

Translating 3D printed pharmaceuticals: from hype to real-world clinical applications

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Abstract

Three-dimensional (3D) printing is a revolutionary technology capable of disrupting pharmaceutical development through the automated production of dose flexible printlets (3D printed drug products) on demand. This versatile technology offers significant advantages for clinical practice and drug development, enabling the creation of small batches of flexible drug products with the potential to personalise medicines to individual patient needs, and expedite drug development timelines within preclinical studies through to first-in-human (FIH) and Phase I clinical trials. Despite the many purported benefits of 3D printing to fabricate medicines, the clinical potential of the technology is yet to be realised. In this timely review, we provide an overview of the latest cutting-edge investigations in 3D printing pharmaceuticals in the pre-clinical and clinical arena, and offer a forward-looking approach towards strategies to aid the translation of 3D printing into the clinic.

Keywords: three-dimensional printing, preclinical studies; early phase drug development, first-in-human trials; oral drug delivery.

1. Introduction

Three-dimensional (3D) printing offers the potential to revolutionise the production of pharmaceuticals targeted to the gastrointestinal (GI) tract by offering a flexible drug product manufacturing platform that can adapt readily to changing market and patient needs (1). By using digital computer-aided design software to produce medicines in a layer-by-layer manner, 3D printing enables the on-demand production of drug products with personalised dosages (2, 3), drug combinations (4-6), geometries (7-9) and release characteristics (10-13); a concept which is currently unattainable and cost inefficient with conventional manufacturing technologies (e.g. tableting and encapsulation). This technology has been forecast to disrupt a wide range of pharmaceutical applications, ranging from expediting the drug development process and providing benefits for pharmaceutical manufacture, to on demand printing of personalised medicines on the front-line and in hard-to-reach areas (Figure 1).

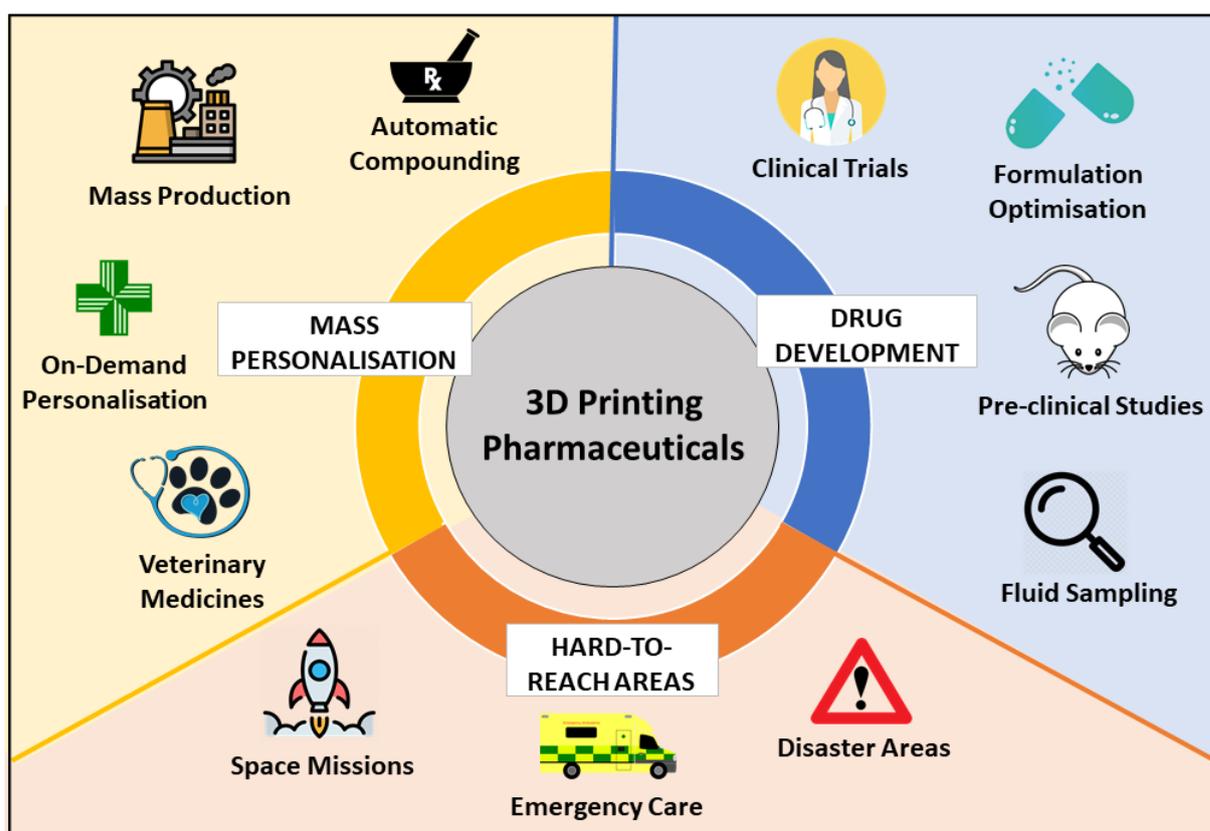


Figure 1. Pharmaceutical Applications of 3D Printing

Due to the potential to readily adapt dosages, 3D printing can provide many benefits for early phase drug development (e.g. pre-clinical, as well as first-in-human through to

Phase I/II clinical trials). These early phase studies involve the *in vivo* administration of a new drug candidate across a wide dosage range (14-16), with the aim to gain an initial understanding of parameters including efficacy, toxicology, tolerability, safety and pharmacokinetic (PK) behaviour in animal models (pre-clinical studies) and humans (clinical trials) (17). Conventional large-scale manufacturing processes (e.g. tableting and encapsulation) do not provide a dose flexible or dose-sparing platform, with smaller scale manufacturing processes (manual filling of capsules, or solutions and suspensions) coming alongside challenges with high labour and solubility issues. 3D printing has the potential to overcome these challenges and streamline, automate and accelerate the manufacturing of dosage forms for pre-clinical and clinical studies, while saving time and reducing costs (18, 19). By implementing 3D printers into a clinical setting, small batches of printlets with the desired dose could be manufactured on demand and immediately before administration, thus avoiding the need for long term stability studies (20, 21).

3D printing also has benefits for formulation optimisation, by enabling the production of patient-friendly formulations to aid medication adherence, such as personalised chewable and flavoured drug products for paediatrics and geriatric patients (22, 23). Printed drug products with fully customisable drug release profiles have also been produced, ranging from immediate and controlled release, through to targeted drug delivery systems to different regions of the gastrointestinal tract (24, 25). 3D printing has also been highlighted as a promising enabling technology to improve the solubility of BCS II and IV drug compounds through the production of solid dispersions. Such opportunities not only provide benefits for new drugs coming into the fore, but also existing drugs which have known formulation challenges that could be improved by using a flexible production platform (26, 27).

