

3D printed medicines: A new branch of digital healthcare

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ABSTRACT

Three-dimensional printing (3DP) is a highly disruptive technology with the potential to change the way that pharmaceuticals are designed, prescribed and produced. Owing to its low cost, diversity, portability and simplicity, fused deposition modeling (FDM) is well suited to a multitude of pharmaceutical applications in digital health. Favourably, through the combination of digital and genomic technologies, FDM enables the remote fabrication of drug delivery systems from 3D models with unique shapes, sizes and dosages, enabling greater control over the release characteristics and hence bioavailability of medications. In turn, this system could accelerate the digital healthcare revolution, enabling medicines to be tailored to the individual needs of each patient on demand. To date, a variety of FDM 3D printed medical products (e.g. implants) have been commercialised for clinical use. However, within pharmaceuticals, certain regulatory hurdles still remain. This article reviews the current state-of-the-art in FDM technology for medical and pharmaceutical research, including its use for personalised treatments and interconnection within digital health networks. The outstanding challenges are also discussed, with a focus on the future developments that are required to facilitate its integration within pharmacies and hospitals.

Keywords: fused deposition modelling, material extrusion, personalized medicines, fused filament fabrication, patient-centric medications, digitized pharmacy.

1. Introduction

Three-dimensional printing (3DP) has gained momentum in many industries as a new and revolutionary manufacturing tool. This additive system is rapidly changing the way that goods are designed and produced; by using a 3D computer model, bespoke objects can be created in a layer-by-layer manner under automation. As such, this technology can bridge the gap between the worlds of imagination and reality. A variety of 3DP technologies are commercially available, however of all the systems, fused deposition modelling (FDM) is at present the most widely investigated 3DP technique within pharmaceuticals (Alhnan et al., 2016; Alomari et al., 2015; Awad et al., 2018; Goole and Amighi, 2016; Norman et al., 2017; Trenfield et al., 2018; Zema et al., 2017). As such, we anticipate that FDM is well suited for implementation in digital health.

FDM 3DP, a branch of material extrusion, is a diverse technology with its current applications ranging from aviation to automobiles, medicines, dentistry, art, jewellery, and footwear (Barnatt, 2016). Within pharmaceuticals, the adoption of FDM is forecast to initiate a paradigm shift in the drug design, formulation and production sectors (Berman, 2012). In particular, FDM 3DP could be applied as a fabrication tool within digital health for the remote manufacture and dispensing of personalised formulations having doses, shapes and sizes optimised to the patient. Such benefits provide flexibility and autonomy to the treatment process, potentially leading to the enhancement of therapy and medication adherence. This review provides an overview on the

revolutionary prospects and opportunities that FDM 3DP holds for pharmaceutical formulation and production, whilst highlighting the outstanding technical and regulatory challenges that require consideration before its progression into common practice.

2. Material extrusion: an overarching principle

Material extrusion is a thermal process; the underpinning principle is the selective dispensing of a molten material through an orifice to generate fine semi-solid strands, which solidify on a build plate to create 3D objects. Materials used with this technology include thermoplastics, clays, waxes, gels, and pastes. As such, material extrusion is a broad term that expands to subsume other prominent techniques, including FDM and semi-solid extrusion. Whilst the terms material extrusion and FDM have often been used interchangeably, FDM deals only with thermoplastic materials (McMains, 2005).

FDM technology, also known as fused filament fabrication (FFF), was originated by Scott Crump in 1988 when he was attempting to craft a toy for his daughter using a simple glue gun (On3DPrinting.com, 2013). He replaced the conventional glue stick with a blend of polyethylene and candle wax and utilised it to construct the toy layers one over the other. The idea was then expanded and an automated version of the process was developed. In 1989, Crump and his wife patented the technology and co-founded their own company, Stratasys, to commercialise their product (Crump, 1992; Stratasys,

2017a). The technology was coined and trademarked as FDM™. A timeline of the current advancements in the FDM process are outlined in Figure 1.

