Additive Manufacturing 34 (2020) 101209

Contents lists available at ScienceDirect

Additive Manufacturing

journal homepage: www.elsevier.com/locate/addma

Review

Pharmaceutical Applications of 3D Printing

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ARTICLE INFO

Keywords:
3D printing
additive manufacturing
drug delivery
drug testing
pharmacy
lab-on-a-chip

ABSTRACT

Although 3D printing (3DP) has long been an integral part of industries such as aviation and automotive, its use in healthcare, especially the pharmaceutical industry, is relatively new and currently receiving close attention. At the beginning of 2018, we reviewed the applications of 3DP for drug delivery and drug testing [1]. Due to the rapid development of this field, it is necessary to summarize the latest development in this field after 2 years. In this article, we reviewed the three major areas in pharmaceutical applications. First, drug delivery system is the most studied subject, including controlled release, polypills, gastrofloating, orodispersibles and microneedles. Second, 3DP also helped the development of pharmaceutical devices, including pharmacy dispensing aids and drug eluting devices. Lastly, we reviewed the pharmaceutical models for drug testing, covering acellular and cellular models. We also summarized the materials used in the mentioned articles and their regulatory status for pharmaceutical applications to provide references for future research.

1. Introduction

Additive manufacturing (AM), or commonly known as 3D printing (3DP), is a method of manufacture whereby an object is built up layer by layer [1–3]. It includes multiple techniques, such as fused deposition modelling (FDM), hot melt extrusion (HME), solid state extrusion (SSE), stereolithography apparatus (SLA), digital light processing (DLP), selective laser sintering (SLS), vat polymerisation and binder jetting [4]. Although widely used in other industries, such as automobile and aerospace, its use in the pharmaceutical field is still in its infancy [5]. Recently, many AM patents have expired [6], which has made this new technology readily available and led to its wide applications in various fields.

The use of AM has brought the pharmaceutical industry a whole step closer to the era of personalised medicine [7–12]. Even when given the same dose, there may be significant inter-individual differences in drug responses [13]. Personalised medicine could result in a lower risk of adverse effects or subtherapeutic benefits due to these dosages outside the therapeutic window [14,15] and could lead to increased adherence and greater satisfaction for patients [16,17]. Personalised medicine also includes suitable dosage forms for special populations, such as paediatric, geriatric, or dysphagic patients so that they are able to utilise medication [18]. While available forms on the market can be altered via breaking/crushing tablets and opening capsules, there may be concerns about inaccurate dosing or inconvenience/ability of the patient to carry out such modifications regularly. Traditional manufacture methods do not provide personalised patient dosing as it is not cost-effective and impractical whereas AM has high accuracy [6], a highly adaptable nature [17] and can be used as an alternative manufacture tool. In a study by Tian et al., a series of tablets containing warfarin were produced, with the dose being varied by changing the tablet size [19]. The resultant tablets had accurate dosage and met the standards required for friability and hardness. In the future, AM technology may be able to produce medications on-demand and be used as a means to increase the accessibility to medicines for those living in remote areas [8,20].

AM can be used to produce complex geometries, which has made the production of certain oral dosage forms and medical devices possible [17,21]. Although its manufacturing speed compared to conventional pharmaceutical mass production is slow, it has its own advantages, such as individualization and relatively low cost for small batch production [22]. Certain AM technologies, e.g., DLP and SLA, are able to create products high in accuracy, making it possible to produce microscale drug delivery systems, such as microneedles (MNs) [23]. Recently, Khaled et al. showed that AM was capable of printing high dose paracetamol tablets, which is not possible by using conventional manufacture methods due to limitations involved in material blending and tabletting compression [24].

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https://doi.org/10.1016/j.addma.2020.101209
Received 14 November 2019; Received in revised form 7 March 2020; Accepted 25 March 2020
Available online 30 April 2020

However, AM has its own set of constraints, namely, the limited materials suitable for pharmaceutical purposes, difficulties associated with high drug loaded filaments [25], inefficiency to be used for large scale production [6,26]. For instance, high drug loading in pharmaceutical manufacturing is preferred because it can reduce the use of excipient and avoid potential material mixing issues. However, increased drug loading can compromise the printability of the materials and result in faulty products [27]. Moreover, as AM is an emerging field with fast growing rate, regulations have not yet been clearly put forth, but it is very likely that there will be issues related to product quality control, privacy concerns and intellectual property rights [8,21,28,29].

In this review, relevant research articles were identified by searching through the Medical Literature Analysis and Retrieval System Online (MEDLINE) and The Excerpta Medica Database (EMBASE). The inclusion criteria are that the article should be in English language and from 2018 onwards. Only results from 2018 onwards were included as there are multiple review articles available summarising the pharmaceutical applications of AM before 2018 [1,30]. Following the identification of relevant articles, duplicates were removed, and the full texts were located. The articles were then screened, and any irrelevant articles were excluded, along with those which full texts could not be found for. A few articles of interest were also identified through the references and included as well.

2. Oral Solid Dosage Forms

2.1. Controlled Release

The release of drug from dosage forms plays a vital role for their subsequent absorption and therapeutic effect. For most oral dosage forms, immediate release (IR) is needed for drug absorption. On the other hand, sustained release allows the slow release of therapeutic compounds, reducing the fluctuations in drug level associated with taking multiple IR dosage forms at regular intervals. This may confer therapeutic benefit [31] and/or patient convenience [32]. Traditional sustained release tablets have a decreasing total surface area as they go through the absorption process inside gastrointestinal tract, resulting in a non-constant drug release. AM can overcome this problem by producing tablets with complex geometries, allowing not only constant sustained-release dissolution profiles to be produced, but also those with customized release profiles.

Zhao et al. printed a spherical shell with an empty internal tetrahedron cavity with an FDM printer using poly (vinyl alcohol) (PVA) [32]. This was then filled with the mixture of PVA and a drug. Upon contact with water, starting from the 4 corners, an increasing area of the tetrahedral shaped core was exposed as the tablet eroded, leading to increased drug dissolution over time (Fig. 1a). The accelerated drug release was potentially useful for certain diseases, such as hypertension, as patients can take this tablet at night and the maximum drug concentration in blood will peak in the morning. In another example, Kadry et al. printed tablets with various infill patterns using an FDM printer [33]. The drug-impregnated filaments were produced by extruding the mixture of diltiazem and hydroxypropyl methylcellulose (HPMC) powder. The results showed that the tablets with hexagonal infill patterns dissolved faster (Fig. 1b). Similarly, Yang et al. also reported that drug release rate was affected by the tablet patterns [34]. The tablet was printed by using an FDM printer, using filaments containing ibuprofen and ethyl cellulose.

In addition, it is known that surface area is proportional to drug release rate, based on which tablets with different release profiles can be designed. Khaled et al. printed tablets with different shapes using an extrusion-based 3D printer with a mixture of paracetamol and excipient as the printing ink [35]. The results showed the tablets with larger surface areas had faster drug release. Similarly, Cui et al. mixed glipizide, poly (vinyl pyrrolidone) (PVP) and HPMC to form a paste which was printed at room temperature to obtain tablets with different grid width, which showed similar trend for drug release [36].