This technology has also been indicated in providing an alternative for pharmaceutical mass manufacture (28). Indeed, in 2016, the world's first 3D printed medicine (Spritam®) was approved by the Food and Drug Administration (FDA), which for the first time enabled the production of a unique drug product which had both high drug loading (up to 1000 mg) and rapid disintegration. The 3D printing method used was an alternative scaled-up binder jet printing manufacturing process, offering a limited number of dose strengths. Another potential application for 3D printed dosage forms is for the mass customisation of drug products, a process which is being used almost exclusively for the

manufacture of hearing aids to date, with 10 million hearing aids currently in circulation globally (24). Due to the high level of design freedom as well as the on-demand capability offered by 3D printing, this technology has been forecast to disrupt the way that we treat patients, away from mass manufacture towards personalised therapies (e.g., with tailored shapes, sizes, dosages and dose combinations) (29, 30), including on the front-line (e.g. in hospital or community pharmacies) Via decentralisation of the manufacturing process, this novel treatment pathway could enable patients to have an easier access to medicines within their community and reduce waiting times for those medicines that , extemporaneous preparation or compounding by a pharmacist (31, 32). 3D printing has also been indicated in producing personalised drug products in hard-to-reach areas, such as within disaster areas, for military operations, low- or middle-income countries, and even for space mission. Due to being digitised in nature, 3DP is well placed to be connected to other digital health technologies, including artificial intelligence and remote diagnostic tools including smart monitors and point-of-care tests, which could be sent to a clinician for data review and generation of a personalised prescription, enabling the easy review and modification of treatments or dosages.

Significant progress has been made over the last 3 years to advance and translate this technology from a theoretical benefit into realistic prospect in pharmaceutical production (33-35). Indeed, the benefits of 3D printing in pharmaceuticals has been well documented, with the evidence-base and investment into the research of 3D printing growing every day. Since 2016, over 3,700 academic papers have been published in this field according to PubMed (search criteria ‘3D printed medicines’ [All fields]), demonstrating the benefits that 3D printing can bring to the pharmaceutical industry and patients alike. However, despite this growing support for printing technologies, regulatory and technical challenges still remain before the widespread adoption of this technology into the pharmaceutical industry will occur.

This review will provide a timely update on the latest innovations in 3D printed medicines, firstly by discussing the five most promising 3D printing technologies within pharmaceuticals, as well as providing an overview on the latest, cutting-edge pre-clinical and clinical research using 3D printed medicines in the clinic. Finally, we will provide an opinion on the remaining barriers to entry of 3D printing technologies in pharmaceuticals,

as well as provide a forward-looking approach towards the widespread adoption of 3D printing in clinical practice.

2. 3D Printing Technologies

3D printing is an umbrella term that include several technologies; according to the American Society of Testing Materials (ASTM) classification there are seven main categories (36): binder jetting, VAT polymerisation, powder bed fusion, material jetting, material extrusion, direct energy deposition and sheet lamination (Figure 2) that can be divided into different subcategories (37). Within pharmaceuticals, five main 3D printing technologies can be distinguished: binder jetting, VAT polymerisation, powder bed fusion, material jetting, material extrusion. These 3D printing technologies and their applications have been extensively reviewed elsewhere (38, 39), and so only a brief description of each technology will be provided in this review.

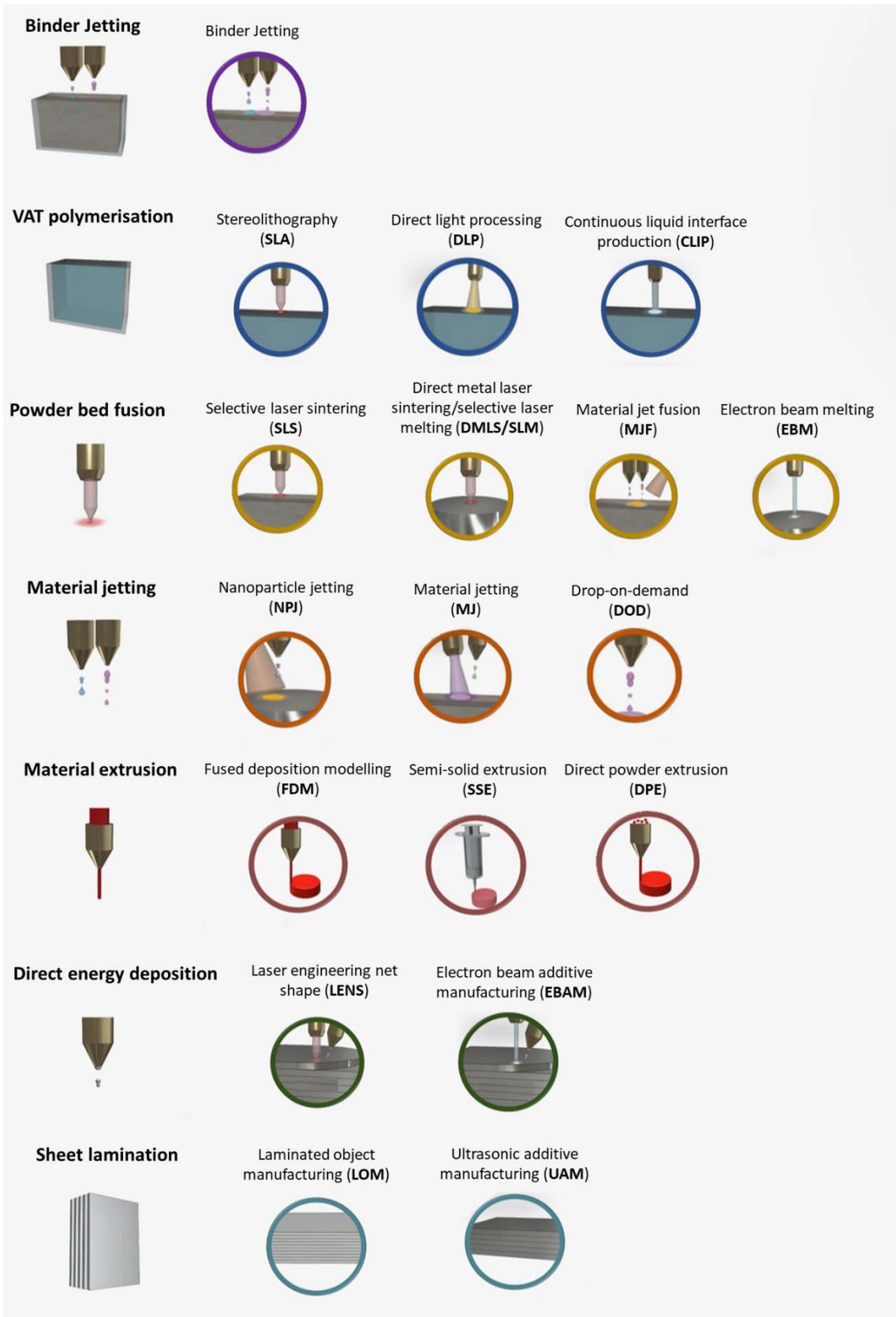


Figure 2. Graphical representation of the different 3DP technologies. Binder jetting; VAT polymerisation (stereolithography, direct light processing and continuous liquid interface production); powder bed fusion (selective laser sintering, direct metal laser