Like any other 3DP technology, the FDM method follows “the 3D’s of 3DP” (Trenfield et al., 2018): (a) design: a 3D shape is designed using a computer-aided design (CAD) software. This shape is digitally divided into horizontal layers and is then loaded into the software of the printer in the form of a stereolithography (.stl) file (Stratasys, 2017a); (b) develop: a suitable thermoplastic drug-loaded filament is developed and then fed into the printer, where it is melted and extruded through a metal nozzle at a specific temperature (McMains, 2005). Most printers allow user-selection of the print head temperature and so an FDM printer can be used to print different polymers and polymer blends; (c) dispense: the extruded filament is subsequently deposited on the flat base of the printer, known as the build plate or platform. The print head moves in a raster pattern, to create the first layer of the object. Upon the completion of each layer, the platform is lowered to allow enough space for a new layer to be deposited. As the filament cools down, it attaches to the previous layer. The process is then repeated until the completion of the object (Figure 2). The resolution of the printed object is dependent upon the thickness of the extruded filament, typically 100 μm in a commercial printer.

Insert Figure 1.

Insert Figure 2.

By simply changing the polymer being printed, FDM has the ability to create complex objects with unique characteristics, such as high mechanical strength and thermal resistance. In medicine, surgeons have explored the possibility of utilising this technology to print anatomical guides and organs specifically adapted to patients, enabling them to train for challenging surgeries (Maxey, 2013). By integrating electronic sensors, these models can provide quantitative analysis on the surgical technique (e.g. duration of a surgery and success rates), and have thus been termed “smart surgical aids” (Qiu et al., 2018). In addition, organ models based on human data obtained using well-established imaging techniques, such as computed tomography (CT) or magnetic resonance imaging (MRI), can also be utilised as means of testing; a process termed biomodelling. For instance, an FDM 3D printed induction port (IP) model, based on the CT scan of a patient’s trachea, was found to be superior to pharmacopoeial IPs, providing more insight into the *in vitro* evaluation of pressurised metered dose inhalers (Berkenfeld et al., 2018). However, compared with other 3DP technologies, for instance stereolithography (SLA), which has been used to print an airway model for inspiratory flow simulation (Collier et al., 2018) or nasal casts for the prediction of drug deposition from nebulisers (Warnken et al., 2018), FDM organ models have limited use as means for *in vitro* evaluation. This can be attributed to the limited resolution of these printers, resulting in a lower printing accuracy or the need for the use of support materials to create complex models.

Additionally, bespoke osteoid casts have been developed as a form of advanced therapy (Karasahin, 2013). These functional devices utilise low-intensity pulsed ultrasound (LIPUS) to stimulate bone healing. This induces mechanical stress on the cells of the fractured bones, reducing their healing duration by up to 38%. Moreover, FDM has been widely used to design patient-specific medical devices, including prosthetics (Nayak et al., 2016) and implants (Janusz et al., 2015), wherein the tailoring of such devices is a requirement (e.g. implants for reconstructive and plastic surgery (He et al., 2006)). An example of such includes the fabrication of functionalised ear prosthesis capable of responding to temperature and pressure (Suaste-Gómez et al., 2016). This smart device has the potential to utilise mechanical stress and changes in temperature to induce electrical potential, enabling it to respond to sound in patients with hearing impairment.

Furthermore, FDM 3DP can be applied in bone tissue engineering, whereby scaffolds have shown to be capable of withstanding high loads of mechanical strain, whilst maintaining increased tissue growth (Chim et al., 2006). In 2017, the U.S. Food and Drug Administration (FDA) issued guidance on the “technical considerations for additive manufactured medical devices”, outlining their expectations on the use of 3DP technologies for the fabrication of medical devices (U.S. Food and Drug Administration, 2017). Thus far, only a few FDM printed medical implants (such as cranial plates or hip joints) have been commercialised, however none were drug-loaded.