This concept of increasing surface area has been used to increase drug release. A novel radiator-like structure, which had 7-8 times the surface area to mass ratio than traditional tablets, was proposed by Isreb et al. (Fig. 1c) [37]. To facilitate drug release, the plates of the "radiator" were kept thin to minimise the thickness of the gel layer which formed on contact with water. In another study, a bi-layer tablet consisting of both an exposed lattice structure and a conventional infilled tablet was produced by Fina et al. The high surface area of the lattice layer provided a rapid drug release in 30 minutes [38] (Fig. 1d).

Tablets with unique drug release profiles were also reported (Fig. 1e). The 'chrono-tablet' consisted of a drug core surrounded by a drug free outer layer, which served to delay the release of drug. The 'pulsatile-tablet' consisted of 3 layers, of which the innermost and outermost layer contained the drug and were separated by a middle drug-free layer, which introduced an adjustable drug free time between the release of the outermost and innermost drug containing layers [33].

In addition to geometry, excipients were also seen as a factor affecting drug release rates [39,40]. Tagami et al. fabricated naftopidil tablets using a semi-solid extrusion printer [40]. Various amount of HPMC, naftopidil and other excipients were mixed to form the printing inks. The results showed that the drug release rate was proportional to the percentage of HPMC. In another study, low dose pramipexole tablets displayed comparable release profiles to conventional tablets, without the use of fillers or disintegrating agents [41].

Moreover, there was also progress on drug release theories, driven by this new technology. For AM, certain materials, such as cellulose, are widely used as drug carriers. However, Higuchi equation, derived from Fickian diffusion laws, cannot be applied to such materials for drug release studies, because these materials swell and cause non-Fickian diffusion. To this end, a mathematical model to predict drug dissolution from such materials was proposed, as an extension of Higuchi equation [42].

2.2. Polypills

There is an increasing number of patients, especially geriatric, on polypharmacy, which raises concerns with medication errors due to regime complexity [3]. Certain diseases, such as cardiovascular disease, are likely to require the use of multiple medications. An increase in the number of medications in an individual's regime may be associated with poorer adherence and therefore poorer health outcomes [43]. A polypill, therefore, would theoretically simplify an individual's medication regime, leading to increased patient convenience and adherence [44]. In 2003, Wald and Law proposed a polypill, which consisted of 6 active ingredients in a preventative strategy to reduce cardiovascular diseases by more than 80%. However, it was highly criticized at the time, as it did not consider the different dosage or combination needs of different individuals, or their changing needs and there were also concerns about chemical incompatibility between components [43].

With the advent of AM technology, these concerns can be addressed. The combination of drugs in a polypill and their specific dosages can be tailored to an individual's current medication plan at the time. As AM is an accurate process, dosing accuracy is a minor concern [45]. In addition, issues with incompatibility can be addressed by separating the drugs by a chemically compatible excipient or compartmentalising each drug to different parts of the tablet [30,46] (Fig. 1f). Maroni et al. manufactured a two-compartment capsular device by FDM [46]. This device is able to convey chemical incompatible drugs or differing drug formulations. The dissolution profile was resulted from the thickness of capsule. The concept of compartmentalization was also applied by Christos et al, in which a tablet containing two anti-diabetic drugs, namely, metformin and glimepiride was printed [47]. The tablets were printed by FDM with two drug-load filaments from two nozzles to segregate the drug inside one tablet.

In a more complex model, Pereira et al. produced 2 architectures of

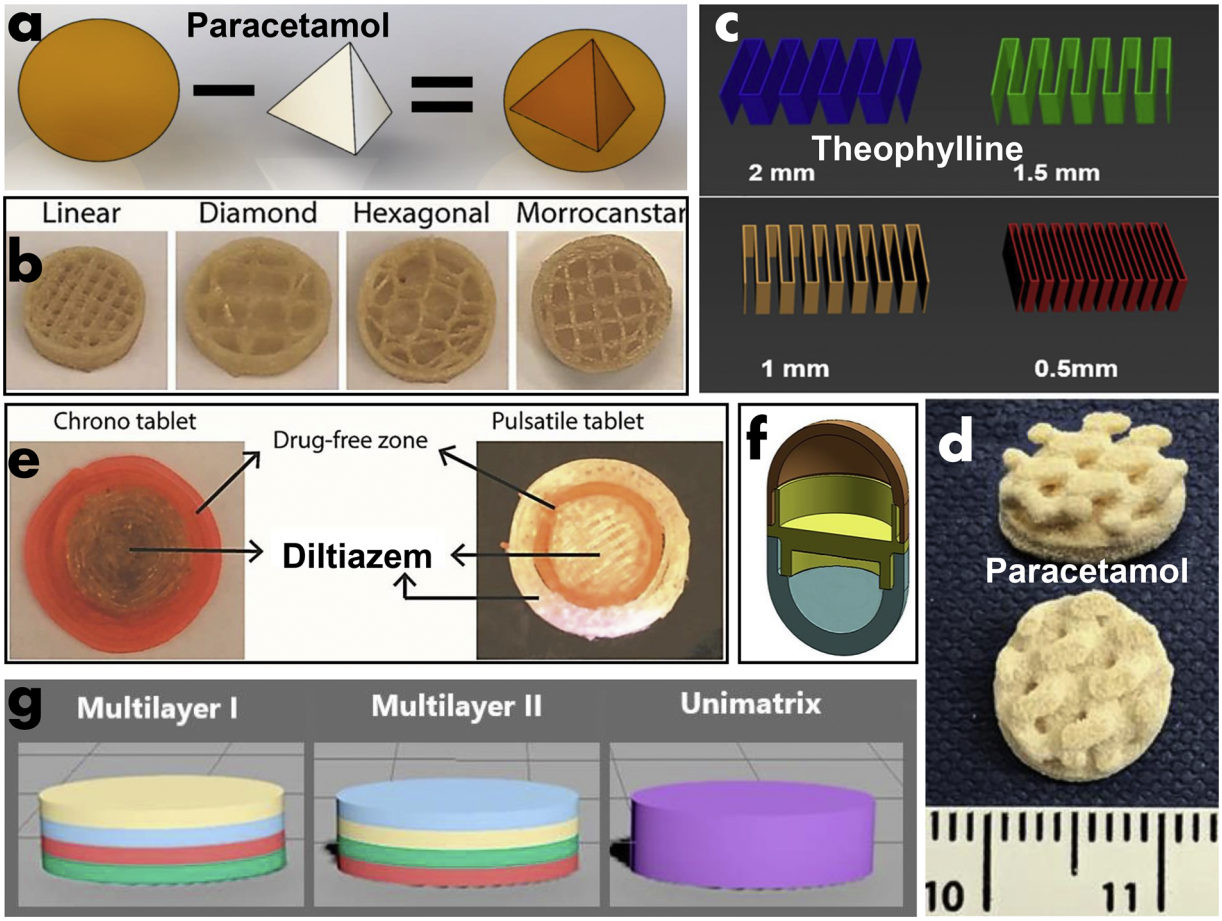

Fig. 1. Oral dosage forms created by AM. (a) Model of 3D printed shell with convex drug release profile. (b) Various infill patterns created by 3D printing. (c) Computer-aided design file of novel radiator-like design. (d) 3D printed bilayer tablet consisting of multiple release profiles. (e) 3D printed "chrono tablet" and "pulsatile tablet". (f) Capsule consisting of two separate compartments. (g) Computer-aided design file of different architectures for a polypill.

polypills containing 4 ingredients: amlodipine, rosuvastatin, indapamide and lisinopril [43]. The two architectures each consisted of 4 layers, each with a different layer (Fig. 1g). A third polypill where all 4 ingredients were mixed together was also created. The authors concluded that while the combined pill only used a single filament to create and therefore could reduce time and financial costs, there may be concerns regarding its stability. In comparison, the multilayered polypill was able to not only cater to different dosages, but the release profile could also be adjusted by changing the stacking order of the different layers.