sintering/selective laser melting, material jet fusion and electron beam melting); material jetting (nanoparticle jetting, material jetting and drop-on-demand); material extrusion (fused deposition modelling, semi-solid extrusion and direct powder extrusion); direct energy deposition (laser engineering net shape and electron beam additive manufacturing); sheet lamination (laminated object manufacturing and ultrasonic additive manufacturing). Adapted with permission from (40).

2.1. *Binder jetting*

Binder jetting is a form of additive manufacturing where a liquid binding solution is selectively deposited with a printer nozzle over a powder bed. The wetted powder particles adhere together causing layer solidification (41). This technology was adapted in 2016 as an alternative mass manufacturing process to produce the first FDA approved 3D printed tablet (Spritam[®] by Aprezia Pharmaceuticals) (42). Binder jetting is highly suitable to produce highly porous, fast dissolving tablets with high drug loadings (43). Spritam[®] dissolves in the mouth in 11s needing only small amount of saliva and can incorporate a dose of up to 1000 mg. However, this technology is also applicable to the production of complex formulations such as near zero-order release dosage forms (44). To avoid the use of organic solvents, pharmaceutical binders could be dissolved in aqueous inks (3).

2.2. *VAT photopolymerization*

Vat photopolymerization uses a laser to induce the solidification of a liquid resin by photopolymerization (45). This process encompasses stereolithography (SLA), digital light processing (DLP), and continuous liquid interface production (CLIP) technologies, being SLA the most used for pharmaceutical purposes (46). SLA has a high degree of resolution necessary to fabricate drug delivery devices with complex structures, such as microneedles for skin delivery (47, 48), bladder devices for intravesical drug delivery (49), hearing aids (50), anti-acne masks personalised to the patient's anatomy (51) or drug loaded scaffolds (52). More recently, this technology was applied to the field of dosage form manufacturing, where it has been employed to produce polypills containing up to six different drugs (5) and reservoir devices for oral drug delivery (53). However, the compatibility of photocurable resins and drugs should be ensured to avoid unwanted chemical reactions between the drugs and the resins (54).

2.3. Powder bed fusion

Powder bed fusion uses a laser to draw a specific pattern on a powder bed, melting the powder particles together to form the 3D object (55). It includes selective laser sintering (SLS), multijet fusion (MJF), direct metal laser sintering/selective laser melting (DMLS/SLM) and electron beam melting (EBM). SLS is the main technology employed in the production of medicines and medical devices (56). In the past, due to the high localised temperatures required to sinter powder materials which may cause drug degradation, this technique has been mostly restricted to the production of medical devices, such as scaffolds (57). However, in 2017, Fina et al. (58) described the use of an alternative diode laser 3D printer to manufacture tablets using SLS without degradation of the drug. Due to the high resolution and precision of the laser, since then, SLS has also been exploited to fabricate printlets with complex gyroid lattice structures (59) and orally disintegrating printlets with Braille and Moon patterns suitable for patients with visual impairment (60).

2.4. Material jetting

Material jetting involves the deposition of liquid droplets of materials on a surface (61-63). This process includes the drop-on-demand (DOD) technique, in which the drops spontaneously solidify, and the nanoparticle jetting (NPJ) and material jetting (MJ) techniques, in which the drops are cured or fused using a heat source or by UV light (64-66). Some examples of the application of these technologies are found in the production of oral films (67), nano- and microparticles with arbitrary geometries (68, 69) and controlled-release tablets (70, 71).

2.5. Material extrusion

2.2.1 Fused deposition modelling

Fused deposition modelling (FDM) is a form of material extrusion in which a polymer filament is heated and extruded through a heated nozzle creating an object layer by layer (72, 73). The drug loaded filaments are usually fabricated by hot melt extrusion (HME) (74-76). This technology allows the manufacture of objects with geometrical shapes not obtainable with powder compaction, such as hollow structures and tablets with different shapes (sphere, torus, cube, pyramid) (77-79). Moreover, it is also possible to modify the

drug release patterns varying the infill percentage (80) to obtain controlled release (81-83) and immediate release (84-87) dosage forms. One of the initial limitations of FDM was the high printing temperatures required for extrusion and printing, which caused a risk of drug degradation (88). However, nowadays the used of new materials has allowed printing at much lower temperatures to overcome this issue (84, 89).

2.2.2. Semi-solid extrusion

Semi-solid extrusion (SSE) is another technology under the material extrusion umbrella. Instead of extruding a filament or powder, SSE employs a syringe-like system to extrude a gel or paste in sequential layers to create the 3D object (90-92). An advantage of this technique compared to FDM and DPE is the lower temperature required for printing, which makes SSE more adequate for thermolabile drugs (93, 94). This technology has been employed to prepare rapid release tablets (95) and gastro-floating tablets (96), as well as polypills with compartmentalised drugs to obtain both immediate and sustained release profiles (6) and orodispersible films (97, 98). Moreover, using SSE it was also possible to print lipid-based dosage forms with different geometries, either to be administered orally (99) or rectally in the form of suppositories (31).

2.2.3. Direct powder extrusion

Direct powder extrusion (DPE) is another type of material extrusion in which powdered material is directly printed using a single screw extruder within a printhead nozzle. The main difference of this technology with FDM is that the filament production step using HME is avoided, reducing optimisation and drug development timelines and making this technology more accessible for clinicians and researchers. Another advantage of DPE is that only small amounts of drug and excipients are needed, making this technique especially suited for preparing formulations for preclinical and clinical studies (100). Since the appearance of this technology in the pharmaceutical field is recent, only a few studies have described the use of DPE to produce dosage forms. However, medicines incorporating tramadol with abuse-deterrent and alcohol-resistant properties were prepared using this technique (101).