3. From plastics to actives: the FDM – HME conjunction

Typically, filaments made out of thermoplastic materials have been used as the feedstock for FDM printers. Examples of thermoplastics include polylactic acid (PLA), acrylonitrile butadiene styrene (ABS), polyvinyl alcohol (PVA) and polycarbonate (PC). Nonetheless, none of these commercialised filaments are regarded as safe for human use. Consequently, the FDM feedstock in pharmaceutical research is created through a process termed hot melt extrusion (HME) (Sandler et al., 2014). HME is widely used in the pharmaceutical industry for the production of solid dispersions of polymers safe for human ingestion to increase the solubility of poorly soluble drugs (Miller et al., 2007). The first step of the extrusion process involves the preparation of the powder mixture. The required amounts of the polymer, drug and/or excipients are carefully weighed and mixed. The acquired homogenous mixture is then poured into the hopper, where it flows into the extruder's barrel. This powder is then subjected to a combination of elevated heat and pressure, causing it to melt. With the aid of the rotating screw, the molten material is then pushed out of a metallic nozzle, shaping it into long strands of filaments. The obtained filaments are then deposited onto a collecting tray, where they are left to cool down. The filaments are then sealed in appropriate packaging and stored in a vacuum desiccator to remove any trapped form of water.

A drug can be integrated into a filament by two methods: through incorporation into the powder mixture prior to the extrusion process or by

impregnating an extruded filament in a suitable drug-containing solution, forcing the drug to diffuse passively into the filament. Several trials to impregnate drugs using passive diffusion have been attempted (Goyanes et al., 2014; Goyanes et al., 2015a; Skowyra et al., 2015). However, the main drawback of this method was the limited drug loading (<2%) associated with it. HME on the hand can incorporate high amounts of drug, providing higher dose flexibility (Verstraete et al., 2018). Additionally, it can be adapted to generate standard recipes suitable for the incorporation of various active ingredients, obviating the need for changing the whole composition. As such, filaments with identical excipients can be utilised to incorporate different drugs (e.g. 5-aminosalicylic acid (5-ASA), captopril, theophylline and prednisolone) (Sadia et al., 2016). Thus, coupling HME with FDM 3DP was found to be a more efficient alternative for enhancing the drug loading.

As shown in Table 1, for extruded filaments to be regarded as suitable for FDM printing, they should possess certain characteristics (Aho et al., 2015; Fuenmayor et al., 2018; Nasereddin et al., 2018). For instance, a diameter ranging between $1.75 - 3.00 \pm 0.05$ mm is required to enable a filament to be loaded into the print head (Melocchi et al., 2015). However, some polymers tend to expand or shrink upon heating and, hence, the selection of a suitable nozzle size is critical. Furthermore, the uniformity of the diameter is essential for ensuring a constant printing process because irregularities can result in inconsistent printing and induce printing failure. As such, the use of lubricants (e.g. magnesium stearate) may aid in reducing the friction between the

extrudate and extruder screw, enabling the filament to exit the nozzle more steadily (Beck et al., 2017; Goyanes et al., 2017a).

The balance between stiffness and brittleness of a filament is critical for printing (Korte and Quodbach, 2018b). This is mainly because excessive stiffness will prevent filaments from being properly bent onto spools and limit their use. As such, this will necessitate the modification of the polymer blend. Excessive brittleness on the other hand, prevents filaments from being properly loaded into the printer's liquifier or causes them to break during the printing process and in some cases this can lead to the blockage of the nozzle. In such cases, the addition of plasticisers aids in reducing the glass transition temperature (T_g) of the polymer and renders the filaments more flexible. However, choosing the right type and amount of plasticiser/s is crucial. This is mainly because excessive flexibility can cause the filament to become too soft and bend inside the liquefier and block it. Consequently, recent work has aimed at predicting the printability of filaments by utilising validation methods to assess their mechanical properties (Fuenmayor et al., 2018; Nasereddin et al., 2018).

1 Table 1: Criteria for consideration when assessing the suitability of filaments for FDM 3DP.

Criteria for consideration	Risk if unmet	Validation methods	Required values	Proposed solutions	Reference
Diameter	Inability to be loaded into the print head	Digital caliper Laser micrometer Ultrasonic thickness gauges	1.75-3.00 mm	Selection of right nozzle (or die) size.	(Melocchi et al., 2015)
Diameter uniformity	Variance in feed rate Deformed prints Printing failure	Visual inspection Digital caliper	Consistent diameter	Use of lubricants	(Fuenmayor et al., 2018)
Stiffness	Prevent filament spooling Prevent the exiting of material from the print head	Dynamic mechanical analysis (DMA) Texture analysis Flexure testing	~1000N/m	Use polymer blends	(Alhijaj et al., 2016; Nasereddin et al., 2018; Zhang et al., 2017)