2.3. Gastrofloating

According to their chemical and solubility properties, drugs taken orally are best absorbed in different part of the gastrointestinal tract. Dipyridamole is one such drug which is absorbed in the acidic environment of the stomach, due to its low solubility which is pH dependant [48]. As such, the gastric retention time is the main factor deciding its absorption.

There are two main types of gastric floating systems used to increase gastric retention time. One is the effervescent systems which use CO_2 to maintain buoyancy, and the other is non-effervescent systems which minimise bulk density to float, as shown in Fig. 2a [49]. AM can easily produce low density objects by changing the infill density setting. Huanbutta and Sangnim produced a system where a drug loaded tablet core was placed within a 3D printed container, consisting of a cap and body. Drug release was facilitated via a pore in the container (Fig. 2b,c). Li et al. used another approach, in which a series of lattice filled dipyridamole tablets were produced [48]. The printing ink is a mixture of HPMCs as hydrophilic matrices and microcrystalline cellulose as the extrusion moulding agent, printed using an extrusion-based printer at room temperature. Various infill rates were used to compare the characteristics of buoyancy and drug release rates (Fig. 2d). As lattice density increased, the increasing weight caused the tablet to sink, which led to an increased drug release rate, similarly to the findings by Huanbutta and Sangnim.

Also using cellulose as the printing materials but with an FMD printer, Chai et al. printed hollow tablet based on FDM by using hydroxypropyl cellulose (HPC) [50]. The drug, namely, domperidone, was incorporated into the into HPC filaments using a hot melt extruder. Due to low density and rigid shells, prolonged floating and release was observed. In another study, a novel AM technique, namely, pressure-assisted microsyringe (PAM) was used to fabricate tablets of different inner structures [51]. With PAM, a variety of conventional pharmaceutical excipients can be printed, for e.g., HPMC, microcrystalline cellulose, PVP and lactose. It is advantageous to use these pharmacopoeial excipients as the printing inks, as the excipients are subject to regulations for pharmaceutical applications.

2.4. Oro-Dispersible

The most common and preferred form of medication taken by patients is oral forms [19,52]. However, oral forms such as tablets, capsules and liquids may represent a challenge to a portion of the populations including paediatrics, geriatric and dysphagia patients [52]. Oro-dispersible tablets are designed to disintegrate in the oral cavity

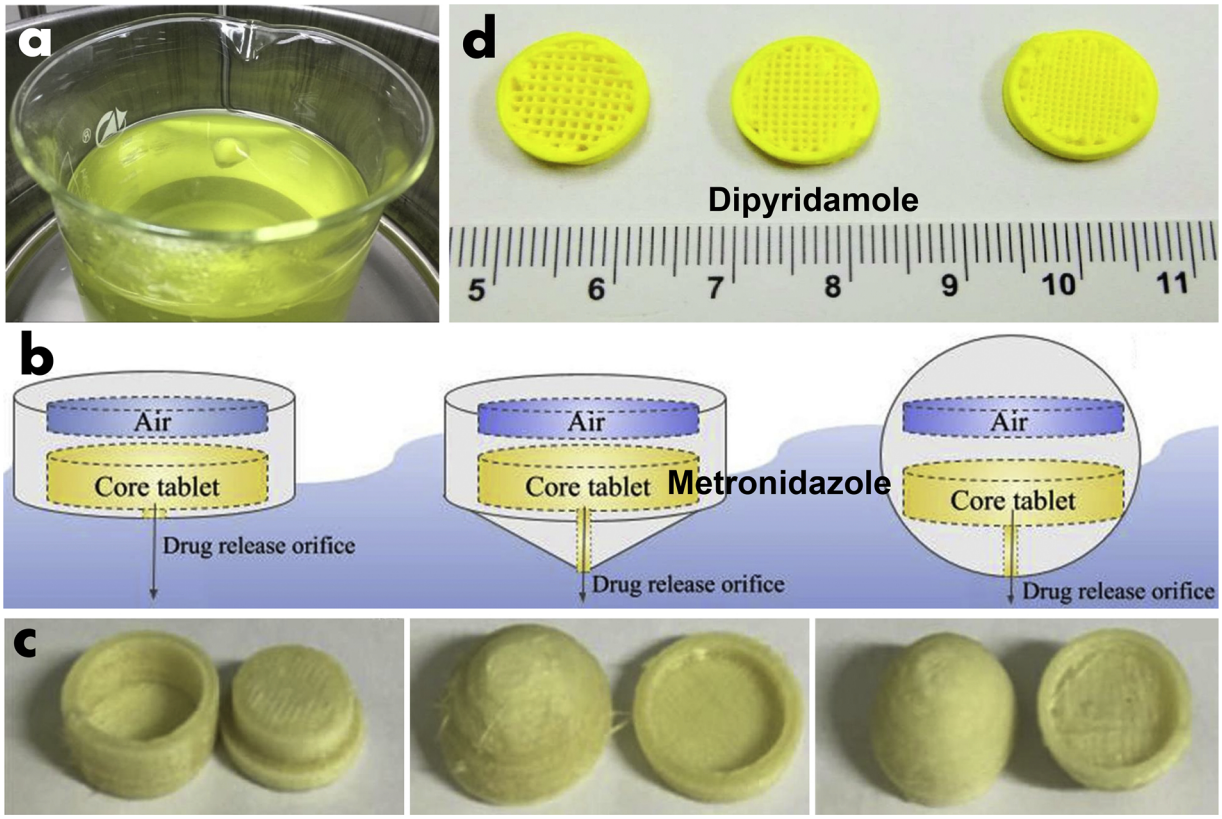

Fig. 2. Gastrofloating tablets. (a) 3D printed gastrofloating tablet exhibiting floating properties. (b) Design of zero-order drug release gastroretentive floating tablets. (c) 3D printed housing of zero-order drug release gastroretentive floating tablets. (d) Various infill percentages of 3D printed dypyridamole containing tablets.

and can be taken without the aid of water. Oro-dispersible tablets are usually associated with a porous structure, leading to a rapid dissolution profile. AM bypasses the large compression forces required in the traditional manufacture method, resulting in a much more porous structure and therefore rapid disintegration. Spritam™ was created using binder jetting and is the first and only US Food and Drug Administration (FDA)-approved AM drug on the market today, dissolving within 2-27 seconds [53]. The same technique was used by Tian et al. to produce oro-dispersible warfarin tablets, which disintegrated within one minute [19]. In addition, SLS was also proven to be capable of creating oro-dispersible paracetamol tablets, with different dissolution rates [52].