3. Pre-clinical Applications

During the drug development process, pre-clinical studies are used to test the safety, efficacy and pharmacokinetic behaviour (including absorption, bioavailability, metabolism and excretion) of new drug candidates using experimental and animal models (17). The data collected crucially aids in deciding which drug candidates to take forward into first-in-human (FIH) clinical trials and provides information such as dosing schedules and expected adverse effects (102, 103). The most common animal model used in preclinical study are rodents which are low cost, easy to handle and have been shown to have physiological similarities with humans (104). Small formulations (e.g. size 9 capsules or mini-tablets), as well as liquid formulations, are typically employed in pre-clinical work as these formulations have geometries that can be administered to small rodents. However, traditional manufacturing processes often hinder the rapid progress through pre-clinical studies, due to being dose inflexible, high cost and causing high waste.

3D printing technologies have been indicated in providing unique benefits for pre-clinical studies over conventional manufacturing processes, including high degree of dose and design flexibility. Due to the high degree of design freedom offered by 3D printing technologies, the production of dosage forms of appropriate geometry and size that contains the exact dosage adapted to the pre-clinical animal model can be achieved. To date, SLS 3D printing has been used to prepare small capsule-shaped devices and 3D printed pellets (miniprintlets of 0.5 mm and 1 mm diameter) that, due to their small size, have potential for administration to rodents and small animals in preclinical studies (105, 106). In recent years, the reduction in the price of 3D printers, as well as miniaturisation and development of user-friendly interfaces, has made it an affordable and accessible technology which is easy to integrate and use in a laboratory setting. Indeed, researchers and laboratory staff can manufacture small batches of printlets in a rapid and on-demand manner ready for use in preclinical studies.

The increasing number of published studies from all over the world using 3D printing in preclinical studies has highlighted the versatility of this technology (Table 1). This section will provide an overview on the types of 3D printed formulations that have been evaluated in preclinical animal models, including oral immediate release drug products, modified release preparations, suppositories, as well as latest advances in regional gastrointestinal targeting and fluid sampling using orally administered 3D printed devices.

3.1. Immediate and Modified Release Oral Drug Products

Several studies have tested 3D printed formulations in animal models to evaluate the pharmacokinetic behaviour of the dosage forms. FDM 3D printing has previously been used to prepare a dual-compartmental dosage unit to physically isolate and control the release of two anti-tuberculosis drugs; rifampicin and isoniazid (Figures 3A, B and C). The drugs were compartmentalised to prevent their simultaneous release into the stomach, avoiding a drug-drug interaction. The *in vivo* evaluation in rats confirmed the ability for the device to release rifampicin first and the delayed and slower release of isoniazid from the dosage unit (Figures 3D and E) (107).

Table 1. Examples of studies that used 3DP in preclinical research.

Formulation	3DP technology	Drug	Animal	Aim	Ref.
Capsule	FDM	Lamivudine	Beagle dog	Fabrication of capsules with different wall thicknesses to modulate drug release and evaluate the regional absorption of the drug in the gastrointestinal tract of dogs.	(108)
Capsule	FDM	Radiotracer [¹⁸ F]FDG	Rat	Fabrication of capsule-shaped devices filled with [¹⁸ F]FDG to track the device through the gastrointestinal tract of rats using medical imaging.	(109)
Capsule	FDM	Octreotide, sodium caprate and paracetamol	Beagle dog	Fabrication of a pressure sensitive capsule for the local release of drugs in the upper gastrointestinal tract.	(110)
Tablet	FDM	Isoniazid and rifampicin B	Rat	Preparation of a dual-compartmental dosage unit to physically isolate and prevent the simultaneous release of two anti-tuberculosis drugs.	(107)
Tablet	FDM	Sodium warfarin	Rat	Manufacture of tablets with different doses of an anti-coagulant drug as an alternative to splitting marketed tablets.	(111)
Tablet	FDM	Diltiazem	Rat	Preparation of pulsatile and chrono controlled-release tablets using drug-free and drug-impregnated filaments.	(112)
Tablet	SSE	Efavirenz, tenofovir and emtricitabine	Pig	Preparation of controlled release tablets containing three drugs for HIV treatment.	(113)
Gastro-floating tablet	FDM	Domperidone	Rabbit	Fabrication of floating tablets with different shell numbers and infill percentages and determination of their gastric residence time by X-ray imaging.	(114)

Gastro-floating device	FDM	Amoxicillin	Rabbit	Fabrication of a floating device to prolong the gastric residence time of a commercial capsule of amoxicillin and determination of the residence time by X-ray imaging.	(115)
Gastro-floating device	FDM	Acyclovir	Beagle dog	Fabrication of a gastroretentive system to prolong the release of a conventional acyclovir tablet and determination of the residence time by X-ray imaging.	(116)
Gastric resident device	FDM	Doxycycline and levonorgestrel	Pig	Development of a gastric resident electronic device capable of delivering drugs and maintaining in vivo wireless communication.	(117)
Pill	SLA	None	Pig and primate	Manufacturing of a pill with an integrated osmotic sampler and microfluidic channels for in vivo sampling in the gut.	(118)
Suppository	SSE	Tacrolimus	Rat	Evaluation of the therapeutic activity of lipid-based tacrolimus suppositories in an experimental animal model of colitis.	(21)

