives [89].

The high precision and flexibility of 3D printing has also been explored as a potential way to tailor medications based on the physical needs and disease state of patients. For instance, blind patients often suffer from the inability to recognize and differentiate medications, especially when taken out from their original packaging. In this regard, 3D printing offers a novel and sophisticated way that allows the printing of tactile patterns

directly onto the surface of tablets, enabling blind and visually impaired patients to identify medications independently (Figure 3D) [90,91]. 3D printing could also be used as a way for controlling or limiting drug abuse. This can be achieved by fabricating abuse-deterrent and alcohol-resistant formulations, wherein these formulations can have immediate [92] or sustained-release characteristics [93].

Apart from personalization, 3D printing has been suggested as an alternative way to mass manufacture tablets with properties that cannot be attained with conventional production methods. In fact, Spritam®, the world's only 3D printed medicine to be approved by the United States (U.S.) Food and Drug Administration (FDA), has been developed for this purpose. This drug product that contains up to 1 g of levetiracetam has been produced using the ZipDose technology (i.e., a binder jetting process) and has the unique property of being able to disintegrate within seconds in presence of just small amounts of liquid [94]. Such fast disintegration properties are normally challenging to obtain using traditional direct compression devices, especially with formulations containing such high drug content.

2.2 Devices: diagnostic/monitoring, implants, drug eluting devices

The ability of 3D printing to be easily combined with 3D scanning and imaging technologies has made it well suited for the fabrication of patient-specific devices. Such devices can be employed for rehabilitation and restoration purposes [36,95–97], wherein the additional tailoring angle makes it more durable and comfortable for the patient, ensuring appropriate fitting and maximizing its efficiency [98]. Moreover, due to the

ability to control the internal structures of the devices, porous prosthesis or lattice-structured medical casts, which are both, light in weight and mechanically strong, can be created [95,99]. These can be comfortably utilized and handled by patients, whilst providing sufficient mechanical support. An example of such is the Osteoid™ cast which apart from the above-mentioned advantages offers the ability to promote bone healing by 38% (Compared to standard plaster casts) using its low-intensity pulsed ultrasound (LIPUS) waves system [99].

The digital nature of 3D printing, makes the technique amenable to interconnection with other digital health technologies, including remote diagnostic and data analysis tools. In this regard, multiple 3D printed devices have been described for diagnostic and drug monitoring purposes [46], which can be applied for pre-clinical and clinical uses. Within pre-clinical applications, 3D printed sensors for bio-signal monitoring in animal models (*e.g.*, Zebrafish [100]) have been described. These can be used to optimize the device performance based on the animal model studied and speed up the collection of data. Within clinics, real-time patient data can be remotely obtained and monitored by clinicians, enabling emergency interventions and early detection of diseases or relapses. These devices can be used to sample gut content (*e.g.*, gut microbiome [101]) or quantify drug and chemicals (*e.g.*, nimesulide, dopamine and uric acid [102]) in blood serum and urine of patients. Alternatively, the blood vessel pressure can be monitored using a 3D printed stent that wirelessly communicates with a semiconductor [103]. This stent is both biocompatible and biodegradable, enabling it to be safely implanted in patients, where the stent naturally dissolves over time. More recently, a 3D printed electronic sensor that

can be directly printed at the point-of-care has been described [104]. The device is used for the identification of the antipsychotic drug quetiapine fumarate in urine samples and can be readily used following its printing, without the need for post-treatment.

A number of different 3D printed implants have been fabricated. These include implants for tissue and bone regeneration [105–107] and cancer treatment [108,109]. Herein, in some cases, the metallic nature of the implants provides an intrinsic antimicrobial effect [110], whilst in other cases additional antibiotics are loaded onto the implants to prevent bacterial colonization [111,112]. In the latter case, the drug release properties can be fine-tuned by altering the 3D design (*e.g.*, microstructure) and printing parameters employed during the fabrication process [113]. As an example, it has been shown that due to the highly porous 3D printed implants, it is possible to achieve an antimicrobial effect that is four times higher than that of analogous solid structures [110].

In terms of drug-eluting devices, a myriad of examples have been described. For instance, a 3D printed bladder device for intravesical delivery of lidocaine hydrochloride has been reported (Figure 4A) [114]. The device was designed to adopt a temporary configuration that allows insertion into and retrieval from the bladder using a urethral catheter. Once inside the bladder, a continuous therapy over 14 days was achieved, after which the device was retrieved. Alternatively, some devices can spontaneously dissolve on their own following the complete drug release [115]. Similarly, bespoke anti-biofilm 3D printed hearing aids containing the two drugs ciprofloxacin and fluocinolone acetonide were fabricated for the treatment of ear infections (Figure 4B) [116]. In the same vein, a wirelessly-controlled 3D printed drug delivery device for the inner ear was also reported

[117]. The device has shown to be suitable for subcutaneous implantation in mice for up to six months, with potential applications in human and other animal models. Within the field of dermatology, nose masks and ear devices were 3D printed from patient 3D scans as anti-acne therapy [35] and wound dressings [34]. The tailoring of these devices allowed for improved adherence and prolonged coverage of the treatment site.

By including an electronic component, it possible to create wireless 3D printed gastro-retentive devices, capable of simultaneously controlling the release of different drugs from separate reservoirs (Figure 4C) [118]. Such a device can reside in the stomach whilst providing wireless communication for up to 15 days. Once disintegrated, the device exits through the pylorus and is excreted. Another device used for local drug delivery was an implantable 3D printed drug reservoir device used for the treatment of acute liver failure (Figure 4D) [119]. This reservoir system is composed of a drug container that was covered with a semi-permeable membrane connected to a port that constantly supplies drug directly to the site of action.

Within dentistry, wearable oral devices that are tailored to each patient have been suggested [37]. These devices can be tuned to achieve desired release properties, whereby the drug release can be maintained for up to 14 consecutive days. In the field of radiology, 3D printed drug-eluting catheters were created containing gentamicin sulphate and methotrexate, wherein they have shown a sustained antimicrobial activity for up to 5 days [120]. Drug-eluting stents for the treatment of obstructive salivary gland disease were also fabricated using 3D printing [121]. The stents were loaded with amoxicillin and

cefotaxime, whereby both drugs were released in a sustained manner and provided an effective antimicrobial activity.

Other examples of drug-laden devices include devices for intrauterine drug delivery, which can be used for different applications such as the treatment of vaginal atrophy, endometrial and ovarian cancers, pelvic organ prolaps contraception, stress urinary incontinence, regulation of the menstrual cycle and as hormone replacement therapy [122–125]. These devices can be in the form 3D printed rings, pessaries, meshes or rods and are typically loaded with different hormones including progesterone, estrone, estradiol and estriol. Similarly, punctal plugs for controlled ocular drug delivery have been developed [126]. The devices were created using DLP 3D printing and were loaded with dexamethasone (Figure 4E). The drug release from the punctal devices was sustained over a period of 7 to 21 days, depending on the composition of the resin formulation.

2.3 Drug testing models

In vitro drug testing models are highly sought after for drug discovery and personalized medicine. Drug discovery is a lengthy and costly process. A series of *in vitro* and *in vivo* studies need to be conducted once a lead compound is identified among thousands of small molecule candidates before clinical studies are conducted. Drug screening is traditionally performed using two-dimensional (2D) cell cultures in Petri dishes and microtiter plates. These 2D cell culture platforms lack extracellular matrix (ECM)-like structure or dynamic fluidic microenvironment. Cells are forced into an arbitrary monolayer and may lose *in-vivo* tissue functionality [127]. Animal models are

intrinsically inaccurate because of their physiological difference from humans [128]. As a result, about 50% experimental drugs fail in clinical trials due to initial screening inaccuracy [129]. *In-vitro* 3D tissue model systems can be used to achieve more accurate test results via mimicking the *in vivo* functions of human organs. The field of 3D tissue model systems has grown exponentially in the past few years and tissue models for a wide variety of diseases ranging from cancer to cardiac and neurological disorders have been developed [130]. The technologies used in developing these tissue models include both scaffold-free methods, such as self-aggregation of cells as suspended spheroids [131–133], and scaffold-based methods with soft hydrogel and hard polymer scaffolds. Scaffold-based culture technologies provide physical support, ranging from simple mechanical structures to ECM-like matrices, on which cells can aggregate, proliferate and migrate [134]. In addition, fragments or slices of primary tissue are also used in *in-vitro* model systems for drug testing [135–137]. The function of primary tissue can only be maintained for a limited time *ex vivo*, and the models based on primary tissue are cumbersome to use.

To reproduce dynamic process of drug absorption, distribution, metabolism, and excretion (ADME), multi-organ tissue model systems have been developed by connecting single-chamber tissue models via microfluidic devices [138,139]. The liver plays a key role in metabolism in human body. A set of enzymes in the liver metabolize and bio-transform all the drugs. Perfusion-based multi-chamber systems containing liver and disease models can better mimic the *in vivo* environment. Therefore, liver models have been employed to make quantitative and qualitative assessment of pharmacodynamics and

pharmacokinetic properties of drug candidates [140,141]. One of the early multi-chamber tissue model systems is a microscale cell culture analog (μCCA) used to predict concentration profiles of a drug and its metabolites [138]. The analog consists of three chambers containing cell lines representing lung cells, fat cells, and liver cells. A hydrogel-cell solution is inserted into the μCCA device modified to accommodate a 3D gel-cell structure [139,142]. Bio-chips, so called tissue chips, containing engineered tissues have also been developed as a surrogate for drug testing. Human or animal cells are built on polymer support to retain the functions related to an intact organ. Gel-based 3D cell cultures suffer from diffusion limitations, which could hinder nutrient and metabolite exchanges. Ma *et al.* [143] developed a 3D perfusion-based two-chamber tissue model system based on porous polymeric scaffolds and demonstrated the testing result of chemotherapy drugs by mimicking patient specific functionality of human liver metabolism.