2.5. Paediatric Preparations

The paediatric population is a special group whose pharmacokinetic and pharmacodynamic properties are different from those of adults [3,42,54]. As such, dosages for this population need to be carefully optimised to prevent adverse effects from toxicity. Syrups are dose-adjustable and are available to use as paediatric formulations, however, they are prone to dosage error [55] and many have unpleasant tastes. A novel solution to this problem is a miniprintlet, which is a mini tablet produced by 3D printing. Compared to syrups, a mini tablet may be easier to administer due to the reduced taste and small size. Furthermore, AM can be used to adjust dosages by controlling the amount of material used [56]. It has been shown to be possible via SLS or FDM. It is also possible to combine different medications into one miniprintlet, to further simplify administration (Fig. 3a).

The shape of the tablet also influences the swallowing process [30]. This could be adapted for use in populations who have difficulty swallowing traditional tablets, e.g., paediatric, geriatrics, people with dysphagia etc. (Fig. 3b). Another dosage form for young children was proposed by Scoutaris et al., where fun shaped chewable tablets which were taste masked. In this study, the bitter taste of indomethacin was masked through H-bonding interactions between the drug and polymer, which was facilitated by hot melt extrusion. The produced drug-loaded filament was then fed into a 3D printer to be printed into fun shapes to increase appeal to younger children [55] (Fig. 3c).

3. Transdermal Microneedle (MN) Patches

Transdermal drug delivery is to deliver the drugs through skin. The limitation of transdermal delivery mainly in the skin itself, especially the stratum corneum [57]. MNs, with an array of needles of a few hundred microns, provide a useful tool to deliver therapeutics through skin by piercing through skin to provide microscale passages. Conventional manufacturing methods, such as microfabrication or moulding, are complex and involving multiple steps. To this end, AM technologies, especially SLA and DLP, provide alternative methods for MN manufacturing.

An SLA printer was used to print biocompatible liquid resin into MN patches which were then washed with alcohol to remove any residuals [57]. Afterwards, insulin-sugar thin layers were deposited onto the MN surface through inkjet printing. Similarly, Uddin et al. fabricated polymeric MNs using an SLA printer and then coated the MNs with cisplatin formulations [58]. It has been shown that the mechanical strength, buckling load and the force required to pierce human skin were important parameters to consider for printing MNs using the SLA printers [59].

For personalization, MNs can be printed on a curved surface, which is challenging with other fabrication methods without AM. Lim et al. fabricated a curved MN patch with varying curvatures to simulate the specific portion of human facial contour by using a DLP printer [60]. It was demonstrated that curved MNs complying with facial contours provided better skin penetration and drug delivery efficacy, as the skin penetration forces could be evenly distributed.

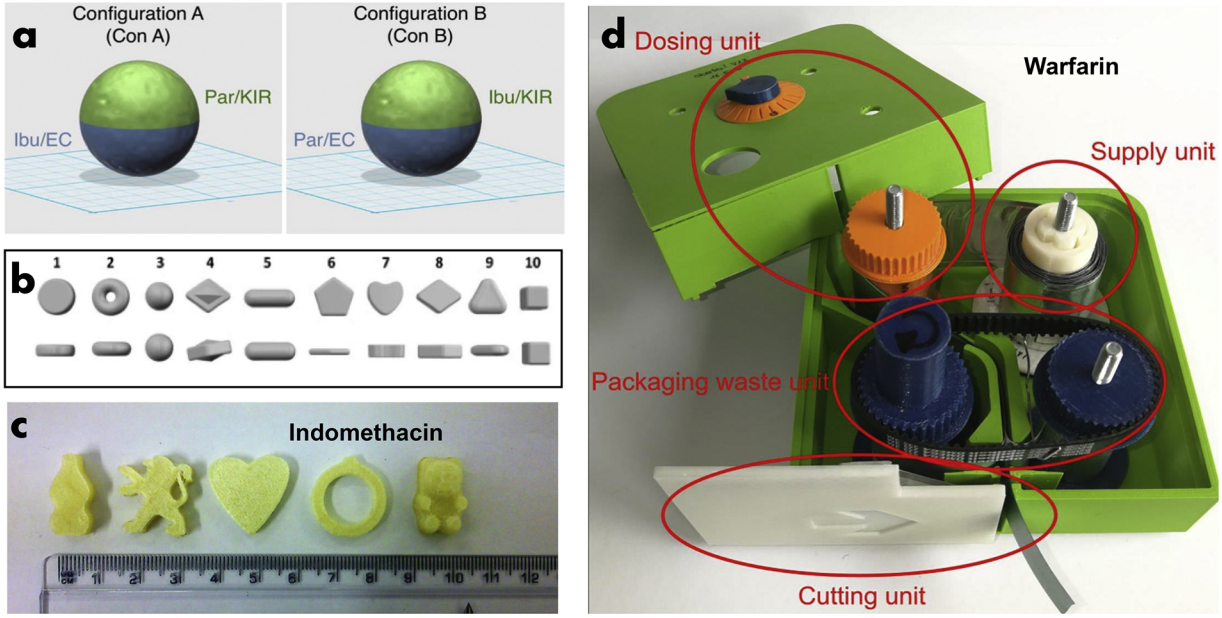

Fig. 3. Designs to aid pharmacy dispensing. (a) Different configurations of a polypill containing ibuprofen and paracetamol. (b) Shape of tablets influence perceived difficulty of swallowing tablets. (c) 3D printed chewable fun-shaped tablets for children. (d) 3D printed dosing device for warfarin film.

In addition to direct MN fabrication, DLP printers has been used to print MN masters, onto which polydimethylsiloxane (PDMS) was cast to create a mould [61]. With the PDMS mould, an active MN patch was fabricated, loaded magnesium microparticles for deeper and faster intradermal drug delivery. This study is a demonstration of the high resolution, i.e., a few microns, that an economical DLP printer can achieve using photocrosslinkable polymers.

Apart from solid MNs, hollow MNs can also be fabricated using SLA. Yeung et al. embedded microfluidic architectures with hollow MNs [62]. The microfluidic channels and MNs were designed as one piece and printed together. This integrated design showed the strength of AM, with which functionally different parts can be manufactured together without the need for further assembly. In this case, the hollow MNs can be used directly for injection via the attached microfluidic channels, instead of being attached to a syringe.

To print MNs, photocrosslinkable liquid pre-polymer solutions can be used. The prepolymer solutions contain macromers and photoinitiators, including methacrylic oligomer, glycol methacrylate, pentamethyl-piperidyl sebacate and phosphine oxide, to achieve high resolution [62]. For other topical applications using hydrogels instead of MN, riboflavin–sodium persulfate–hydroquinone (initiator–catalyst–inhibitor) was also reported, as the photosensitive components for keratin printing [63].

In terms of MN printing technology, it is noted that vat printing is a common approach, which prints 3D objects with photopolymerization, i.e., to expose liquid polymers to ultraviolet or visible light to turn liquid into solids. The advantage of vat printing is high resolution, which is necessary to obtain MNs with sharp tips for skin penetration. Compared with moulding, however, vat printing also has its disadvantages. First, the candidate materials are limited to photocrosslinkable polymers while a variety of materials can be used for moulding method. Second, the photocurable polymer solutions contain photoinitiators, which can be a concern because of their potential toxicity.