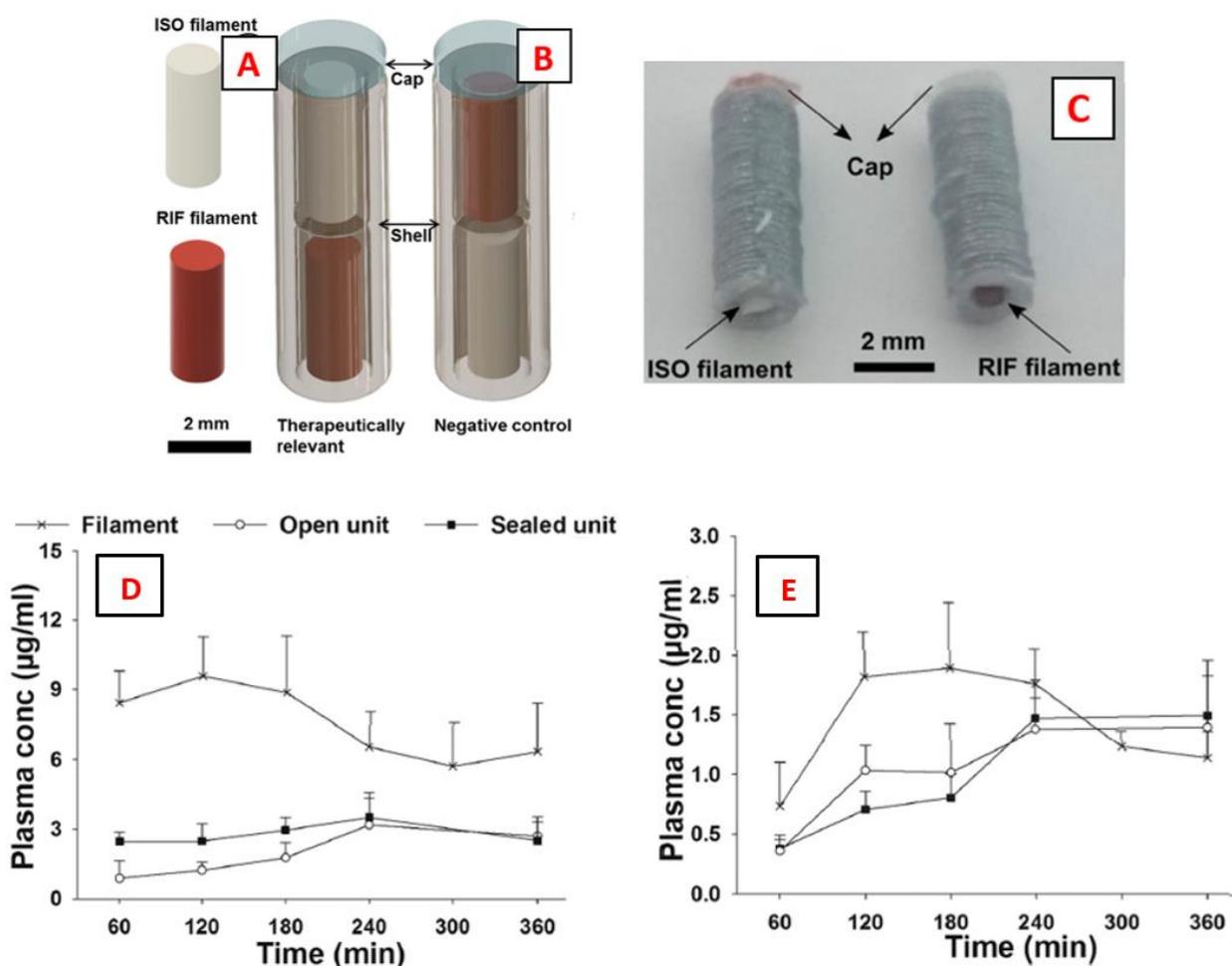


Figure 3. Schematic representation of isoniazid and rifampicin hot-melt extruded drug filaments (A) and the dual-compartmental dosage units (B). In (C) it can be seen a photograph of the final 3D printed dual-compartmental dosage units. On the right, in vivo

drug release profiles of isoniazid (D) and rifampicin (E) in fasted rats after oral administration of free filaments and dual compartmental dosage units with and without sealing (107).

FDM technology has also been used to manufacture 3D printed tablets with different doses of warfarin, a narrow therapeutic index drug which conventionally requires splitting of commercially available tablets to achieve the correct dosage (Figures 4A and B) (111). After administration to rats, the 3D printed tablets showed a more desirable pharmacokinetic behaviour due to a more sustained drug release compared to the warfarin administered as a solution (Figure 4C).

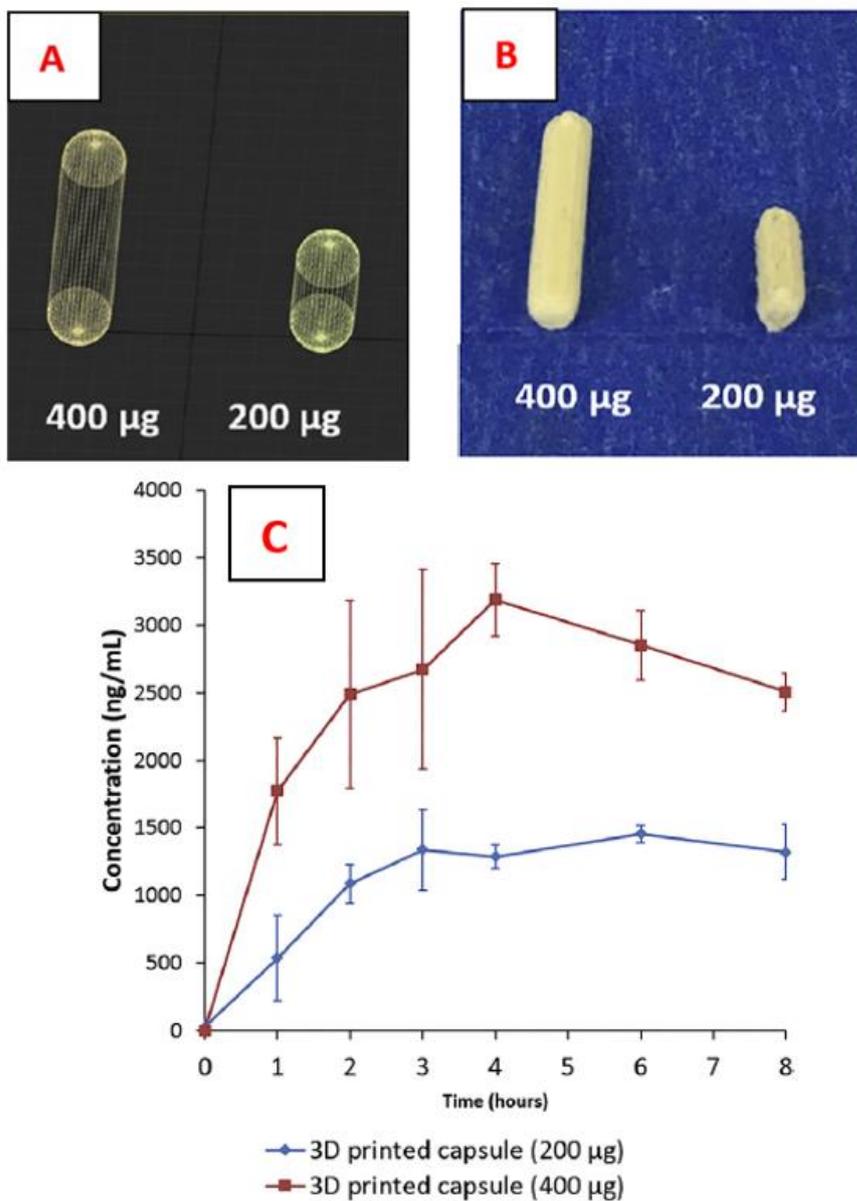


Figure 4. Rendered image (A) and photograph (B) of 3D printed tablets adapted in size for oral gavage administration in rats. Figure (C) shows the *in vivo* drug release profiles of warfarin in rats after oral dosing of 200 or 400 μg from warfarin solution and warfarin loaded 3D printed tablets (111).