One of the challenges for tissue model systems is to faithfully recapitulate *in vivo* biology and microenvironmental factors of human physiological or pathophysiological systems. An ideal tissue model would provide a tissue-specific or disease-specific microenvironment where cells can proliferate, aggregate and differentiate, and would include cell-to-cell and cell-to-ECM interactions, tissue-specific stiffness, oxygen, nutrient and metabolic waste gradients, and a combination of tissue-specific scaffolding cells [144]. Such biocomplexity presents a daunting task for tissue model design and manufacturing. Many 3D bioprinting technologies are being developed to achieve structural and material biomimicry of tissue by taking advantage of precise position and

composition control capability of the additive manufacturing approach [145–147]. On the other hand, stem cell technology is making significant progress in organoid development, overcoming the limitations of cell lines and primary cells that are used in traditional tissue engineering approaches. The combination of 3D bioprinting and stem cell technologies may hold the key to further advancement in the tissue model system field.

Another challenge for tissue model systems is the high throughput requirement for drug screening, including the compatibility with currently available assays to evaluate drug toxicity and effectiveness. Tissue model systems need to be low-cost, easy-to-assemble, reproducible, scalable, and compatible with liquid handling and imaging equipment. Despite recent advancements in tissue model systems, application of 3D cell culture in high throughput screening and high-content screening remains a challenge, especially for imaging cells in 3D matrices [134]. For multi-chamber 3D tissue model systems, design, fabrication, and system integration require further engineering innovation to bring tissue model systems to drug screening practice [148,149]. Device miniaturization, automatic liquid handling and imaging, and other easy-to-implement sensing techniques to monitor 3D cell culture progression are some of the areas that will help ensure high throughput drug screening with 3D tissue model systems.

3. MATERIALS AND THEIR PROCESSING CHARACTERISTICS

Section 2 has provided a review of different products manufactured for PM. Most of these products, except those drug testing models, may be considered as drug products. This section will review materials used for PM in the context of manufacturing. For more

detailed discussion on these materials, readers are referred to other published resources [150,151].

A drug delivery system usually consists of one or multiple active pharmaceutical ingredients (APIs) and inactive excipients. Excipients provide the form (*e.g.*, as solid oral dosage form) and different functions (*e.g.*, controlled or delayed release). Seoane-Viaño et al. provide a comprehensive review of API and excipient compositions for different dosage form and release patterns [152]. The mass fraction of APIs varies by product and can range from less than 1% to over 50%. When the fraction of APIs increases, the impact of APIs on the behaviors and manufacturability of the material also increases [153]. Thus, to determine the process parameters for manufacturing, the composition of the drug delivery system needs to be carefully selected and considered. Herein, common excipient materials will first be reviewed, then followed by a discussion of the effects of APIs.

Table 1 lists common excipient materials used for pharmaceutical applications along with their processing characteristics and applicable manufacturing processes. Extrusion-based processes have been explored most frequently among different categories of AM processes, accounting for 83% of published papers during 2015-2019, due to the wide variety of available materials [154]. Thus, the discussion in this section will focus on the material characteristics relevant to extrusion-based processes. Konta *et al.,* reviewed and discussed advantages and disadvantages of each AM process and reviewed three common polymers in details, including polyvinyl alcohol (PVA), polylactic acid (PLA), and polycaprolactone (PCL) [155]. Azad *et al.* reviewed polymeric materials used in extrusion-based processes [154]. Pereira *et al.* reviewed the manufacturability of a comprehensive

list of material compositions in the context of the coupled use of hot melt extrusion (HME) and fused deposition modeling (FDM) processes [156]. Zidan *et al.,* reviewed the extrudability of drug-loaded pastes for semi-solid extrusion (SSE) [157]. Based on these reviews, material processing characteristics to be considered include, but are not limited to, glass transition temperature, melting temperature, rheological properties (viscosity, storage modulus (G'), loss modulus (G"), yield stress, and flow behavior index which measures the degree of non-Newtonian behaviors), solubility, and miscibility between polymers and APIs. Multiple excipient materials can be mixed to achieve better mechanical properties and desired material characteristics for fabrication [158]. The viscosity, which is a function of temperature and shear rate, is among the most important properties determining the printability of the material blend. Generally, a viscosity ranging between 100 to 1000 Pa·s at the apparent shear rate of the nozzle is considered the ideal operating viscosity window [159]. A lower melting temperature is also desired to prevent degradation of thermolabile drugs [160]. The miscibility between polymers and APIs should not be overlooked when formulating the material blend as it plays an important role in the rheological properties of the material blend and thus, its processability [154].

Different approaches can be implemented to load drugs or APIs onto the matrix of the excipient materials. For FDM-based processes, APIs can be either impregnated into the filament or dry mixed with pellets of the filament or powder of matrix material and then the drug loaded filament can be fabricated through HME, with the latter being the common practice [161]. For SSE processes, the APIs are added during a wet-mixing

process used to fabricate the paste. For powder-based processes, API particles can be mixed directly with the excipient powders [162]. For photopolymerization-based processes, the API can be suspended or dissolved in the liquid resin. Soluble and insoluble (or poorly soluble) APIs have distinct effects on the manufacturability of the material mixture [163]. Soluble APIs can work as plasticizers to soften the filament and improve its printability [65] or to increase flowability of paste [163]. However, if the fraction of API exceeds its solubility level, the API particles beyond the solubility level will behave like insoluble APIs [164]. Poorly soluble APIs form a solid dispersion and have an effect similar to having inorganic fillers in the mixture, causing an increase in yield stress [165].

Given the complex nature of material behaviors and the variety of material blends required for PM, researchers have attempted to create guidelines for material selection and processing parameters [156,166–168]. Elbadawi *et al.*, first demonstrated the feasibility of using machine learning algorithms to predict the printability of material blends [159] and later created a web-based pharmaceutical software as a predictive tool [169]. More recently, the software has been shown to be an accurate tool for not only predicting process parameters but also for forecasting the drug release profile for over 900 drug delivery systems [170].

4. REVIEW OF PROCESSING TECHNIQUES

4.1 Extrusion-based processes

Extrusion-based technologies are collectively known as material extrusion. These technologies generally follow the same basic principles, where they are all thermal processes that involve the melting of materials through an orifice at the end of the printhead. At the start of the printing process, the platform moves to its highest level, approaching the printhead. At each layer, the printhead moves in a raster pattern based on the 3D design of the object and deposits the molten material on a platform. The platform is then lowered, allowing for enough space for the subsequent layer to be created. This process is repeated until the final object is formed. Material extrusion employs different types of materials, such thermoplastic polymers, clays, waxes, gels, chocolate, and pastes. Currently, extrusion-based technologies are classified into three subset technologies: FDM, SSE, and direct powder extrusion (DPE), wherein the main difference between them lies in the feed material.

The motivations for using extrusion-based 3D printing for personalized medicines is their ability to control the drug release by adjusting different factors such as the geometric shape, polymer content and infill percentage of the dosage form. The latter refers to the degree to which the internal structure is filled with solid materials (ranges from 0%, hollow structure; to 100%, completely solid structure) and is a feature specific to extrusion-based technologies. This offers an additional way to modify the drug release properties, enabling the fabrication of 3D printed tablets with controlled [28,171] as well as immediate release properties [59,71,172]. Furthermore, material extrusion printers

offer the additional option of being able to print with multiple materials in the same printing layer, which is another feature unique to this technology. This allows the engineering of multi-drug 3D printed tablets or those with complex release properties, which are otherwise impractical to attain using other technologies [173,174].

4.1.1. Fused deposition modelling (FDM)

FDM uses a thermoplastic filament that is heated and pushed through a heated metallic nozzle (Figure 5) [175]. Although this technology is commonly used for the creation of models and prototypes, it is the most researched 3D printing technology within pharmacy. As an example, FDM 3D printing has been abundantly used to fabricate tablets with complex shapes [16,17,68] and hollow structures [176–178], both of which cannot be easily produced with conventional methods such as direct compaction [179]. The change in the surface area-to-volume ratio allows the modification of the drug release pattern, thus tablets with different shapes and sizes will behave differently. In general, FDM tablets are characterized for having high mechanical strength and thermal resistance [180]. When first introduced, the main limitation to the use of FDM 3D printing was the high temperatures needed for printing, posing a risk for degradation of thermolabile drugs [160]. Later on, this challenge was overcome with the use of new fabrication materials which permitted printing at much lower temperatures, safeguarding the integrity of the drugs [172,181,182]. The other limitation to FDM is that for drug-loaded applications the filaments are typically created using HME [55,73,183], which instigates an additional procedure and makes the process more complex and time-consuming.