Brittleness	Improper loading into the print head	Tensile testing	~0.15-0.2	Use of plasticisers	(Prasad and Smyth, 2015)
	Breaking inside the liquifier during the loading or printing process	Torsional strength	%Pa (10 ⁴)		
Softness	Compression between the driving gears in the print head	Shore hardness Tensile testing	-	Reducing the amount of plasticiser	(Fuenmayor et al., 2018; Prasad and Smyth, 2015)

4. The FDM revolution and its transition into digital health

Extensive studies have been conducted on FDM's potential to fabricate diverse forms of pharmaceutical products (Cunha-Filho et al., 2017), including tablets (Goyanes et al., 2015a; Zhao et al., 2018), which are also referred to using the term “printlets” (Goyanes et al., 2017a), capsules (Maroni et al., 2017; Melocchi et al., 2018; Smith et al., 2018), beads and catheters (Weisman et al., 2015), orodispersible films (Ehtezazi et al., 2018; Jamróz et al., 2017a), topical masks (Goyanes et al., 2016), transdermal microneedles (Luzuriaga et al., 2018), vaginal rings (Fu et al., 2018), intra-uterine devices (IUD) and subcutaneous devices (Genina et al., 2016; Holländer et al., 2016). The primary incentives behind the prevalent use of FDM in the pharmaceutical field are summarised in Table 2.

1 **Table 2: The primary incentives behind the prevalent use of FDM 3DP for pharmaceutical research.**

Primary incentives	Examples	References
Personalisation of dosing	Flexibility in drug loading	(Skowyra et al., 2015)
Customisation of dosage forms	For preclinical testing in animals	(Arafat et al., 2018a; Chai et al., 2017; Genina et al., 2017; Goyanes et al., 2018)
	Patient-centric dosage forms	(Goyanes et al., 2017b; Scoutaris et al., 2018)
	Transforming pre-existing dosage forms to other forms	(Beck et al., 2017)
Drug synthesis	Remote digitisation of the blueprints for print and synthesis	(Kitson et al., 2018)

2

Modification of drug release

Varying infill percentage

(Chai et al., 2017; Goyanes et al., 2014)

Tuning the polymer matrix composition

(Ehtezazi et al., 2017; Goyanes et al., 2017a; Jamróz et al., 2017b; Kempin et al., 2017; Okwuosa et al., 2016)

Modulating the structural shape or arrangement

(Arafat et al., 2018b; Goyanes et al., 2015c; Kadry et al., 2018; Lim et al., 2016; Sadia et al., 2018; Yang et al., 2018)

Modifying the external shell thickness or composition

(Gioumouxouzis et al., 2017; Okwuosa et al., 2017)

Drug combinations	Combining two or more drugs in a single dosage form	(Gioumouxouzis et al., 2018; Goyanes et al., 2015d)
	Use of incompatible drugs	(Maroni et al., 2017; Melocchi et al., 2018)
Adaptation of medicated devices	Topical masks	(Goyanes et al., 2016; Muwaffak et al., 2017)
	Vaginal rings	(Fu et al., 2018)
	Intra-uterine devices	(Genina et al., 2016; Holländer et al., 2016)
	Subcutaneous devices	(Genina et al., 2016)
	Transdermal microneedles	(Luzuriaga et al., 2018)
	Mouthguards	(Liang et al., 2018)

4.1. Versatile platform for drug delivery

The huge diversity between humans affects the way that drugs function in their bodies. Due to the complexity of the human body, different factors, including age, sex, disease/health state, and human genes, play a role in the pharmacokinetic (PK) and pharmacodynamic (PD) behaviour of drugs (Abuhelwa et al., 2017; Ashiru et al., 2008; de la Cruz-Moreno et al., 2017; Fadda et al., 2010; Freire et al., 2011; Hatton et al., 2018; Hens et al., 2017; Hens et al., 2018; Jamei et al., 2009; Leong et al., 2002; Liu et al., 2009; Merchant et al., 2016; Nicolas et al., 2009; Sadée and Dai, 2005; Smart et al., 2014; Taherali et al., 2018; Varum et al., 2013; Wang et al., 2015). Therefore, different individuals will require different dose regimens or dosage forms, which are not always readily available (Sahlgren et al., 2017). Studies have shown that most drug success rates are low during early phases of clinical trials (Wong et al., 2018), resulting in a considerable financial burden for the pharmaceutical industry. Following the introduction of the Precision Medicines Initiative in 2015, there has been a considerable interest towards the personalisation of therapy (Collins and Varmus, 2015). Consequently, pharmaceutical researchers have been aiming to find a single platform capable of tailoring medication based on patients' necessities, preferences and individual features (U.S. Food and Drug Administration, 2013). Owing to its unique features and versatility, FDM 3DP can be easily adapted to fabricate virtually any desired dosage form with a defined release profile (Awad et al., 2018; Kadry et al., 2018; Tagami et al., 2018; Trenfield et al., 2018). These printed medications are characterised by having precise spatial