Drug-free and drug-impregnated filaments for FDM printing have also been prepared using a single-screw HME using diltiazem as model drug. The study showed that by modifying process parameters including the infill percentage and the number of shells, both sustained and immediate-release tablets were obtained. The fabrication of both pulsatile and chrono controlled-release tablets was also achieved by alternating the use of the placebo and drug-loaded filaments (Figure 5). The *in vivo* release profiles obtained from administration of the tablets to rats were consistent with those obtained *in vitro* (112).

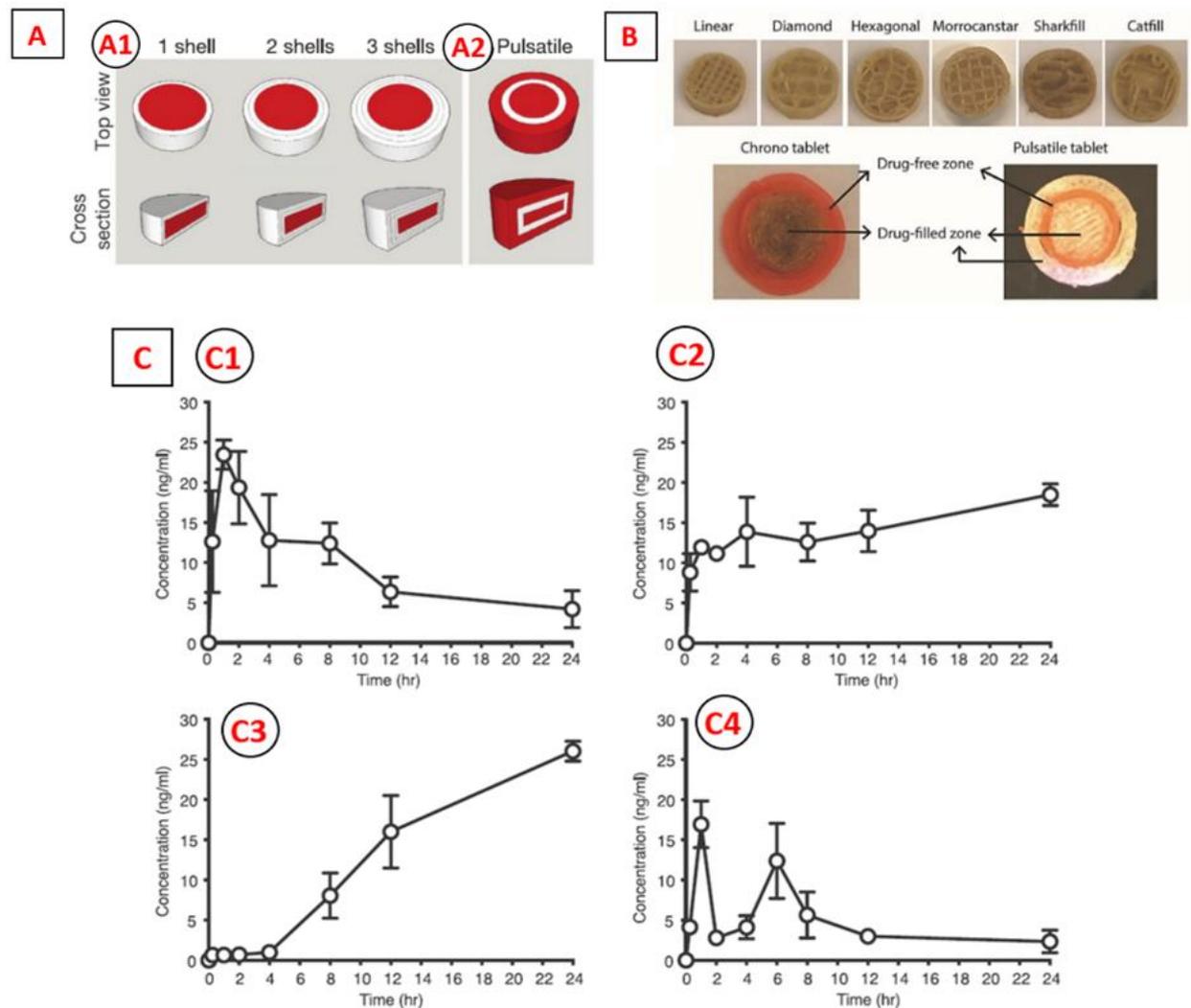


Figure 5. (A) Design of chrono controlled-release (A1) and pulsatile (A2) tablets. Drug-free layers are coloured in grey and drug-loaded layers in red. (B) Photographs of printlets with varying infill density and infill patterns, as well as chrono and pulsatile printlets. (C) Drug absorption profiles after oral administration of (C1) immediate-, (C2) extended-, (C3) chrono- and (C4) pulsatile-release tablets (112).

In one study, FDM printing was used to print four different polymer-based capsules containing a radiotracer to evaluate intestinal behaviour after administration to rats was assessed using PET/CT imaging (109) (Figure 6). Although the capsules were fabricated with the recommended sizes for rodent administration, the devices did not empty from the stomach of the animals; an inconsistency previously reported by other authors (119). Subsequent studies found that the size of the device and the use of anaesthetic agents influence the gastric emptying of dosage forms (105). The findings highlighted in this study highlight the critical importance to evaluate the impact of a number of variables

(including dosage form suitability and anaesthetisation) on the performance of the chosen pre-clinical formulation prior to the study being initiated.