4.1.2. Semi-solid extrusion (SSE)

Unlike FDM, SSE extrudes semi-solid materials, such as gels, waxes, chocolate, or pastes, which are typically contained inside a heated plastic or metallic syringe [26,184,185]. Due to this, the technology can be used at lower printing temperatures [186], making it better suited for thermosensitive drugs compared to FDM [187]. SSE has been exploited for the preparation of oral 3D printed tablets with a wide range of release properties, such as orodispersible [61,188], immediate [54,189] and sustained release formulations [53,190]. Additionally, SSE has been employed for the fabrication of floating gastroretentive tablets (i.e., dosage forms that provide a prolonged drug release in the gastric region) and rectal formulations [191]. The soft nature of some SSE formulations has also made it possible to create chewable formulations, which are suitable for children, the elderly or patients with dysphagia [18]. It was demonstrated that this fabrication method can be employed in a hospital pharmacy, where on-demand dosage forms with various doses, colors and flavors can be prepared based on the needs and preferences of children with rare diseases. Within preclinical studies, SSE has also been used to fabricate different dosage forms (*e.g.,* capsules [192] and suppositories [193]) that are suitable for specific animal models being studied.

Compared to other 3D printing technologies, SSE has one of the lowest resolutions, making it currently one of its main limitations. As such, it is difficult to use it for the preparation of intricate dosage forms or devices with fine structural features. On the other hand, there is potential to use coaxial SSE to fabricate core-shell structures in a

continuous manner which significantly increases the throughput [194]. Such a process is still under development and aims to achieve more precise control of the fabricated structures [195].

4.1.3. Direct powder extrusion (DPE)

DPE is a more recent material extrusion process wherein powdered materials are directly extruded through a miniature HME embedded within the printhead nozzle [196,197]. Herein, the powder feedstock is mixed and loaded into the hopper. A screw rotates, pushing down the powder through the heated barrel and into the nozzle. Whilst the printhead moves based on the 3D design, the combination of elevated pressure and temperature causes the molten material to exit through the metallic nozzle, depositing it onto the build platform. The final objects that are created are similar to those obtained using FDM 3D printing in terms of mechanical and geometric properties. However, with DPE, the additional HME process which precedes FDM printing is circumvented, making it faster and more convenient for use by clinicians and researchers. Furthermore, unlike HME, DPE requires only small amounts of powders, making it well suited for use with expensive (*e.g.*, orphan drugs [198]) or controlled drugs (*e.g.* opioid medications [93]), or in early preclinical and clinical studies [70,196]. Currently, there are only a few number of printers based on this system, including FabRx's M3dimaker [196] and Triastek's melt extrusion deposition printer [199].

4.2 Photopolymerization-based processes

Photopolymerization refers to the crosslinking of photopolymer resins in the presence of a photoinitiator when exposed to a light source (*e.g.*, visible light or ultraviolet (UV)) [200]. Xu *et al.,* reviewed the use of different photopolymerization processes for drug delivery and medical devices [201]. Stereolithography (SLA) is typically utilized to process photopolymers for the fabrication of 3D constructs in a layer-by-layer manner. Conventional SLA uses a single laser beam to trace the geometry of each pattern in a single layer [202]. Digital light processing (DLP) is a projection-based system, which utilizes a projection of ultraviolet or visible light from a digital projector to cure the whole layer with one-time exposure [203]. Other photopolymerization-based processes include two-photon polymerization (2PP), continuous liquid interface production (CLIP) and volumetric printing . In recent decades, benefiting from the advances in 3D printing technologies and materials [204], both conventional SLA and DLP have been investigated in the field of PM, especially for the fabrication of drug-encapsulated tablets customized for specific patients. The drugs used include 4-aminosalicylic acid for tuberculosis [205], acetaminophen (also known as paracetamol) for pain [64], ibuprofen for fever [206], and theophylline for lung diseases [207]. As the carriers of the embedded drugs, the photopolymers used include poly(ethylene glycol) diacrylate (PEGDA), poly(2-hydroxyethyl methacrylate) (pHEMA), and poly(ethylene glycol) dimethacrylate (PEGDMA) [205].

Conventional SLA has been utilized for the fabrication of patient-customized tablets with a controllable and precise release of the encapsulated drugs [208]. Specifically, Martinez *et al.* fabricated various shapes of tablets containing acetaminophen and found

that the release rate of the drug can be tuned by changing the surface area-to-volume ratio (Figure 6A) [64]. They also fabricated a multi-layered tablet containing 6 different drugs, including naproxen, aspirin, acetaminophen, caffeine, chloramphenicol, and prednisolone. Each drug can be precisely controlled with an individual release profile (Figure 6B) [27]. Xu *et al.,* successfully formed polyprintlets with an oral dosage form containing 4 drugs: irbesartan, hydrochlorothiazide, amlodipine, and atenolol [78]. They also fabricated an indwelling bladder device for the delivery of lidocaine hydrochloride to treat interstitial cystitis and bladder pain [114]. Sun *et al.,* successfully developed a simple and inexpensive way to fabricate tablets with a customized shape and a desirable drug release profile containing one or multiple drugs [209]. Wang *et al.,* utilized PEGDA to print tablets containing 4-aminosalicylic acid (4-ASA) and acetaminophen and the drug release rate was found to be dependent on the composition of the formulations, but independent of dissolution pH (Figure 6C) [205]. Martinez *et al.,* fabricated ibuprofen-loaded softgels and studied the effect of water content within the hydrogel on the drug release rate (Figure 6D) [206].

DLP has also drawn much attention in PM for the fabrication of dosage forms with controllable release profiles [210]. For example, Kadry *et al.* deployed DLP-based 3D bioprinter to fabricate oral tablets with various drug release rates using a solution composed of the photo-crosslinkable materials PEGDA and PEGDMA, photoinitiator, and theophylline (Figure 7A). They reported that the release rate of the encapsulated drug was proportional to the porosity of the formed tablets [207]. Tao *et al.* mixed nanoparticles and a drug within a GelMA-based solution to produce nerve conduits with

a customized shape and size (Figure 7B). With the release of the encapsulated drug 4-((5,10-dimethyl-6-oxo-6,10-dihydro-5H-pyrimido[5,4-b]thieno[3,2-e][1,4]diazepin-2-yl)amino) benzenesulfonamide, the regeneration of the peripheral nerves was facilitated [211]. Krkobabić *et al.* were able to maintain a continuous release of the encapsulated acetaminophen up to 8 hours with its release kinetics described by Korsmeyer-Peppas kinetics (Figure 7C). In addition, it was reported that the addition of hydrophilic polymers could facilitate the drug release rate [212]. Stanojević *et al.* tailored the release rate of atomoxetine by varying the thickness and drug content of the tablets formed with PEGDA and PEG 400 shown in (Figure 7D) [213]. CLIP, similar to the DLP process, offers high resolution and high throughput and is becoming popular for fabrication of microneedles for drug delivery [214,215].

Although conventional SLA and DLP have made significant progress in manufacturing tablets with a customized dosage form and controllable release profile, there are still several concerns of photopolymerization-based PM, including the toxicity of the photopolymerization materials, the potential incorrect function of the drugs due to UV effect on the spontaneous locomotor activity of the drugs, and the unexpected reaction between the photopolymers and the encapsulated drugs [78,216–218].

4.3 Powder-based processes

Powder-based technologies, termed as powder bed fusion (PBF) technologies, create objects using thermal energy resulting from both, elevated temperature and an energy source, that is transferred to powdered feed materials causing them to consolidate

[219,220]. A PBF printing platform is often composed of five main parts: (I) a build (or printing) platform/tank, in which solid objects are created, (II) an energy source (*e.g.*, laser beam), which initiates the consolidation of the powder particles, (III) a powder reservoir platform/tank or hopper, which holds the fresh powder prior to its transfer to the build platform, (IV) a mechanical roller, which transfers and flattens the fresh powder from the reservoir platform onto the build platform at the start of each layer, and (V) a powder container, which recovers and recycles unprocessed powder materials. A typical PBF printing pattern entails raising the build platform to its uppermost point and lowering the reservoir platform to a point that allows it to hold enough powder for the printing job. At the beginning of each layer, a fresh layer of powder is distributed onto the build platform and levelled with the aid of roller [221]. Once the selected temperatures are reached, the energy source within the printer gets activated and scans through the powder in the build platform following a pattern based on the 3D file uploaded. In doing so, the powder particles within the scanned regions are consolidated into solid objects. Subsequently, the build platform moves down, the reservoir platform moves upwards whilst the roller moves to the side, making enough space for another fresh layer of powder to be spread in preparation for the printing of the next layer. This process is repeated until the whole print job has been finished, after which the printer is left to cool down [222]. The printed objects are then retrieved, and the loose powder is removed with a brush or using compressed air. Occasionally, additional coatings or polishing may be needed to improve the mechanical properties of the final objects.

Depending on the form and amount of energy transmitted, PBF can be classified into four subset technologies: selective laser sintering (SLS), selective laser melting (SLM) / direct metal laser sintering (DMLS), electron beam melting (EBM) and multi-jet fusion (MJF) (Figure 8). One of the main advantages of PBF technologies is the ability of the loose powder materials to act as supports, enabling the fabrication of intricate structures, such as gyroid lattices [67], which when created using other processes cannot maintain their integrity throughout the fabrication process or may require additional steps to be made.

4.3.1 Selective laser sintering (SLS)

SLS 3D printing employs a laser beam that 'sinters', or superficially melts the surface of adjacent powder particles, causing them to fuse together [162,223,224]. The laser beam is guided to specific positions on the powder bed using lenses and Galvano-mirrors. Herein, the feed materials are typically in the form of thermoplastic polymers, wherein the drug particles are mixed with polymer powder prior to printing. Different types of lasers are often employed in SLS 3D printing, such as neodymium-doped yttrium aluminium garnet (Nd:YAG), diode, fiber and carbon dioxide (CO_2) lasers, with the latter currently being the most frequently used type [225]. As each laser has a different wavelength, the absorption depth of materials will differ depending on the laser employed.