distribution of drug and excipients, which is unachievable by most of the other fabrication methods (Goyanes et al., 2015d).

FDM technology has the potential to programme drug delivery systems to target specific regions in the human body due to the wide range of polymeric matrices available. As such, FDM 3DP can be described as a “flexible-dose dispenser” (Pietrzak et al., 2015), permitting the fabrication of dosage forms with varying doses, having release profiles ranging from immediate (Jamróz et al., 2017b; Solanki et al., 2018) all the way through to sustained (Verstraete et al., 2018) and modified release (Goyanes et al., 2017a), without the need for additional processing, such as coating (Goyanes et al., 2015b). Hence, this technology provides a more sophisticated approach for the engineering of pharmaceutical devices.

In 2014, the first attempt to investigate FDM 3DP for the preparation of oral pharmaceutical formulations was made (Goyanes et al., 2014). The work demonstrated that the printing settings were major determinants of the drug release profile. An example of such is the interior layout or infill percentage, which constitutes the percentage of filling inside the exterior shell of 3D printed tablets. Tablets containing less infill material exhibited a faster drug release and the ones having higher infill material showed extended release profiles. This was mainly attributed to the different swelling ratios associated with the polymer density. Interestingly, at lower infill percentages (<20%), the overall density of 3D printed tablets are reduced, promoting their buoyancy. This floating effect can be utilised to increase their residence time in the

gastric region, prolonging drug release, a phenomenon known as gastroretention (Chai et al., 2017). Such a finding is particularly significant for weakly basic drugs, as it will enhance their bioavailability. However, this is highly dependent upon a patient's diet and the amount of gastric fluids present in the stomach, and thus a high variability in performance in the clinic can be anticipated.

Alternatively, channelled devices were explored to maximise the drug release from immediate release formulations (Figure 3A) (Sadia et al., 2018). By controlling the different aspects of the channels (e.g. width, length and configuration), the drug release could be tailored to meet the required specification. Such complex geometries are challenging to produce using conventional manufacturing processes. Similarly, caplets containing internal gaps, termed gaplets, were produced to facilitate fragmentation of fast release tablets, obviating the need for disintegrants (Figure 3B) (Arafat et al., 2018b). Comparably, 3D printed networks with controlled release properties and having varying densities were also fabricated (Korte and Quodbach, 2018a).

Insert figure 3.

Mass, which can be controlled via changing the size of the 3D printed tablets, can also be utilised to control the drug release (Skowrya et al., 2015). Results have shown that owing to their higher surface area to mass ratio, smaller tablets exhibit faster drug release. Similarly, the change in the geometrical shape of a 3D printed tablet was found to influence the drug release

behaviour (Goyanes et al., 2015c). 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 ratio of the surface area relative to the volume of the tablets altered the time needed for the complete drug release. Therefore, the fastest drug release was observed from the pyramid tablet, whereas, the slowest release was from the cylinder tablet. Favourably, all the 3D printed tablets displayed weight and dose accuracy.

In fact, although often overlooked, the shape, size and colour of a medication can be significant determinants of the effectiveness of a treatment plan. An open-label, randomised patient acceptability study demonstrated that patients prefer swallowing some shapes over others, thus influencing their compliance to medications (Goyanes et al., 2017b) (Figure 4A). Results showed that the torus shape was the most preferable in terms of ease of handling and swallowing (Figure 4B). The tilted diamond shape on the other hand, scored lowest in terms of swallowing preference. This perception of difficulty in swallowing was perhaps driven by the sharpness of the edges of this shape. However, interestingly, the sphere tablets were harder to swallow compared to the diamond ones. Additionally, the outcomes of the study have shown that sizes 2 and 3 tablets were mostly preferred (Figure 4C). In terms of colours, the majority of the patients believed that the addition of a colorant made the tablets more appealing. This can be a principal factor when dealing with certain age groups, such as paediatric and geriatric patients, both of which generally suffer from poor medication acceptability.