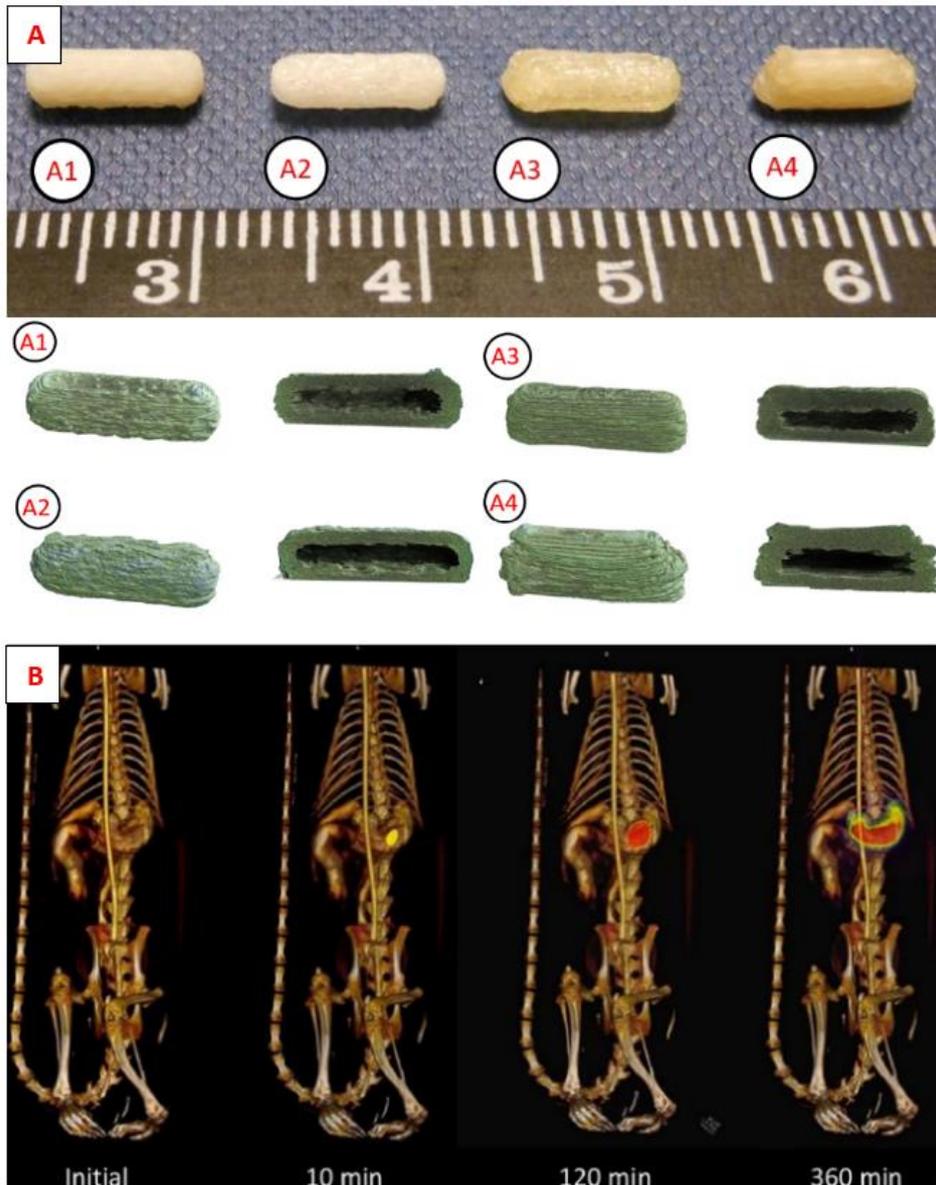


Figure 6. (A) Above, from left to right pictures of 3D printed capsules made of (A1) Kollicoat IR, (A2) Klucel EF, (A3) Aqualon N7 and (A4) Aquasolve-LG. Below, micro-CT images of the same 3D printed capsules. (B) Fused PET/CT images prior to the administration of the Klucel device and 10, 120 and 360 min post-administration (109).

SSE has also been employed within preclinical research for the fabrication of controlled release tablets containing three drugs (efavirenz, tenofovir disoproxil fumarate and emtricitabine) for HIV treatment (Figure 7). The 3D printed tablets were administered to

pigs, and the results of the study showed an enhanced bioavailability of the drugs formulated in the 3D printed tablet compared to the marketed formulation (113).

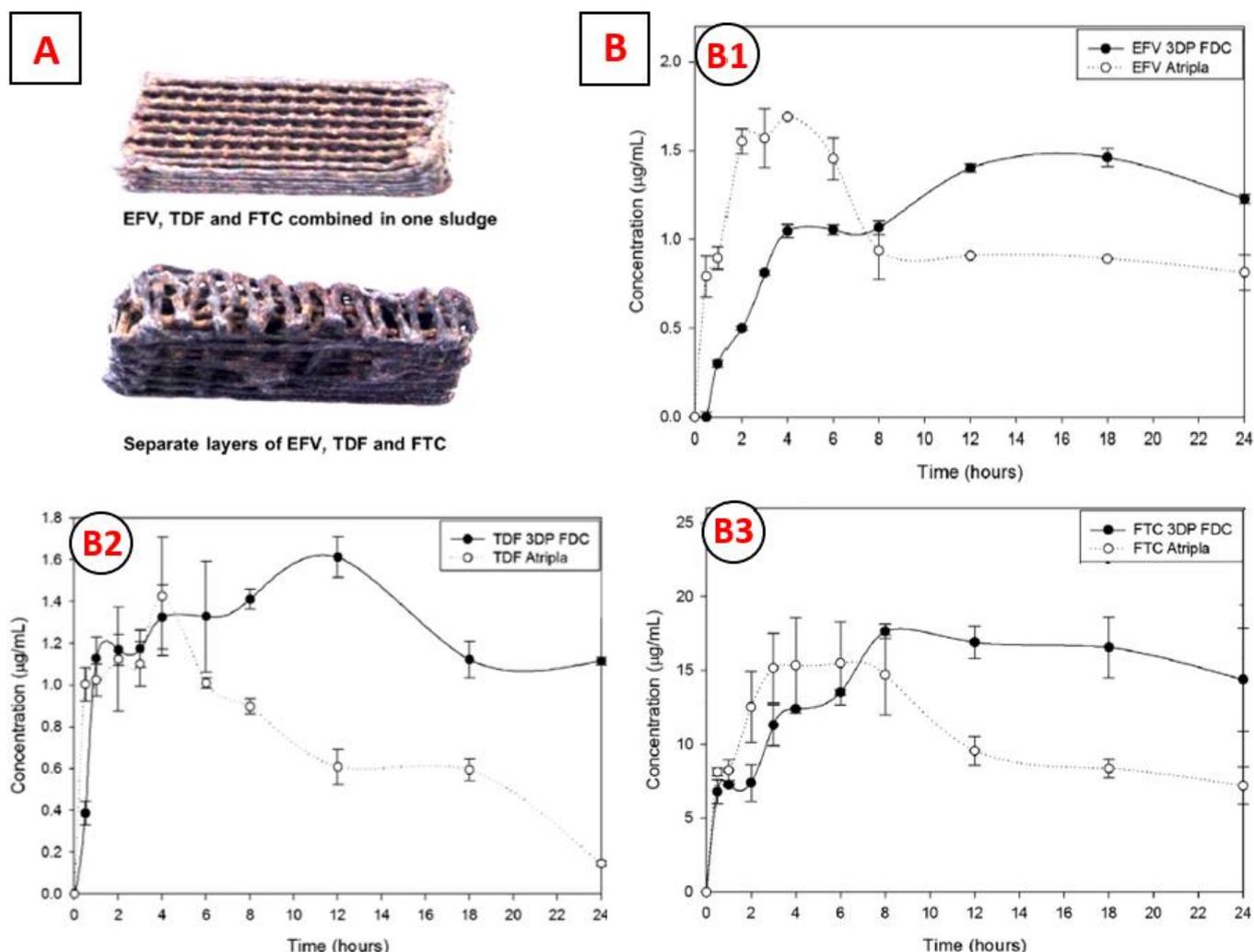


Figure 7. (A) Photograph of two designs for the 3D printed controlled release fixed dose combination tablets. (B) *In vivo* plasma drug concentrations for (B1) efavirenz, (B2) tenofovir and (B3) emtricitabine (113).