Of the different PBF technologies, SLS 3D printing is the most commonly explored for PM application. One of the unique features of SLS 3D printing is its ability to generate highly porous tablets, which is attained by using a low laser scanning speed that loosely

binds the powder particles on the surface. With the absence of compression forces, liquids quickly penetrate into the tablets, causing them to disintegrate. As such, orally disintegrating SLS tablets have shown to disintegrate within less than 4 seconds [226,227].

4.3.2 Selective laser melting (SLM) and direct metal laser sintering (DMLS)

The SLM and DMLS processes are generally similar to SLS but employ higher laser power and once the photons are absorbed by the powder particles, the laser heating causes them to completely melt and fuse [228]. As such their main feedstock materials are metal granules (*e.g.,* stainless steel, cobalt chrome, aluminium, and titanium). SLM differs from DMLS in that it employs single component metal (*e.g.,* pure aluminium) which at a particular melting temperature can fully melt [229], whereas DMLS uses metal alloys (*e.g.,* titanium alloy) that melt at various temperatures and thus, requires the use of high temperatures for complete fusion to occur. The high mechanical properties of SLM and DMLS objects make them well suited for the fabrication of personalized metallic implants [111,230].

4.3.3 Electron beam melting (EBM)

Unlike the other PBF technologies, EBM uses an electron beam instead of a laser beam, wherein its greater intensity results in temperatures of up to 1000 °C, causing the complete melting of powdered materials [231,232]. Typically, a tungsten filament is used to generate electrons, which are collimated into a thin beam with an electromagnetic coil [233]. The electrons then generate kinetic energy which heats the powder bed. The latter

causes an increase in the negative charge of the bed, which is dissipated using helium gas during the printing process [234]. Like SLM and DMLS, EBM uses metals and alloy powders, but due to its higher intensity, larger powder particle sizes can be used compared to other PBF processes [235,236]. Nonetheless, not all metals can be used for EBM, with cobalt chrome and titanium being the most prevalently used ones.

4.3.4 Multi-jet fusion (MJF)

MJF differs from other PBF technologies in that it uses an infrared (IR) lamp as its energy source and that one type of feedstock material is typically used (e.g., nylon, PA 12). Moreover, MJF requires two supplementary components [222]: (I) a fusion agent, that is jetted onto the printing regions, ensuring that only the areas covered by it are consolidated, and (II) a detailing agent, which absorbs thermal energy from the object's exterior sides and reduces thermal bleeding. Together, these two agents enhance the printing quality, speed and accuracy. Although MJF is yet to be used for drug delivery, it has been explored for the creation of bespoke orthoses [97] and prostheses [36].

4.4 Jetting-based processes

Inkjet printing is an additive manufacturing process in which small amounts of ink are deposited in a drop-by-drop manner to create a 3D object [237]. The inkjet printing process involves three steps: (1) generation of droplets, (2) deposition of droplets on a substrate, and (3) solidification of the droplets on the substrate. There are two approaches for inkjet printing, continuous ejection and drop-on-demand. In the

continuous ejection approach, the bioink is ejected through a nozzle, forming a continuous jet of material; hydrodynamic instability converts this continuous jet of material into a droplet stream [238]. Although the stream of droplets cannot be readily controlled, a catcher can collect undesired droplets. A slower, more controllable approach for inkjet printing is the drop-on-demand approach; in this approach, high-resolution structures can be obtained by ejecting small droplets (>10 mm) through the orifice of a nozzle via the application of pressure from a piezoelectric or thermal actuator [239]. Through spatial control over one or more printheads in the inkjet printer, droplets can be deposited with much higher resolution than the continuous ejection approach [240].

Two drop-on-demand approaches are currently in wide use, thermal inkjet printing (Figure 9A) and piezoelectric inkjet printing (Figure 9B). In thermal inkjet printing, an electric pulse that reaches the printhead causes heating of a thin film resistor; vaporization of fluid in contact with the resistor leads to the formation of a vapor bubble. This vapor bubble increases the pressure in the reservoir; collapse of the bubble leads to a pressure pulse and subsequent ejection of a droplet by the nozzle. The bioink temperature profile, bioink viscosity, and the number of pressure pulses determine the droplet size; droplets between 10 and 150 pL in size can be obtained using this approach [241]. Thermal inkjet printing also benefits from high print speeds and low device costs [242,243]. Piezoelectric inkjet printing involves the use of a voltage pulse to mechanically deform a piezoelectric element, which causes a pressure wave in the reservoir and results in droplet ejection from the nozzle. Parameters that determine the droplet size include

printhead resonance frequency and nozzle size [244]. Unlike thermal inkjet printing, piezoelectric inkjet printing can be used with heat-sensitive bioinks without concern [244]. Moreover, the piezoelectric inkjet printing approach provides good control over droplet size. On the other hand, the voltage pulses associated with piezoelectric inkjet printing may alter the structure of cell membranes; as such, thermal inkjet printing is preferable to piezoelectric inkjet printing for cell printing [245,246].

An important consideration associated with inkjet printing approaches is the viscosity of the bioink. In order to obtain microscale droplets (around 10 mm in size), small nozzles are typically utilized [239]. To avoid clogging of the nozzle, bioinks with a low shear viscosity (30 mPa·s) are typically used for printing bioinks [247–249]. Microvalve-based approaches may allow for the printing of bioinks with higher viscosities; this approach involves the use of an electromechanical valve that includes a solenoid valve. When a voltage pulse reaches the valve, the solenoid valve creates a magnetic field, which actuates a plunger upward and enables the ejection of the bioink from the nozzle. The frequency of drop release and the droplet size can be modulated by controlling the valve closure via changes to the voltage pulse; it should be noted that the microvalve-based approach can be operated in either continuous ejection mode or drop-on-demand mode [250]. An acoustic approach has also been developed that eliminates the use of a nozzle to control the droplet size; as such, this approach can be used with a wider variety of bioinks. [251,252]. In the acoustic approach, an ultrasound field generates an acoustic force, which in turn releases a droplet from the air-liquid interface; a bioink with a viscosity of 150 mPa·s can be deposited using this approach [253]. Demirci et al. deposited

human Raji cells, AML-12 hepatocytes, and HL-1 cardiomyocytes within droplets of approximately 37 mm in diameter at rates up to 10,000 droplets per second; they showed cell viabilities of greater than 89.8% using this approach [254]. Foresti et al. used a subwavelength Fabry−Perot resonator to generate an acoustophoretic force and obtain droplet printing; they demonstrated printing of bioinks with viscosities of 0.5−25,000 mPa·s using this approach [255]. The advantages of inkjet printing include low cost, the ability to deposit inks with good accuracy and reproducibility, and the ability to deposit multiple inks during a given printing procedure [237]. The limitations of inkjet printing include shortcomings associated with bioink viscosity and bioink functionality. Montenegro-Nicolini et al. described applying a model drug, lysozyme, on a polymer film containing chitosan and hydroxypropyl methylcellulose using thermal inkjet printing [256]. This film showed appropriate mucoadhesive and mechanical properties for buccal drug delivery. Arshad et al. prepared indomethacin films using piezoelectric inkjet printing [257]. Indomethacin-only films were shown to be crystalline; in contrast, films containing indomethacin and polyvinylpyrrolidone were shown to be amorphous. 40-50% of the drug was shown to pass through rat skin using a Franz diffusion cell approach.

Material jetting is another jetting technology, which involves spraying of materials on the substrate during the inkjet printing process. For example, the PolyJet approach involves the spraying of material from nozzles and material curing using UV light; no postprocessing steps are required [258,259]. Although this approach is expensive, materials made up of thin layers can be created using this approach. The Multi Jet Modeling (MJM) method that has been commercialized by 3D Systems also uses UV light

curing; in this case, an acrylic photopolymer serves as the bulk material and a wax serves as the supporting material [260]. Like the PolyJet approach, no post-processing steps are needed; however, materials made using this approach typically exhibit low strength [258]. These two approaches are variations of binder jetting (previously referred to as three-dimensional printing) [261–263]. Binder jetting involves the selective deposition of a laser light-curable liquid binding agent via inkjet printing onto a bed that contains material in powder form. Any material that can be prepared as a spreadable powder with appropriate particle dimensions, including low cost coarse powders, can be processed using this approach [263]. The binder permeates the powder particles; after drying and curing of a given layer, a recoating system such as a counter-rotating roller is used to apply a new powder layer directly above the just-cured layer. The printed layers are stitched to one another via the binder. The loose powder can support overhanging features and is removed after the printing process. The porous features in structures that are manufactured using binder jetting can be infiltrated with other materials during postprocessing to enhance the strength of the structures. One advantage of this approach is that it can be performed at room temperature; as such, the structures manufactured using this approach do not contain residual stresses. In addition, several parts can be manufactured during a single build process; only a few layers are needed to separate the parts in the bed [264]. The major disadvantage of this approach is that binder jetted structures exhibit low strength and high surface roughness values, which preclude their use in medical devices [263,265–268]. Post-processing steps on binder jetted materials can be extensive; in addition to improving the strength of the structure via infiltration or

sintering processes, post-processing steps such as grading and polishing are often needed to improve the uniformity of the surface of the structure [269,270]. Moreover, commercial binder jetting products typically use thermal or piezoelectric nozzles (Figure 9); the nozzle type limits the viscosity and the operating temperature of the sprayed liquid [263]. The VX series products from Voxeljet and the ProJet series products from 3D Systems utilize binder jetting technology [263]. Desktop Metal and HP have demonstrated the use of binder jetting to create metal parts, which may have medical applications [271].