4. Pharmaceutical Devices

4.1. Dose Dispensing Aids

Outside the pharmaceutical industry, one of the major uses of AM is to develop prototypes. Traditionally, prototyping required the use of specially made dies or moulds, which were costly and time consuming to obtain. With AM, highly customised models can be created quickly and easily modified and reprinted. AM is a relatively low-cost process, without the need for multiple specialised equipment [2]. There are also many biodegradable and environmentally friendly materials available on the market today, minimising the impact on the environment.

Recently, AM emerged as a powerful tool to create prototypes of a pharmacy dispensing device, which is useful for personalized medicine. Niese et al. developed a prototype of a pharmacy dispensing device for a continuous film loaded with an active ingredient, with the intention of encouraging flexible dosing and personalised medicine [64]. In this study, an orodispersible warfarin film strip was created, sandwiched between 2 foils for storage, and used as the test product. The dosing device was produced in line with the European Pharmacopoeia and consisted of a dosing dial unit, cutting unit, supply unit and waste packaging unit. To use the device, the dosing dial was turned to the needed dosage and the connected supply unit would correspondingly roll out the dialled amount. The drug loaded strip was dispensed from a slot and the waste packing was rolled up onto a separate roll. The device had high dose flexibility while retaining low production costs, with no electrical parts were included, which fits into the Class 1 category (Fig. 3d).

4.2. Drug Eluting Devices

Drug eluting dosages forms, allow the sustained release of a therapeutic agent for a much longer duration than oral dosage forms, reducing the patient's need for frequent dosing. This greatly minimises problems with non-adherence, whether intentional or unintentional [1]. Compared with systemic delivery, this local delivery system can reduce the exposure of healthy tissues to the drug, therefore decreasing the risk of adverse effects [39]. In some cases, using an implantable device provides additional benefits over other delivery systems, for example, intraocular injections associated with complications of increased ocular pressure whereas sustained release devices are not [65].

Drug eluting implants on the market today are available for various applications, such as contraception, cardiovascular disease, ocular delivery, peritoneal delivery and opioid addiction [1,66]. However, the available formulations are limited in terms of shape, ingredients, and

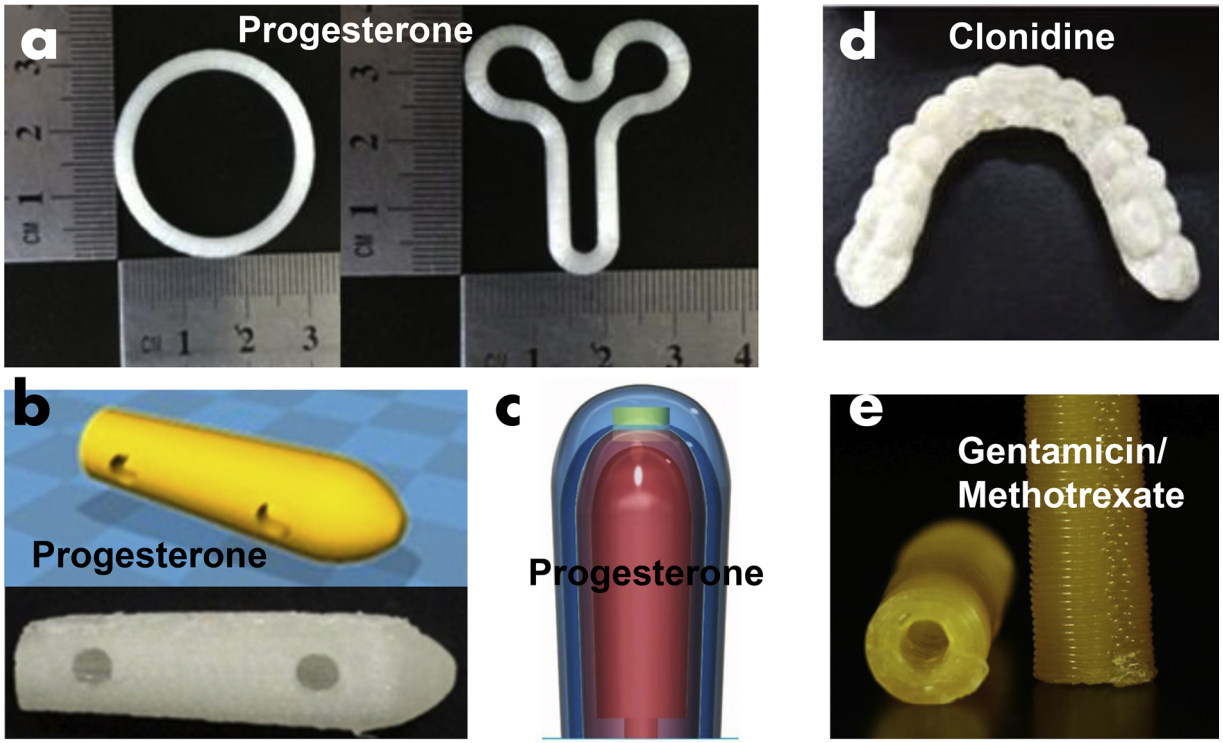

Fig. 4. 3D printed drug eluting dosage forms. (a) 3D printed vaginal rings with personalised shapes for controlled drug release. (b) Computer aided design file of and 3D printed suppository shell for controlled drug release. (c) Computer aided design file of a matryoshka-type suppository shell for controlled drug release. (d) 3D printed personalised orthodontic retainers for sustained release of clonidine hydrochloride. (e) 3D printed catheters for sustained release of antibiotics and chemotherapeutics.

dose. AM can be used to overcome this by manipulating dosage, geometry and drug release profile of the dosage forms. The recent developments in this area include hormone-containing dosage forms for gynaecological applications, implants for cancer therapy, drug laden orthodontic retainers and drug-eluting catheters.

To fabricate hormone eluting constructs, FDM has been used. Tappa et al. fabricated customizable devices by using polycaprolactone (PCL) biodegradable polymers [67]. The drugs, including estrogen and progesterone, were encapsulated in the filaments with an extruder. In this study, 3 types of dosage forms were prepared, namely, subcutaneous implants, intrauterine devices and pessaries. It has been demonstrated that FDM can be used to print drug-laden filaments, albeit high temperature was needed to melt the filaments during the printing process. In another study, Fu et al. used FDM to create a series of controlled-release progesterone vaginal rings with varied shapes and dosages [68] (Fig. 4a). The drug, namely, progesterone was mixed with poly (ethylene glycol) PEG 4000 and then extruded with PCL and poly (lactic acid) (PLA) to make filaments. The printed vaginal rings showed sustained release of progesterone for more than 7 days.

The idea of customised suppositories was taken even further in another study, where an FDM printer was used to create water-soluble suppository shells to customise the release profile of the active drug. PVA filament was used to print the suppository shells with a various number and sizes of holes, then filled with drug laden macrogels containing the drug progesterone (Fig. 4b). Another type of formulation produced was a matryoshka type suppository with multilayered shells, each containing different drugs [69] (Fig. 4c). Preparation of suppositories with several drugs and varying drug release rates is challenging with conventional production methods. With the help of a 3D printer, however, this can be easily achieved. AM technology can be used for personalized medicine by offering a relatively simple tool for making pharmacy preparations.