Insert figure 4.

Unlike conventional production methods, FDM 3DP enables the immediate adaptation of dosage forms to suit any form of testing by altering the 3D structure. As such, this can be considered as a major clinical benefit, hastening the drug development process by expediting its progress into the pre-clinical and clinical phases. Whilst most research on 3D printed pharmaceuticals involves *in vitro* testing, studies using animal models have been recently carried out (Arafat et al., 2018a; Chai et al., 2017; Genina et al., 2017; Goyanes et al., 2018). Owing to the simplicity of the FDM adaptation process, the 3D printed tablets can be easily modified to be suited to a certain animal model. For instance, size 9 hollow capsules were specially tailored for administration in rats (Goyanes et al., 2018). When tested, results have shown that each formulation exhibited a different disintegration time, related to the properties of the polymer. Interestingly, the capsules that remained whole showed no signs of tracer release or gastric emptying from the stomach (Figure 5). This finding is quite important as it shows that, although size 9 capsules are often marketed as suitable for rat administration, their use is actually only limited to immediate release applications. With delayed or sustained release formulations, the results obtained using size 9 capsules may be misleading as, due to their inability to empty from the gastric region, they may behave as gastroretentive formulations in rats instead. This finding highlights a relatively common error made by formulators; the inappropriate selection of a suitable animal model for formulation testing (Afonso-Pereira et al., 2018; Hatton et al., 2015; Schulze et al., 2005; Varum et al., 2010). As

such, there is a requirement for the evaluation of alternative dosage forms or animal models for preclinical testing.

Insert figure 5.

Unlike other 3DP technologies, FDM can prepare medications incorporating multiple polymers or actives in a single print, a process known as dual FDM printing. The suitability of employing dual FDM printing to prepare controlled delivery systems has been investigated, wherein different arrangements (multilayer caplets and DuoCaplets), were fabricated (Goyanes et al., 2015d). In the multilayer caplets, each layer consisted of one drug, with the following layer consisting of another. Conversely, the DuoCaplets contained one drug in the centre of the tablet with a corona containing the other. Whilst the *in vitro* dissolution studies showed that drug release from the multilayer caplets was solely dependent upon the characteristics of the polymer, the outer layer was the rate-limiting step for drug release from the DuoCaplets.

FDM 3DP can also be utilised to create hollow capsule shells with distinct dual compartments (Maroni et al., 2017; Melocchi et al., 2018). The individual compartments can be fabricated using the same (Figure 6A) or different (Figure 6B) materials and/or thicknesses, whereby the drug release from each compartment could be initiated at different time points (Figure 7). As these compartments are precisely sealed, they can be filled with powders or even liquids (Markl et al., 2017; Okwuosa et al., 2018). This development is of high value for creating tailored drug delivery systems incorporating different drugs (e.g. metformin and glimepiride (Gioumouxouzis et al., 2018)) or drug doses,

especially because the drugs can co-formulated even if they are chemically incompatible.

Insert figure 6.

Insert figure 7.

4.2. FDM 3DP as a digitised tool

Digital health is multi-disciplinary domain that interconnects health systems by using data obtained from health information (e.g. disease state and genetic information) and communication technologies (e.g. computational technologies and smart devices) to enhance therapy and provide personalised forms of medications (U.S. Food and Drug Administration, 2018). Implantable or wearable sensors can be utilised to remotely monitor the health/disease state of patients (Alhnan et al., 2016). The derived data could then be analysed, providing information on treatment requirements (e.g. drug, doses and dosage forms). This can be followed by the implementation of the 3D's of FDM 3DP (Trenfield et al., 2018). Whilst the design phase can be straightforward for most applications, some patients may require more complex dosage forms or medical devices, requiring the use of 3D scanning. 3D scanning is a process that involves the use of a 3D scanner device to analyse and gather highly detailed data from an object (e.g. its shape, colour and measurements). Collected data are then utilised to construct digitised 3D models. As such, this can generate models of virtually any real-world object,