Another important application of binder jetting is for the manufacturing of tablets; a tablet, Spritam®, that does not require water sipping was approved by the FDA for distribution in 2015 [272]. Yu et al. prepared multi-layered drug delivery devices with doughnut shapes containing acetaminophen using 3D printing [273]. These devices degraded by erosion of the inner aperture and outer peripheral regions of the drug delivery device. The dose loaded in the drug delivery device can be altered by modulating the device height. Wang et al. used 3D printing to create formulations that contained the drug pseudoephedrine hydrochloride, and the carriers hydroxypropyl methylcellulose (HPMC) and Kollidon SR that exhibited near zero-order controlled release [274]. The release rate and the HPMC amount in the formulation were shown to be correlated. The binder jetting approach can also be used to manufacture bioactive calcium phosphate-based bone graft materials; for example, Inzana et al. demonstrated manufacturing of calcium phosphate scaffolds using binder jetting and demonstrated the osteoconductivity of these materials in a murine model [275]. Fielding et al. showed that doping the calcium phosphate powder with silicon oxide and zinc oxide served to improve collagen

production, osteocalcin production, and new blood vessel formation in a murine model [276].

7. REGULATORY CONSIDERATIONS AND QUALITY CONTROL

The current regulatory environment supports advancing the regulatory science and research to facilitate development of 3D printed drug products. Regulatory science and research can provide data and methods that inform the regulatory decision-making and provide guidance to sponsors. Various regulatory authorities encourage innovation in pharmaceutical manufacturing including the adoption of 3D printing technologies to manufacture drug products utilizing approaches recommended by International Council for Harmonization (ICH) Q8 [277], Q9 [278], Q10 [279], and Q11 [280]. These ICH guidelines describe not only the implementation of risk-based (ICH Q9), systematic and science-based approaches (ICH Q8 and ICH Q11), but also the adoption of robust pharmaceutical quality systems (ICH Q10) that can establish an increased level of understanding of innovative pharmaceutical processes and products such as 3D printing technologies and 3D printed drug products. Similarly, the U.S. FDA Guidance for Industry "*PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*" provides the regulatory framework (Process analytical technology, PAT) for development and implementation of innovative pharmaceutical development (e.g., 3D printing), manufacturing, and quality assurance [281]. Application of this framework to 3D printing processes should be founded on thorough understanding of 3D printing technologies with implementation of control strategies and on-line, in-line, at-

line, or off-line testing methodologies for monitoring the critical quality attributes (CQA) of printed drug products. The FDA also released Guidance for Industry "*Technical Considerations for Additive Manufactured Medical Devices*" to provide the Agency's initial thinking on technical considerations specific to devices manufactured by 3D printing technologies [282]. The guidance outlines technical considerations associated with 3D printing processes, and recommendations for testing and characterization for devices that include at least one additively manufactured component or additively fabricated step.

As the pharmaceutical industry and regulatory agencies gain more experience and knowledge on 3D printing processes and 3D printed drug products, several regulatory aspects may be considered for linking the principles and theories to practice and implementation. Below are examples of these aspects that may be applied to one or more 3D printing technologies.

- **Performance of 3D printed products:** 3D printed drug products have the same expectations in terms of safety, efficacy and quality as any drug products manufactured using other techniques.
- **Raw materials and intermediates:** Given the variety of 3D printing technologies, materials, geometries and designs, there is no one-size-fits-all control strategy that may be applicable in all cases. 3D printing processes may require control over certain critical characteristics of raw materials and intermediates. For instance, particle size distribution and flow characteristics of powder bed are critical material attributes that should be controlled in inkjet and laser sintering 3D printing. The selection of control

approach, e.g., PAT tools, for a certain 3D printing technology maybe based on product and process understanding. The determination of the critical characteristics of an intermediate product may be also considered. For example, rheological, extrudability, and melt-flow properties of drug loaded pastes and mixtures may be critical for extrusion-based 3D printing [283]. Therefore, the critical material attributes of raw materials and intermediate products should be linked to the product CQAs and the needs of the 3D printing process [157].

- **Equipment control:** It is important to consider equipment control aspects for 3D printing processes. Pressure-aided microextrusion (PAM), FMD, SLS, inkjet, droplet-on-demand, and other 3D printing processes may require special maintenance, calibration, and periodic review to ensure their performance. Development of performance evaluation scheme along with acceptance criteria for each 3D printing process may be considered to ensure process robustness and consistent operation over time. Risk assessment and mitigation strategies may be developed for 3D printing processes to ensure the products printed are of uniform quality and characteristics [284]. The thorough understanding of the risks, printing defects, and failure modes associated with a printing process help in assessment of manufacturing changes and process improvements that may occur over the lifecycle of 3D printed product. Knowledge of risks and failure modes is also useful to make risk-based decisions.
- **Process monitoring and sampling:** The principles of process monitoring may be also applied to 3D printing processes. As variations over time may impact segments of the batch processes in 3D printing lines, consideration should be given to the selection of a

suitable monitoring tool (off-line versus on-line, in-line, or at-line) and monitoring frequency of certain 3D printing processes that run in a continuous operation. Sample size, frequency of measurement, and acquisition time should be considered for flow of raw materials, process dynamics, and throughput rate of the printing process. Potential root causes of failure modes and correction plans of any sampling devices employed should be understood. Linking the critical printing parameters (*e.g.,* extrusion pressure, melt flow rate, feeding rate of binder liquid, powder flow rate) to the sample schedule should be also considered. Flexible monitoring frequency may be used where more samples are collected in situations of more disturbances occur to the printing process. These situations can be seen during changing of printing cartridges in PAM printing, filling tanks of powder and binder liquid in inkjet printing, among others.

- **Scale-up:** Scale-up of 3D printing processes may be achieved in several ways including adding more printing heads to a printing line (increasing the throughput rate) or using parallel units (scale out). These scale-up approaches may affect the critical process parameters and sampling schedule; therefore, these effects should be considered during development of 3D printing processes.
- **Quality and GMP consideration:** The current good manufacturing practices (cGMP) do not preclude the introduction of 3D printing technologies in manufacturing drug products [285]. Various aspects may be considered when implementing 3D printing in a centralized GMP environment. For example, challenges of implementing 3D printing into an existing pharmaceutical quality system; achieving state-of-control over 3D printing processes during start-up, shutdown, product collection and in-process

sampling, establishing process validation schemes and continuous process verification plan; consideration for raw material variability; establishing standard operating procedures for handling of raw materials, intermediates, and in-process samples; determination of operator qualification and plans for continual training; and setting the cleaning and cleaning validation procedures, among others.

- **Global software control:** Most 3D printing processes are designed as autonomous systems with specific local controls over the critical parameters of the printing process [286]. Nevertheless, the integration of 3D printing processes into a production line may require some global coordination of the entire process flow. A second-level software control system may be then needed to supervise, synchronize, and align the operation of each process integrated in the entire process. The functions of the control system include coordination of flow of raw and intermediate materials, event-based control, and exception handling. A high degree of automation with minimal handling by the operators may be built in over the integrated hardware and software control units. Controls are also needed for the product design files that provide the instructions for the 3D printing process.

6. FUTURE OUTLOOK

The adoption of 3D printing for PM within healthcare will transform the way medicines are produced. When combined with other digital health technologies, a closed-loop system, which involves diagnosis, monitoring, digital prescribing, and on-demand dispensing, can be created. This modern, decentralized healthcare model may replace current healthcare systems, improving the accessibility to treatments and permitting rapid, remote interventions. However, to enable the translation of these concepts from research into clinics, there is a need for thorough regulatory and legal framework that realistically supports the integration of these technologies within healthcare. Within this guidance several considerations need to be addressed, including how current 3D printing platforms can be safely adapted for pharmaceutical production, what is the best way to safely exploit these technologies for PM, and where in the pharmaceutical pipeline is 3D printing best suited.

To address the first concern, numerous attempts have been made to implement *in situ* analytical techniques that allow for quality control monitoring in a non-destructive manner. Examples of such include the use of near infrared (NIR) and Raman spectroscopy for drug quantification, solid state determination, identification of chemical interactions, moisture content measurements and determination of disintegration properties [287–294]. The techniques can also be used for polypills [82], whereby NIR hyperspectral imaging can be employed to determine the spatial distribution of drug agents within the dosage form [295]. Likewise, imaging techniques and artificial vision can be used to

inspect the geometric features of the dosage form and determine the printing accuracy [294,296,297].

In terms of the safety of these technologies, this is often described from two aspects; the printers themselves and the printing feedstock. With regards to the 3D printers, most systems were not developed for pharmaceutical applications and as such, do not comply with GMP requirements for drug products. Thus, whilst they might be suited for the fabrication of medical devices and prothesis, they are inappropriate for use with drug-laden products. This has led multiple pharmaceutical companies to develop GMP-approved 3D printers. An example of such is FabRx's world's first pharmaceutical 3D printer, the M3DIMAKER™, which was specifically developed for the preparation of personalized medicines [298]. More recently, Merck have revealed their own 3D printing platform that aims at reducing the time needed for clinical trials [299]. Perhaps, in the near future, more GMP compliant printers will hit the market, further supporting the implementation of 3D printing within healthcare.