Apart from gynaecological applications, there were also 3DP implants developed for anti-cancer therapy. Cho et al. printed a nanogel disc carrying drugs to prevent postsurgical complications [70]. To prepare the printing ink, a thickening agent, namely, the poloxamer 407, was mixed with the drugs, namely, paclitaxel and rapamycin, to form a sol, which was then printed into a disc shape. The drug laden disc can be implanted intraperitoneally to prevent peritoneal adhesions after surgery and to eradicate residual tumor tissues. Similarly, Farto-Vaamonde et al. incorporated drugs into filaments at different stages of production, either before printing (resulting in a sustained-release profile), or after printing (resulting in an immediate release profile) [71]. By combining these two techniques, a scaffold impregnated with two different drugs, one fast release and another slow release was created. In the scaffold, prednisolone has anti-inflammatory effect, while dexamethasone can induce osteogenic differentiation, both of which useful for bone regeneration.

Non-implantable drug eluting devices such as clonidine loaded orthodontic retainers have also been reported (Fig. 4d). The drug clonidine hydrochloride was mixed with PEG 4000, PLA, PCL and a non-ionic surfactant, Tween 80, and the resultant mixture was extruded to obtain the filaments. Using an FDM printer, the filaments were printed into a retainer, based on dimensions of the 3D scan of a human volunteer. Although the original 3D printed retainer exhibited an initial burst-release followed by a sustained-release profile, it was eliminated after the retainers were washed with buffered solution to remove clonidine present on the surface [72].

Another study explored the possibility of creating on-demand personalised catheters, where FDM was used to produce gentamycin and methotrexate loaded catheters [73] (Fig. 4e). The drugs were mixed with PLA to form filaments using an extruder. Both gentamycin and methotrexate catheters had sustained drug release for at least 5 days. It was demonstrated that AM had the potential to construct drug laden catheters impregnated with antibiotics and chemotherapeutics for localized drug delivery.

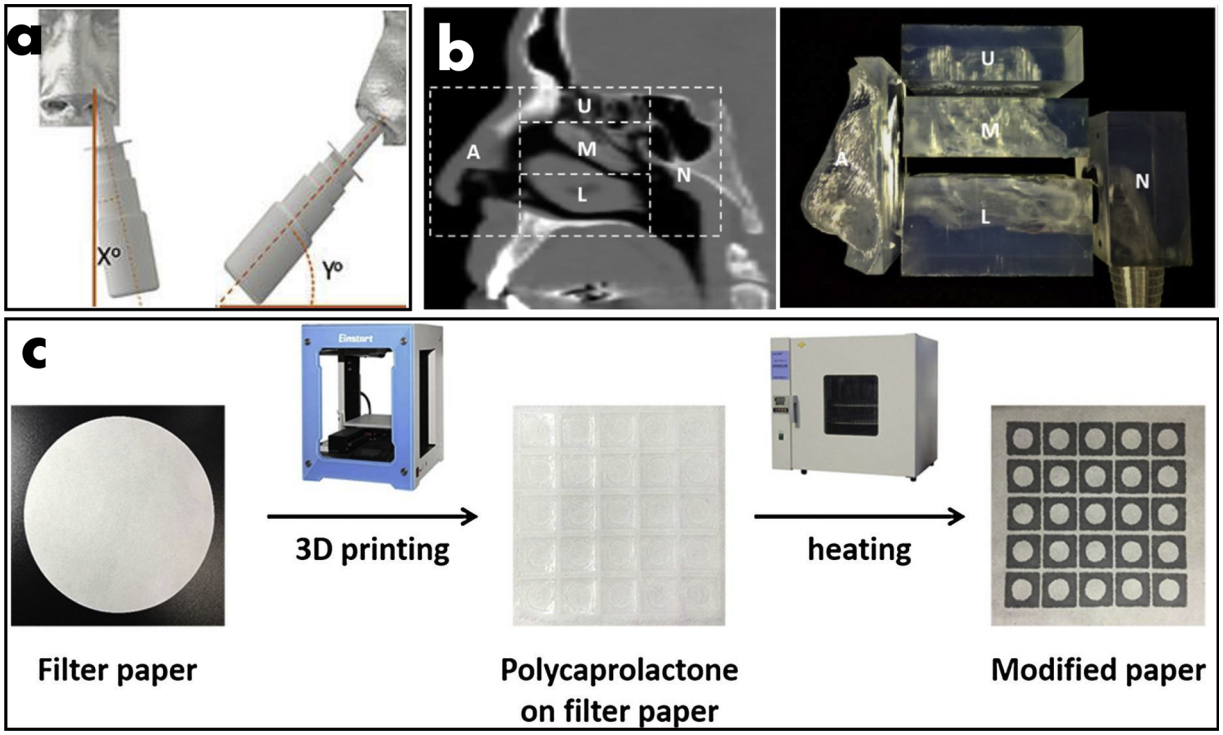

Fig. 5. 3D printing of acellular models. (a) Measurement of optimal angle for nasal spray administration. (b) CT scan and 3D printed model of adult nasal passage. (c) Preparation of paper-based analytical devices prepared with polycaprolactone.

5. Pharmaceutical Models for Drug Testing

5.1. Acellular Models

Models have been used as an aid to enhance learning for a long time. AM technology allows us to take this one step further to develop individualised 3D models, which would allow a personalised approach, leading to a more patient-centred care. This is demonstrated in the following studies on drug delivery through human airway.

In the first study, 3DP nasal replicas were used to determine the optimal angle a nasal spray should be used for a specific patient (Fig. 5a) [74]. Ten individualised nasal models were printed and connected to a vacuum pump to simulate inspiratory airflow (Fig. 5b). The angle of administration was changed via a 360° vice connected to an automatic actuator, and deposition was measured after each spray. Based on a series of readings, a mathematical model was applied to predict the optimal angle.

In the second study, Spence et al. produced different designs of a device to deliver high flow nasal-cannula (HFNC) therapy [75]. The prototypes were designed by computerized simulation and then printed using a Stratasys Objet printer, using liquid photocurable polymers. In case higher heat resistance was needed, the heating section was printed by using a 3D Systems SLS printer, using thermoplastic powders. With the fast prototyping capability, a new device was developed for administering HFNC therapy and simultaneous on-demand pharmaceutical aerosols to the lungs.

In addition to airway modelling, a new approach for testing traditional chinese medicine (TCM) was also reported, using paper-based analytical devices (PADs). Guo et al. used FDM printing as a fast and inexpensive method to create a PAD to determine the activity of mulberry leaves [76]. A layer of PCL was deposited on a sheet of filter paper, avoiding a central circular shape. The paper was then heated so the PCL penetrated the paper to form a hydrophobic barrier surrounding a central circle, creating the PAD (Fig. 5c). It was shown that bioassays of the TCM was efficient by using such a PAD.

5.2. Cellular Models

Organ-on-a-chip models, are small-scale models which not only depict the structure and function of the target organ, but also mimic the natural extracellular environment, resulting in a more accurate prediction of the *in vivo* response [77,78]. Such biorelevant models could potentially replace current animal models for uses such as drug response and toxicology screening. By reducing the number of animals used in preclinical studies, it may be possible to reduce the cost of development and time to market [79], as well as decrease ethical issues regarding laboratory animals. As a model, it could also be used as an educational tool for researchers. For example, organoid models of disease, also called disease-on-a-chip models, have been used to study the physiology and mechanism of a whole range of diseases from fibrosis to cancer to ischemia, possibly bringing us closer to the development of precision pharmacotherapy [78,80].