including body parts. Such applications have already been commercialised within the dentistry and audiology sectors, whereby 3DP is used to mass customise invisible braces and hearing aids, respectively (Ye, 2015). Within pharmaceuticals, the use of FDM could permit the fabrication of medicated drug delivery devices adapted to patients (Figure 8) (Goyanes et al., 2016; Liang et al., 2018; Muwaffak et al., 2017). Their adaptation allows enhanced fixation of the devices and provides prolonged therapeutic effects. Moreover, they are less likely to cause discomfort, enhancing adherence to medication.

Insert figure 8.

Four-dimensional printing (4DP) is a novel technology that utilises 3DP to fabricate objects having the capability to transform over time (Tibbits, 2014). These smart 3D objects are programmed to respond to a specific stimulus, such as light, temperature, water or pH, causing them to undergo predetermined changes. The programming process is dependent upon two criteria: the use of smart material and the smart design of the 3D structure (Gladman et al., 2016). By combining the basic concepts of FDM 3DP and pH-responsive polymers, 4D functional systems have been fabricated (Nadgorny et al., 2016). Poly(2-vinylpyridine), a pH-responsive polymer, was utilised as the polymer backbone in this study. Following their printing, the 3D printed structures were cross-linked and quaternised, producing smart hydrogels. These functional hydrogels exhibited reversible pH-mediated responses, making them potentially useful for employment as flow-regulating valves and macroporous membranes. Though this invention did not

incorporate a drug, it can perhaps set the scene for upcoming opportunities with this technology wherein the stimulus can be utilised for local drug delivery to certain organs. As such, the use of advanced technologies such as 4DP for the development phase will likely provide more optimised treatments, reducing the difference in therapeutic effects due to patients' inter- and intra-variability. Finally, the compact size and ease of handling of the FDM 3D printers will allow the dispensing phase to be done at the nearest clinic or hospital. The adoption of this digitised framework could enhance the healthcare system, facilitating patient autonomy in the treatment pathway and making medications personalised and more readily accessible to patients.

5. Current outstanding issues and hurdles

It is clear that integrating 3DP into clinical practice could accelerate the digital healthcare revolution, changing the way that medicines are designed and prescribed for patients. However, as with all new technologies entering the digital health sector, adoption is often slow and can come alongside a number of challenges. The healthcare sector is notoriously resistant to change, likely due to the fact that established regulatory guidelines and clinical processes have been in place for many years. Whilst this is understandable to maintain patient safety, it can often hinder the ready uptake of modern day technological advances. Indeed, to accelerate uptake of 3DP into practice, a solid evidence-base is required to prove it will be beneficial and safe not only for patients, but also for the clinicians using the technology everyday.

Thus far, 3D printed pharmaceuticals have only been tested in *in vitro* or *in vivo* animal models, with the only studies involving human subjects being an acceptability assessment (Goyanes et al., 2017b) and an evaluation study (Liang et al., 2018), both of which were fabricated using FDM. Moreover, whilst the different studies have shown the abundant advantages of this technology, none of these data have been combined into a single study to provide proof on the clinical benefits and outcomes of personalised medications. As such, to date, the proposed beneficial attributes of this technology remain hypothetical, with no PK/PD data showing the anticipated superior drug absorption and gastrointestinal transit behaviours of these 3D printed formulations. However, with the rapid advancement in this technology and the current filaments being composed of generally regarded as safe (GRAS) excipients, it is only a matter of time until 3D printed preparations can enter into clinical phase trials. Nonetheless, for this to be achieved, the technology must first be able to overcome its existing outstanding issues and challenges, enabling it to advance towards the phenomenon of the “ideal 3D printer” (Trenfield et al., 2018).

Firstly, as this method consists of a two-step thermal process (extrusion and printing), with both being associated with elevated temperatures (most commonly >150°C), there is an increased likelihood for a drug substance to degrade (Goyanes et al., 2015a). Current advancements have shown that processing temperatures can be lowered to 40-90°C (Kempin et al., 2018; Kollamaram et al., 2018). With additional screening for new excipients

capable of further reducing the processing conditions, it is likely that FDM 3DP will be able to print at room temperature in the future.