Finally, the question concerning the best way for positioning 3D printing within pharmacy is currently a hot topic, with multiple scenarios being presented by different pharmaceutical stakeholders. As an example, some foresee 3D printing as a modern way to dispense extemporaneous preparation in pharmacies and hospitals, wherein raw drugs and excipients can be used solely or mixed with crushed commercial products to fabricate the desired dosage forms. Others anticipate that pharmaceutical manufacturing facilities will start producing pre-packaged, drug cartridges that are suitable for on-demand printing in pharmacies or hospitals. More optimistic views envision that the printing

process can be even performed in one's own home using their own smartphones. Whether these models will be eventually implemented, or newer ones will be developed is yet to be known, but the recent interest seen from different pharmaceutical stakeholders, including pharmacists, researchers, industrial partners and regulatory agencies, appears promising, wherein the current ongoing conversations are testament to this.

DISCLOSURES

Alvaro Goyanes and Abdul W Basit are co-founders of FabRx.

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Figure Captions List

Fig. 1 Graphical representation of the different 3D printing technologies. Reprinted with permission from [180]. SLA, stereolithography; DLP, direct light processing; CLIP, continuous liquid interface production; BJ, binder jetting; SLS, selective laser sintering; DMLS/SLM, direct metal laser sintering/selective laser melting; MJF, multi-jet fusion; EBM, electron beam melting; NPJ, nanoparticle jetting; MJ, material jetting; DoD, drop-on-demand; LENS, laser engineering net shape; EBAM, electron beam additive manufacturing; LOM, laminated object manufacturing; UAM, ultrasonic additive manufacturing; FDM, Fused deposition modelling; DPE, direct powder extrusion; and SSE, semi-solid extrusion.

Fig. 2 (A) 3D design of the prepared FDM 3D printed tablets in their (top) top view and (bottom) side view; from left to right: 1 disc, 2 torus, 3 sphere, 4 tilted diamond, 5 capsule, 6 pentagon, 7 heart, 8 diamond, 9 triangle and 10 cube [17]. (B) Images of SLS 3D printed gyroid lattice solid dosage forms composed of the different polymer formulations, including (from left to right) polyethylene oxide, Eudragit L100-55, ethyl cellulose and Eudragit RL [67]. (C) Images of the FDM channeled tablets with decreasing channel size from left to right, containing (top) 9 long channels and (bottom) 18 short channels [20]. (D) Image of SSE 3D printed drug-loaded orodispersible film imprinted with a QR code containing information about the dosage form, in its (left) extended and (right) folded forms [300]. (E) Images of FDM 3D printed capsule shells in different sizes including sizes (from left to right) 000, 00 and 0 [75]. Images were reprinted with permissions from their original sources.

Fig. 3 (A) Raman mapping mage of an SLA 3D printed 6-layer polypill showing the spatial separation of layers, wherein different colors refer to different drugs embedded in individual layers [27]. (B) Scanning electron microscopy (SEM) image of an SLS 3D printed dual miniprintlet containing two drug/polymer regions, namely acetaminophen embedded within a Kollicoat IR matrix (shown in green) and Ibuprofen embedded in an ethyl cellulose matrix (shown in blue) [85]. (C) Image of FDM 3D printed fruit chewable formulations in the shapes of a (from left to right) palm, cherry, Smurf, banana and tablet [88]. (D) Images of SLS 3D printed tablets containing the 26 Braille alphabets on their surface [90]. Images were reprinted with permissions from their original sources.

Fig. 4 (A) Image of an SLA 3D printed hollow bladder device (top left) before and (top right) after filling with 10% drug loading mixture; and (bottom) the hollow 10% device when stretched [114]. (B) (top) 3D scan model of the hearing aid and (bottom) image of the DLP 3D printed hearing aids (from left to right) fabricated without drug, with ciprofloxacin-fluocinolone acetonide 6%–0.5%

and 12%–1%, respectively [116]. (C) (left) 3D design and (top right) image of the gastric-resident electronics device showing its different components; (bottom left) X-ray image showing the deployed gastric-resident electronics device in a porcine stomach [118]. (D) Schematic illustration of the drug delivery to liver tissue from the 3D printed reservoir system after its implantation in vivo [119]. (E) Graphical illustration of the use a DLP 3D printed punctal device for controlled ocular drug delivery [126]. SEM images of the devices are shown on the right, including devices loaded with (top) 10% dexamethasone, and (bottom) 20% dexamethasone an PEG400. Images were reprinted with permissions from their original sources.

Fig. 5 Graphical illustration of the different components of the FDM 3D printing process. Reprinted with permission from [301].

Fig. 6 Conventional SLA-based precision medicine: (A) various shapes of tablets containing acetaminophen with a tunable drug release rate by changing the ratio of surface area over volume [64], (B) fabrication of a multi-layered polypill containing 6 different types of drugs [27], (C) fabrication of 4-ASA and acetaminophen-loaded tablets with a controllable release profile by changing the hydrogel composition [205], and (d) ibuprofen-loaded soft gels with a controllable drug release rate by changing the water content [206].

Fig. 7 DLP-based precision medicine: (A) tablets with various content and releases profiles [207], (B) 3D printed nerve conduits with an encapsulated drug to facilitate the regeneration of the peripheral nerves [211], (C) tablets with an increased drug release rate by the addition of hydrophilic polymer [212], and (D) tablets with a customized release rate by controlling the thickness and encapsulated drug content [213].

Fig. 8 Graphical illustration of (A) selective laser sintering, (B) selective laser melting and direct metal laser sintering, (C) electron beam melting and (D) multi-jet fusion 3D printing technologies. Reprinted with permission from [220].

Fig. 9 Printheads commonly used in BJ-3DP process a) Thermal printhead which contains a heater inside the chamber and b) Piezoelectric printhead that contains piezo element both of which cause a pressure build up inside the chambers jetting process. Reprinted from [302], Copyright (2021), with permission from Elsevier.

Table Caption List

Table 1 Common materials and their processing characteristics [154–156,159,161,162,303,304]

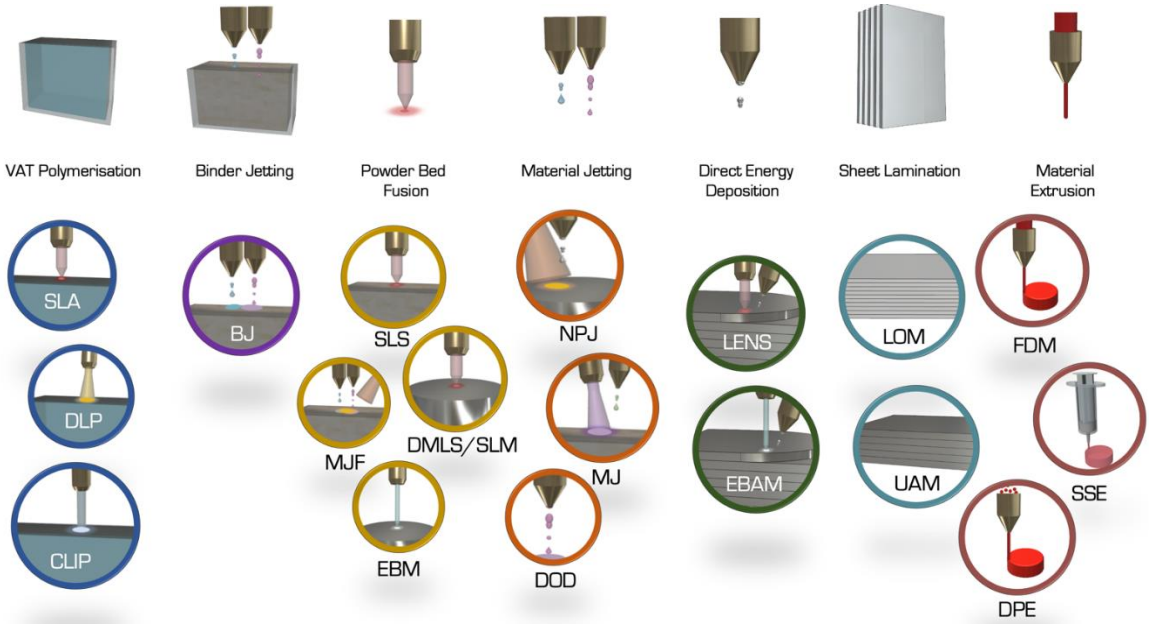

Fig. 1 Graphical representation of the different 3D printing technologies. Reprinted with permission from [180]. SLA, stereolithography; DLP, digital light processing; CLIP, continuous liquid interface production; BJ, binder jetting; SLS, selective laser sintering; DMLS/SLM, direct metal laser sintering/selective laser melting; MJF, multi-jet fusion; EBM, electron beam melting; NPJ, nanoparticle jetting; MJ, material jetting; DoD, drop-on-demand; LENS, laser engineering net shape; EBAM, electron beam additive manufacturing; LOM, laminated object manufacturing; UAM, ultrasonic additive manufacturing; FDM, Fused deposition modelling; SSE, semi-solid extrusion; and DPE, direct powder extrusion.