Traditionally, the process to etch channels in microfluidic devices was a costly and time-consuming process which had to be done in a cleanroom with equipment which was not always readily accessible in developing countries. In addition, this method was not able to generate complex designs. With the advent of AM, simpler, more cost-effective methods become available.

Ozbolat et al. used Carbopol as a sacrificial ink to produce microfluidic channels [81]. To produce the device, a base layer of PDMS was first poured and cured. A layer of sacrificial Carbopol ink was printed on the top of the base and a rectangular frame to house the upper layer of PDMS was also printed. The upper layer of PDMS was then poured and cured, before the device was trimmed to remove the frame and flushed to remove the Carbopol layer. Although not demonstrated in the experiment by Ozbolat et al., there is potential for complex channels to be generated using this new technique. This model is potentially useful for drug screening and as point-of-care devices.

A similar model using a similar method was created of the convoluted renal proximal tubule by Homan et al. (Fig. 6a) [82]. The convoluted proximal tubule is the site most frequently damaged by drug. The chip was printed using a gelatine-fibrin hydrogel, and the

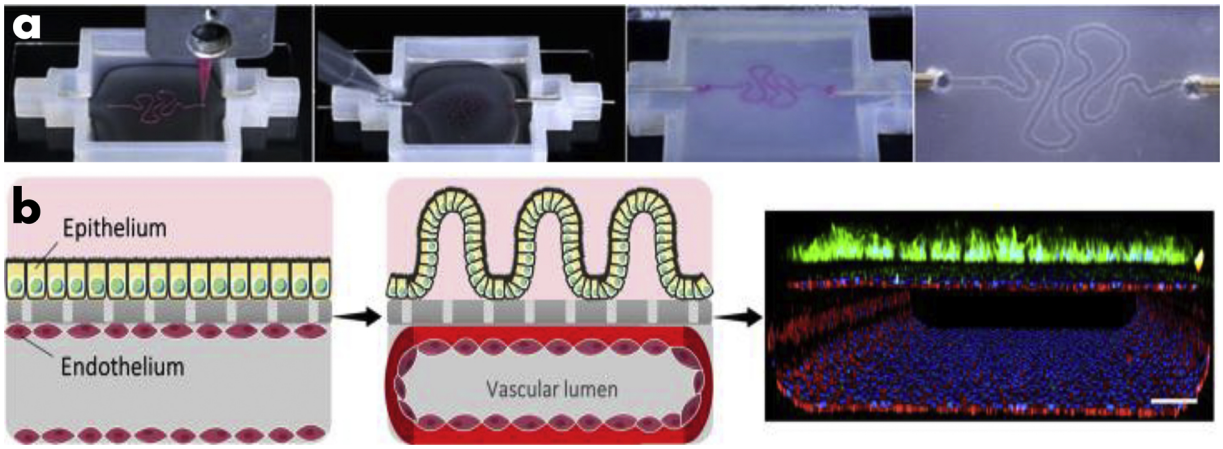

Fig. 6. 3D printing of cellular models. (a) Renal microfluidic device created using 3D printed sacrificial Pluronic® ink. (b) Schematic of intestinal epithelium and endothelium differentiating to form a villus epithelium and vascular lumen respectively, and an immunofluorescence micrograph visualising this.

sacrificial material used was a triblock copolymer of polyethylene-polypropylene-polyethylene, namely, Pluronic® F127. The model was used to test the toxicity of cyclosporine A, which was commonly given following transplant surgery to prevent body rejection.

Another study by Jalili-Firoozinezhad et al. investigated the efficacy of radiation countermeasure drug by using a gut-on-a-chip model [83]. The model not only included epithelial and endothelial cells, but controlled cyclic suction was also applied to mimic the stress felt the cells during physiological peristalsis movement. Under these conditions, epithelial cells were shown to undergo villus differentiation, similar to that inside the human body (Fig. 6b).

In addition to organ-on-a-chip models, full-sized tissue/organ models have also been studied, using a tissue engineering approach. It involves growing cells on scaffolds, to create a functional construct which can be used to replace/repair damaged tissues or organs. Traditionally, cells were seeded on a scaffold and allowed to grow [84]. The ability of these cells to attach and successfully grow is heavily determined by the properties of the matrix [85]. A major hurdle was the adhesion of cells to the scaffold, which could be influenced by surface area. As AM allows for relatively quick and easy customisation of the matrix properties, porosity and shape could easily be modified [11]. On the other hand, different material choices used for printing the scaffold can also affect cell adhesion and should be considered [86].

There has been rapid development on AM enabled cellular models for drug testing. To this end, the readers are referred to an excellent review for tissue engineered constructs for modelling of disease progression and drug screening [87].

6. Biomaterials and Excipients

The materials and excipients used in the previously mentioned articles and their approval status in Australia are shown in the table below.

7. Challenges and Directions

Although AM is an exciting new field which shows promise to enhance the pharmaceutical field, especially in terms of personalised medicine, there are many challenges facing the implementation of AM, including the standardisation of printers [91], the paucity of safe and usable materials, development of non-destructive analytical methods [92,93], regulatory issues, and possible unintended consequences [20].

7.1. Printing Materials and Methods

Compared to AM techniques, there is comparatively limited data on the materials themselves. We summarized the materials used for pharmaceutical printing in Table 1. Studies have been done on drop-on-demand printing and suitable binders [94]. Using caffeine as the model drug, it was shown that particle size of the binder affected the friability of the resulting tablet, whereas viscosity was inversely affected the dissolution and dispersion [95].

The technique used most frequently is FDM [96] while other techniques, such as SLS, were also used [85]. The intrinsic issue with printing active pharmaceutics using FDM is the degradation of thermolabile substances [17,45,97,98]. In addition to the printing, the drug is also heated in the preparation of the drug laden filament as it undergoes HME and it is this process rather than the printing process where thermolabile drugs are associated with degradation. There have been a few studies done specifically focusing on FDM materials [54] to counteract this problem, with one study showing that thermal degradation can be avoided by using select excipients with lower melting points, hence lowering the overall printing temperature [98]. Another study showed that printing temperatures could also be lowered by using water as a temporary plasticiser [43]. However, it has to be kept in mind that changing excipients can influence factors, such as dissolution rate [99]. Other problems in regards to materials used for FDM include needing a uniform filament diameter, flexibility and tensile strength [54,99,100]. Other methods, such as HME, has also been studied, to avoid the heat degradation associated with FDM. However, there are other problems on extrudability for HME [101,102]. A study suggested the use of a two-component crosslinkable gel. The two components are injected in a coordinated fashion and chemically react to solidify, therefore eliminating the need for heat, irradiation or solvents altogether [103].

Material extrusion avoids the high temperatures required in FDM [104, 105], but is limited by water sensitive drugs. A study by Acosta-Velaz et al. was done to create biocompatible photocurable inks for hydrophobic drugs for use in material jetting [45]. Vat polymerisation is limited by the lack of usable polymers, as many of the monomers can be toxic or lead to stability issues [106]. The material toxicity is even more of a concern for bioprinting where bioinks are used to create tissue-like structures [107].