Further to the elevated temperatures, the additional HME step associated with this technology can also be time-consuming, as the filaments are not readily available and their printability is influenced by several attributes (refer to section 3). Thus, the FDM technology needs to undergo further advancement, where the requirement for pre-prepared filaments should be abandoned, and instead the printers should be adapted to print using raw materials (e.g. pellets or powders). Currently, there are a few FDM printers that utilise pellets as their starting materials, however, this technology is still in its infancy and the printers suffer from several complications (e.g. material blobbing due to long cool down duration, incorrect layer filling and print warping) (Whyman et al., 2018).

Favourably, in terms of cost and portability, FDM 3D printers are well suited for integration in a pharmacy or hospital for the on-demand manufacturing of personalised dosages. A proposed treatment pathway could involve patient-specific data being sent to a healthcare practitioner for review, from either a physical or digital intervention (e.g. from smartphone applications). The clinician could then produce a digital prescription (or 'e-prescription') tailored to the patient requirements, enabling a formulation to be designed and sent to a local FDM printer for dispensing. However, for this to be achievable, it is clear that compatible software platforms that enable cross-communication between the different technologies are required (Brookes, 2017). Moreover,

issues surrounding data security and protection require consideration to protect the sensitive information of patients. To achieve this, communication between software developers, technological innovators, healthcare practitioners and regulatory agencies are required to enable standardisation across the sector.

Moreover, currently commercialised FDM 3D printers do not meet the good manufacturing practice (GMP) requirements, which may render the 3D printed products unsafe for human consumption. Thus, this calls for the need for quality control (QC) measurements to ensure policies imposed by regulatory bodies are met (Di Prima et al., 2016). Firstly, the isolation of the 3D printers can reduce the risk of product contamination and perhaps provide more control over changes in environmental conditions (Preis et al., 2015). Fortunately, as FDM 3D printed tablets have been shown to have good mechanical properties, tests such as friability and hardness, are likely not to be needed. On the other hand, whilst in theory the 3D printed tablets should contain a “personalised dose of the drug”; the actual drug content has to be validated. Moreover, as both the FDM and HME processes have shown to alter the physical states of drugs molecules (e.g. crystalline/amorphous states), thus influencing their stability, solubility and dissolution rates (Murdande et al., 2011), analytical assay is essential to predict the drug performance.

However, destructive characterisation methods, such as *in vitro* dissolution and disintegration testing, high-performance liquid chromatography (HPLC)

and UV–vis spectrophotometry, can't be used in this scenario. As such, non-destructive methods may be required, such as process analytical technologies (PAT), including near-infrared (NIR) spectroscopy (Donoso and Ghaly, 2005a, b; Donoso et al., 2003) or Raman spectroscopy (Lee, 2009), could be used instead (Trenfield et al., 2018). Additionally, changing the printing parameters (e.g. shape, size or infill) will also change the overall performance of 3D printed tablets. Hence, this necessitates the need for an assay capable of predicting the drug content and bioavailability with respect to the change in printing factors. More preferably, the proposed analytical devices or strategies should be integrated within the printers (Sandler and Preis, 2016), to ensure batch-to-batch uniformity and accelerate the final dose dispensing process.

6. Conclusion

3DP is set to cause a digital revolution within healthcare. Owing to its simplicity, diversity and portability, we anticipate that FDM 3DP might be particularly well suited to be used within digital health domains. Unlike conventional manufacturing technologies, FDM 3DP enables the production of bespoke, patient-specific dosage drug products on-demand, with precise dosing, high reproducibility and strong mechanical properties. Moreover, the production of complex dosage forms can be attained, such as by accommodating numerous polymeric matrices and actives or by programming dosage forms to exhibit tailored effects or target specific organs. The technology has advanced further making it possible to combine it with other technologies to create more complex and “smart” delivery systems. Yet, it is well understood that digital health is not limited to this single 3DP technology, as other 3DP platforms might prove to also be beneficial. Nonetheless, all the 3DP technologies are currently restrained by technical and quality control hurdles, limiting their progression. Once overcome, their forward movement and implementation into practice could be attained, changing the face of pharmaceutical manufacture and initiating a new era of digital health.

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9 References

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