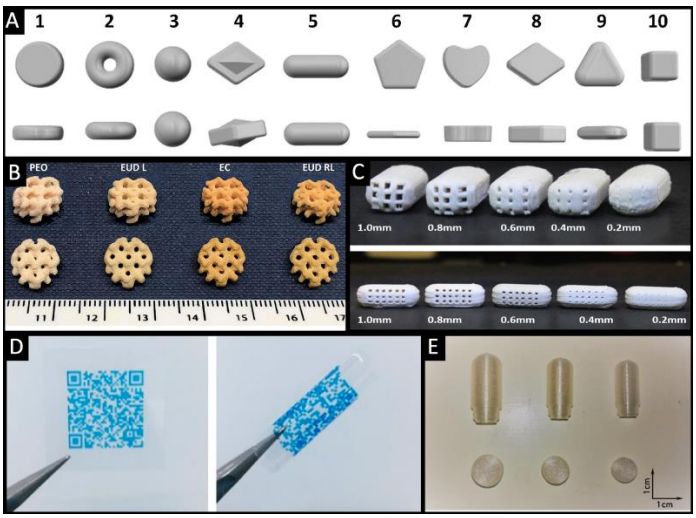

Fig. 2 (A) 3D design of the prepared FDM 3D printed tablets in their (top) top view and (bottom) side view; from left to right: 1 disc, 2 torus, 3 sphere, 4 tilted diamond, 5 capsule, 6 pentagon, 7 heart, 8 diamond, 9 triangle and 10 cube [17]. (B) Images of SLS 3D printed gyroid lattice solid dosage forms composed of the different polymer formulations, including (from left to right) polyethylene oxide, Eudragit L100-55, ethyl cellulose and Eudragit RL [67]. (C) Images of the FDM channeled tablets with decreasing channel size from left to right, containing (top) 9 long channels and (bottom) 18 short channels [20]. (D) Image of SSE 3D printed drug-loaded orodispersible film imprinted with a QR code containing information about the dosage form, in its (left) extended and (right) folded forms [300]. (E) Images of FDM 3D printed capsule shells in different sizes including sizes (from left to right) 000, 00 and 0 [75]. Images were reprinted with permissions from their original sources.

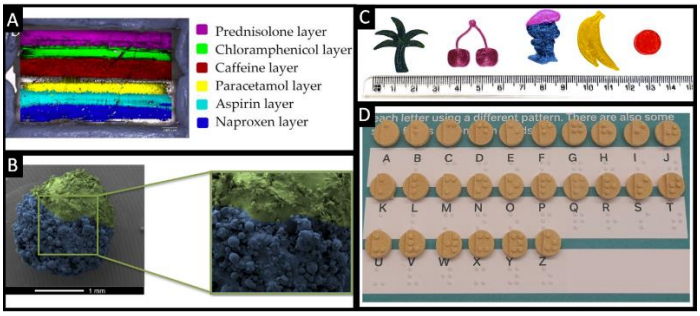

Fig. 3 (A) Raman mapping mage of an SLA 3D printed 6-layer polypill showing the spatial separation of layers, wherein different colors refer to different drugs embedded in individual layers [27]. (B) Scanning electron microscopy (SEM) image of an SLS 3D printed dual miniprintlet containing two drug/polymer regions, namely acetaminophen embedded within a Kollicoat IR matrix (shown in green) and Ibuprofen embedded in an ethyl cellulose matrix (shown in blue) [85]. (C) Image of FDM 3D printed fruit chewable formulations in the shapes of a (from left to right) palm, cherry, Smurf, banana and tablet [88]. (D) Images of SLS 3D printed tablets containing the 26 Braille alphabets on their surface [90]. Images were reprinted with permissions from their original sources.

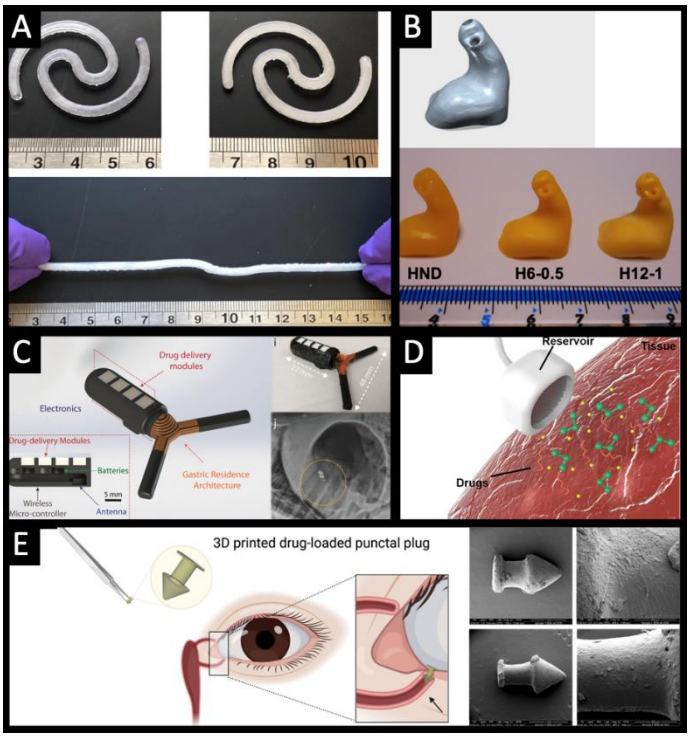

Fig. 4 (A) Image of an SLA 3D printed hollow bladder device (top left) before and (top right) after filling with 10% drug loading mixture; and (bottom) the hollow 10% device when stretched [114]. (B) (top) 3D scan model of the hearing aid and (bottom) image of the DLP 3D printed hearing aids (from left to right) fabricated without drug, with ciprofloxacin-fluocinolone acetonide 6%–0.5% and 12%–1%, respectively [116]. (C) (left) 3D design and (top right) image of the gastric-resident electronics device showing its different components; (bottom left) X-ray image showing the deployed gastric-resident electronics device in a porcine stomach [118]. (D) Schematic illustration of the drug delivery to liver tissue from the 3D printed reservoir system after its implantation in vivo [119]. (E) Graphical illustration of the use a DLP 3D printed punctal device for controlled ocular drug delivery [126]. SEM images of the devices are shown on the right, including devices loaded with (top) 10% dexamethasone, and (bottom) 20% dexamethasone an PEG400. Images were reprinted with permissions from their original sources.

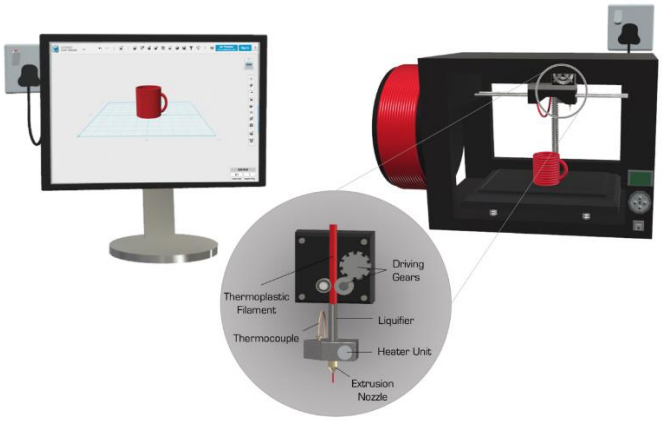

Fig. 5 Graphical illustration of the different components of the FDM 3D printing process. Reprinted with permission from [301].

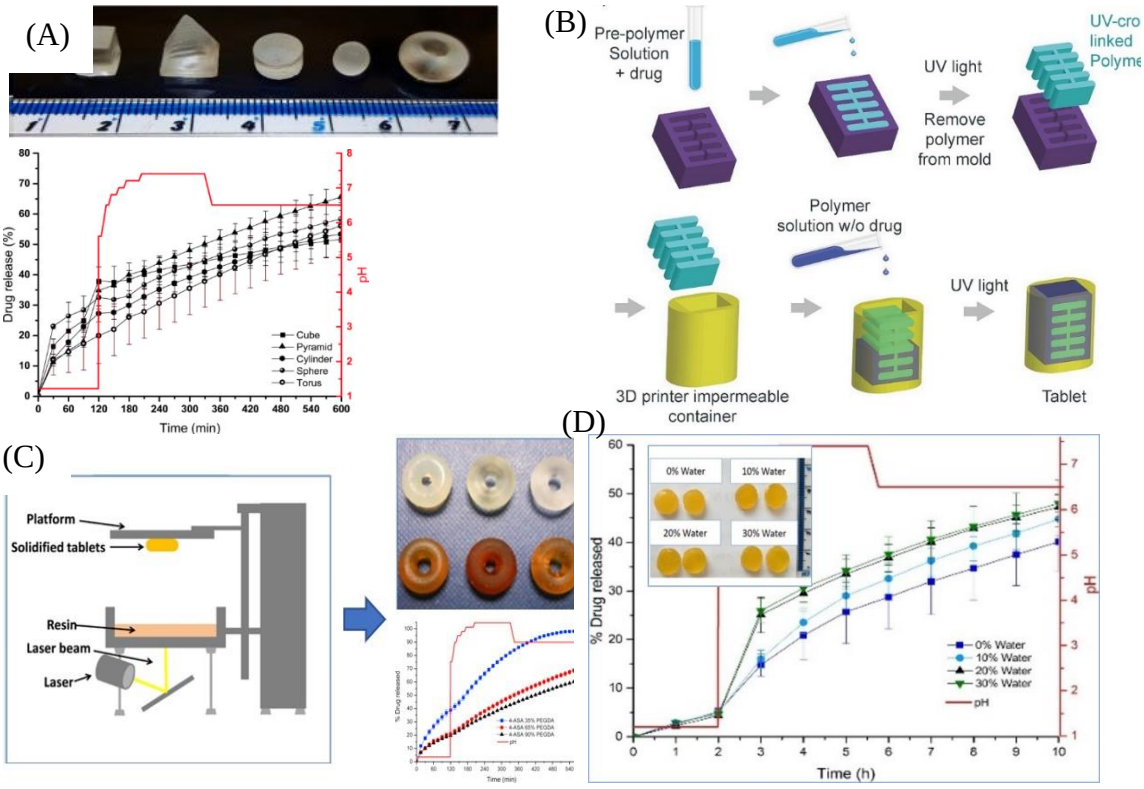

Fig. 6 Conventional SLA-based precision medicine: (A) various shapes of tablets containing acetaminophen with a tunable drug release rate by changing the ratio of surface area over volume [64], (B) fabrication of a multi-layered polypill containing 6 different types of drugs [27], (C) fabrication of 4-ASA and acetaminophen-loaded tablets with a controllable release profile by changing the hydrogel composition [205], and (D) ibuprofen-loaded softgels with a controllable drug release rate by changing the water content [206].