7.2. Regulations and Guidelines

As a new manufacture technology, AM does not require special regulations. The existing regulatory framework may still be valid for AM pharmaceutical products. However, different from mass manufacturing, AM-enabled personalized medicine can become a challenge. As new regulations are needed to implement the clinical applications of AM pharmaceutical drug products, which can be made in pharmacy,

Table 1
Biomaterials for AM used in mentioned articles.

No.	Equipment	Materials	Material approval status	Ref.
1	Binder jetting, Fochif Mechatronics	D-sucrose, Pregelatinized starch, PVP K30, Microcrystalline cellulose (MCC), Silicon dioxide	Yes	[19]
2	Extrusion, RegenHU	PVP K25, Primellose® (croscarmellose sodium)	Yes	[24]
3	FDM, Flashforge Creator Pro	PVA	Yes	[32]
4	FDM, MakerBot Replicator	HPMC (AFFINISOL™ HPMC HME 15 L V)	Yes	[33]
5	Extrusion, Fochif Mechatronics Tech. MAM II	Lactose, PVP K30, MCC (Pharmacel® 101), HPMC (Methocel® E15, K100LV)	Yes	[36]
6	Extrusion, MakerBot Replicator	PEG 100K, PEG 200 K, PEG 300 K, PEG 600 K, PEG 900 K, PEG 6 K	Yes	[37]
7	SLS, Sintratec Kit	PEG 1 M, Eudragit® L100-55 (Methacrylic Acid[2], Ethyl Acrylate), Ethyl Cellulose, Eudragit® RL (Methacrylic Acid[2], Ethyl Acrylate, Low content of methacrylic acid ester with quaternary ammonium groups [a]), Candurin© Gold Sheen (Titanium Dioxide, Potassium Aluminium Silicate [b], Iron Oxide)	[a]No information was found about this ingredient on TGA. However, Evonik's website markets Eudragit® products towards pharmaceutical companies as excipients [88]. [b]No information was found about this ingredient on TGA. However, Merck's website markets Candurin© Gold sheen towards pharmaceutical companies [89].	[38]
8	Extrusion, Cellink Inkredible	HPMC (METOLOSE® SR 90SH), Mannitol, PEG 4000, PVP (Kollidon® CL-F)	Yes	[40]
9	FDM	Eudragit® EPO (Dimethylaminoethyl Methacrylate[1], Butyl Methacrylate[1], Methyl Methacrylate), PEG 2 M, 5 M (POLYOX WSR N10, N80)	Yes	[41]
10	FDM, MakerBot Replicator	PVA (Parteck MXP), Sorbitol, Titanium Dioxide	Yes	[43]
11	SLS, Sintratec Kit	Kollicoat IR (PVA/PEG graft copolymer) [c] Ethyl Cellulose, Candurin© Gold Sheen (Titanium Dioxide, Potassium Aluminium Silicate, Iron Oxide)	[c]Although PVA and PEG are approved individually, no information about the graft copolymer was found on the TGA. However, the copolymer is approved for pharmaceutical use in various other countries including the EU [90].	[44]
12	FDM, MakerBot Replicator	Eudragit® RL PO (Ethyl Acrylate, Methyl Methacrylate, Low content of methacrylic acid ester with quaternary ammonium groups [a]), PLA[2] (Resomer), Triethyl Citrate, Citric acid monohydrate, PEG 400, PVA (Mowiol), Calcium stearate, Mannitol	[a]No information was found about this ingredient on TGA. However, Evonik's website markets Eudragit® products towards pharmaceutical companies as excipients [88].	[47]
13	Extrusion, Fochif Mechatronics MAM II	HPMC K4M (Methocel™), HPMC E15 (Methocel™) MCC PH101, Lactose, PVP K30	Yes	[48]
14	FDM, Tiertime UP mini2	PVA	Yes	[49]
15	SLS, Sintratec Kit	HPMC, Kollidon® VA 64 (Vinylpyrrolidone[3], Vinyl Acetate[1]), Candurin© Gold Sheen (Titanium Dioxide, Potassium Aluminium Silicate[b], Iron Oxide)	[b] No information was found about this ingredient on TGA. However, Merck's website markets Candurin© Gold sheen towards pharmaceutical companies [89].	[52]
16	FDM, Airwolf HD2xR	Hypromellose Acetate Succinate (HPMCAS)[1], PEG 6000	Yes	[55]
17	FDM	PVA, Sorbitol	Yes	[56]
18	FDM, Manli Tech. CF-12410B	PLA[2], PCL, PEG 4000, Polysorbate 80 (Tween® 80)	Yes	[68]
19	FDM, Ninjabot FDM-200W	PVA, PEG 4000, PEG 6000	Yes	[69]
20	FDM, Manli Tech. CF-12410B	PLA[2], PCL, PEG 4000, Polysorbate 80 (Tween® 80)	Yes	[72]
21	FDM, MakerBot	PLA[2]	Yes	[73]

[1] Only approved as excipient use in S4 products only.
[2] Only approved as excipient use in over the counter (OTC) and S4 products only.
[3] Only approved as excipient use in Listed and S4 products only. (S4 refers to prescription drugs, https://www.tga.gov.au/scheduling-basics).

doctor's office or at home.

Currently, there is a lack of specific guidance or regulations regarding AM therapeutics, although there have been proposals [108] and technical innovation for AM products [109]. Before AM is accepted in the pharmaceutical industry and pharmacy practice for personalization medicine, detailed regulations will need to be laid down as there will inevitably be concerns about efficacy, safety, intellectual properties, ethics, privacy and patient rights among other issues. To this end, it is difficult to provide a general guidance that can provide specific prescription for every fabrication and for every individual. Instead, a common framework that can allow this technology to manufacture pharmaceutical products under existing regulations may be more realistic [26,53,79,93].

7.3. Pharmacy Practice

Many studies agree that AM offers much potential in terms of personalised medicine and that it will introduce a new era of digital health. It is often the case that there are unintended consequences in the wake of these big changes, of which Kaae et al. mentioned a few that may occur, should we choose to adopt AM in pharmacy practice [110]. The goal of personalised medicine is to introduce more effective care, which comes hand in hand with self-monitoring and a new role in decisions regarding their health. A proportion of patients may not appreciate the increased need to self-monitor for a variety of reasons, whether it be due to time constraints or a constant reminder of illness. This may also be the case with an increased role in decision making regarding treatment options and their own health [110].

An idea put forth by several articles is the use of this technology by patients in their own home [31,111]. While this would increase accessibility and convenience to patients, it also comes with a many safety concerns which would need to be addressed by the construction of new set regulations [96]. There are also concerns that the use of AM in pharmacies could introduce a source of medication errors via mechanisms, such as technological confusion and changed medication appearance. Other concerns include the environmental impact of creating AM materials, specifically filaments used in FDM [112].

8. Conclusion

In summary, AM has great potential to bring about a revolution in pharmaceutical manufacture and practice, especially around personalised medication. It has greatly enhanced the production and properties of novel forms such as orodispersible tablets, gastrofloating tablets and polypills. The quick production of customised models is unique to AM and can be utilized in areas such as personalised implants and bioengineering models. The application of AM is expected to increase in the pharmaceutical industry since AM tablets firstly gained the US FDA approval in 2015. However, before AM can become the new norm, regulations and guidelines must be drawn up in preparation for issues bound to appear. The unmet needs from pharmacy practice and pharmaceutical industry will combine to become the driving force for this new technology to find its many applications in this field.

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.

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