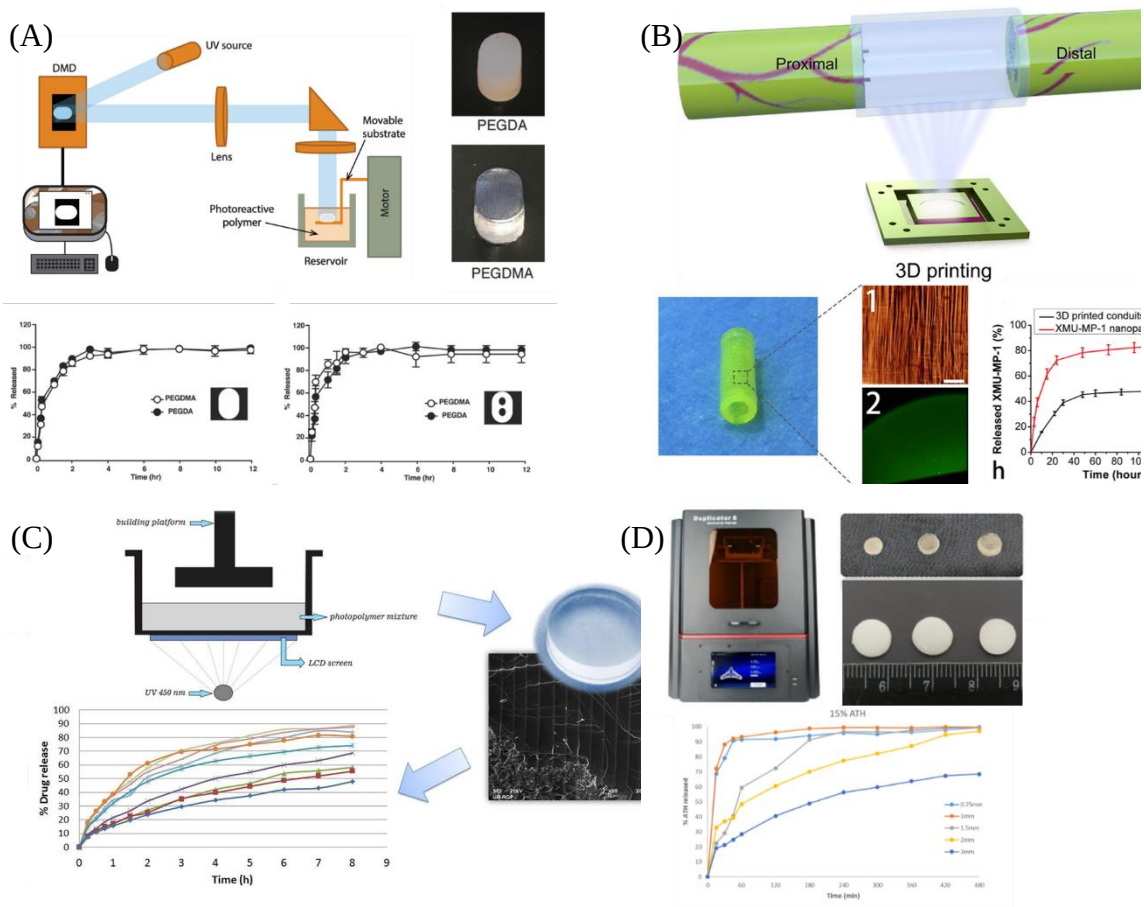

Fig. 7 DLP-based precision medicine: (A) tablets with various content and releases profiles [207], (B) 3D printed nerve conduits with an encapsulated drug to facilitate the regeneration of the peripheral nerves [211], (C) tablets with an increased drug release rate by the addition of hydrophilic polymer [212], and (D) tablets with a customized release rate by controlling the thickness and encapsulated drug content [213].

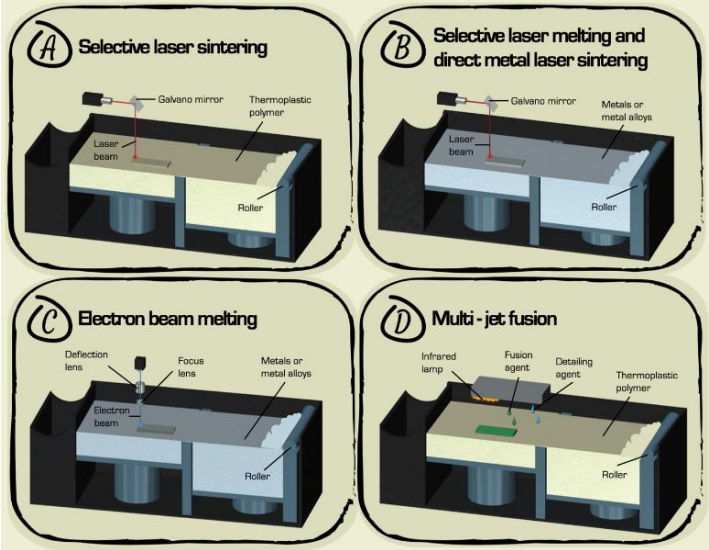

Fig. 8 Graphical illustration of (A) selective laser sintering, (B) selective laser melting and direct metal laser sintering, (C) electron beam melting and (D) multi-jet fusion 3D printing technologies. Reprinted with permission from [220].

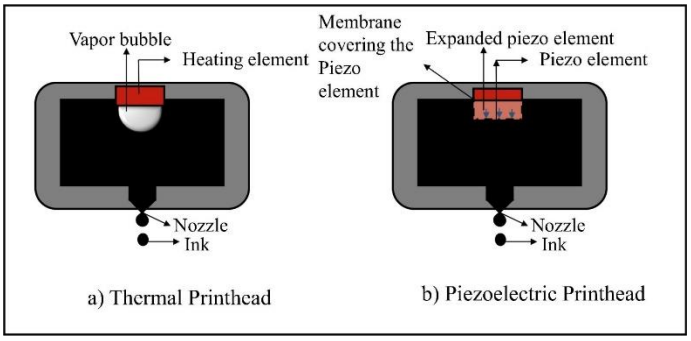

Fig. 9 Printheads commonly used in the binder jetting 3D printing process (A) Thermal printhead which contains a heater inside the chamber, and (B) Piezoelectric printhead that contains piezo element both of which cause a pressure build up inside the chambers jetting process. Reprinted from [302], Copyright (2021), with permission from Elsevier.

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Materials	**T_m (°C)**	**T_g (°C)**	**Solubility**	**Bio-degradable**	**Applications and characteristics**	**Applicable processes**
Vinyl Polymers						
Polymethacrylate (PMA)	376-395	49-60	Y (pH ~6-7.4)	Y	Coatings, resistant to acidic	FDM
Polymethylmethacrylate (PMMA)	160	105	N – water Y – organic solvents	N	Coatings, sustained release	FDM/SLS
Polyvinyl alcohol (PVA)	180 to 228	85	Y	Y	Tablets, immediate release in hydrochloric acid, controlled release	FDM/SLS
Polyacrylic acid (PAA)	180-250	106	Y	Y	Delayed and sustained release	FDM
Polyesters						
Polylactic acid (PLA)	150 to 175	60 to 65	Y – chlorinated solvents	Y	Tablets, delayed release	FDM/SLS
Polycaprolactone (PCL)	55 to 60	-54 to -60	Y – organic solvent, chloroform, chloromethanes and a trihalomethane.	Y	Scaffold, implant	FDM/SLS
Polylactic glycolic acid (PLGA)		45 to 50	Y – chloroform, chloromethanes and a trihalomethane.	Y	Sustained release	FDM
Polyglycolic acid (PGA)	225 to 230	35 to 40	Y – hexafluoro-isopropanol	Y		FDM
Polyethylene glycol (PEG)	40 to 68		Y	N	Sustained release, liquid photopolymer	SLA
Poly (ethylene glycol) diacrylate (PEGDA)	5 to 10		Varies	Y	Liquid photopolymer	SLA
Cellulose Ethers						
Methylcellulose (MC)	290 to 305	150 to 160	Y	Y	Thickening agent, controlled release	FDM/SSE
Hydroxypropyl cellulose (HPC)	130 (softening) 260 (charring)	-25 to 0	Y – cold N – hot	Y	Controlled release, coating, binder	FDM/SSE/SLS
Hydroxypropyl methylcellulose (HPMC)	225 to 230 (charring)	165 to 198	Y – cold Gels when heated	Y	Thickening binder, coating, controlled release	FDM/SSE/DOP/SLS
Ethyl cellulose (EC)	152 to 162	129 to 133	N – water Y - chloroform	Y	Sustained release, coating	FDM/SSE/SLS

[1] Zanaboni P., Wootton R., Adoption of telemedicine: from pilot stage to routine delivery, BMC Medical Informatics and Decision Making, 12 (2012) 1-1.