Gastroretentive systems are a strategy used to prolong the formulation gastric residence time have also been fabricated by 3D printing and tested in animal models. For instance, a conventional acyclovir sustained-release tablet was inserted into a gastroretentive system prepared by FDM and administered to Beagle dogs (Figure 8A). X-ray imaging showed that the device stayed in the stomach for more than 12 h (Figure 8B), and the *in vivo* pharmacokinetic analysis confirmed the prolonged release and absorption of acyclovir (Figure 8C) (116). The same approach has been used in another study (115) to prolong the release of amoxicillin in the stomach for the treatment of *H. Pylori* infection.

The gastroretentive device was also fabricated by FDM and a commercial capsule of amoxicillin was inserted into the printed device. The capsule in the floating 3D printed device was administered to rabbits and the residence time in the stomach was evaluated by X-ray imaging, which showed that the gastroretentive system remained in the stomach for 10 h. In another study, FDM was used to print intragastric floating tablets for the sustained release of domperidone (114). Unlike the works mentioned above, in this study the drug was loaded into the filaments which were then printed on hollow tablets with different shell numbers and infill percentages. The floating tablets were given to rabbits and their stomach residence time was determined by X-ray imaging. The images showed that the devices remained in the stomach for at least 10 h, and the results from pharmacokinetic studies indicated that the floating tablets exhibited a prolonged release when compared with commercial tablets of domperidone.

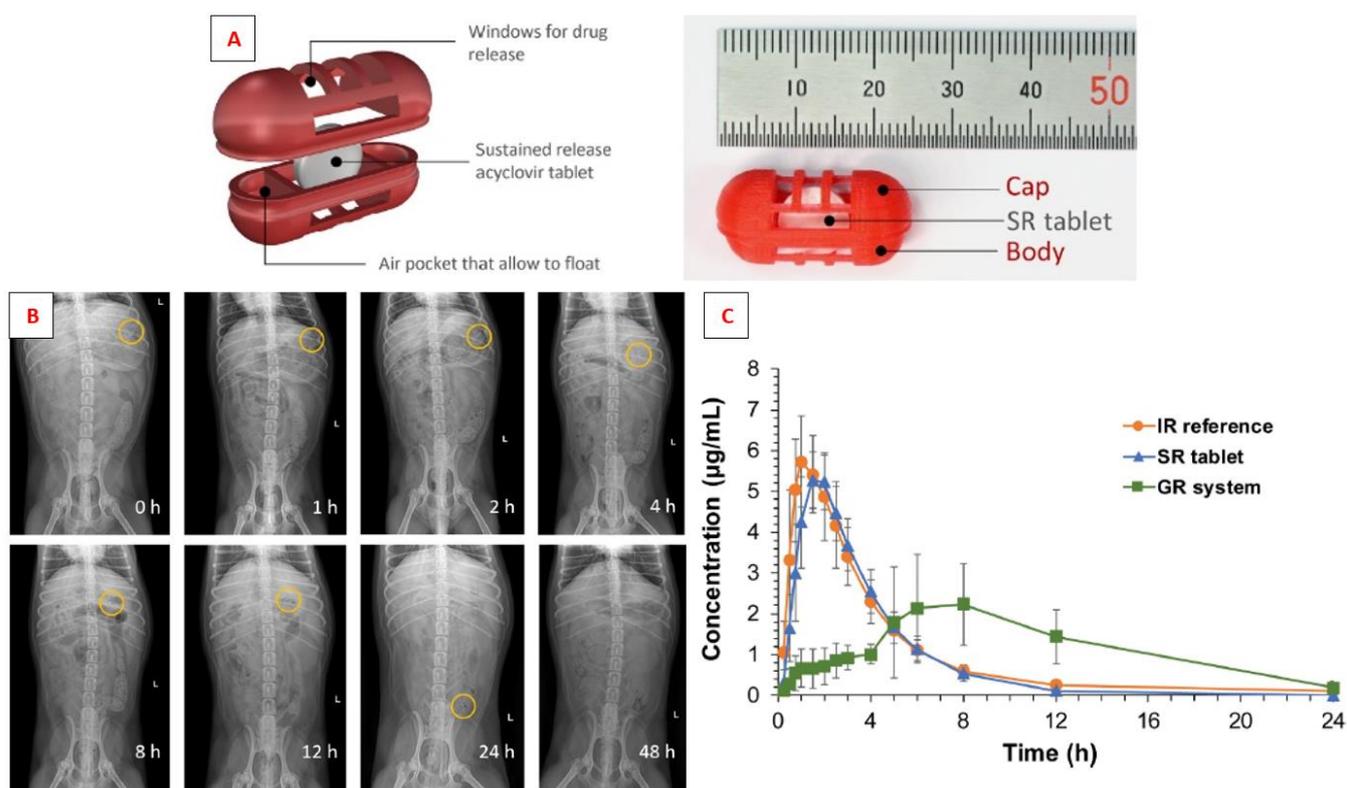


Figure 8. (A) Photograph of a gastroretentive system composed of a 3D printed gastro-floating device and acyclovir tablet inside the device. (B) Abdominal X-ray images indicating the positions of the gastroretentive system (device from photograph A, indicated with a circle) in the gastrointestinal tract of a beagle dog following oral administration for 48 h. (C) *In vivo* pharmacokinetics of acyclovir in the dogs after oral

administration of immediate-release (IR) and sustained-release (SR) tablets alone or included into the gastroretentive system (GR) (116).

In another study, capsule shells were printed and filled with a drug-loaded vehicle containing lamivudine (Figure 9). By controlling the wall thickness of the capsules it was possible to obtain different release profiles, with the final aim of delaying the release of the drug from the formulation, which allowed the evaluation of regional drug absorption in Beagle dogs (108).

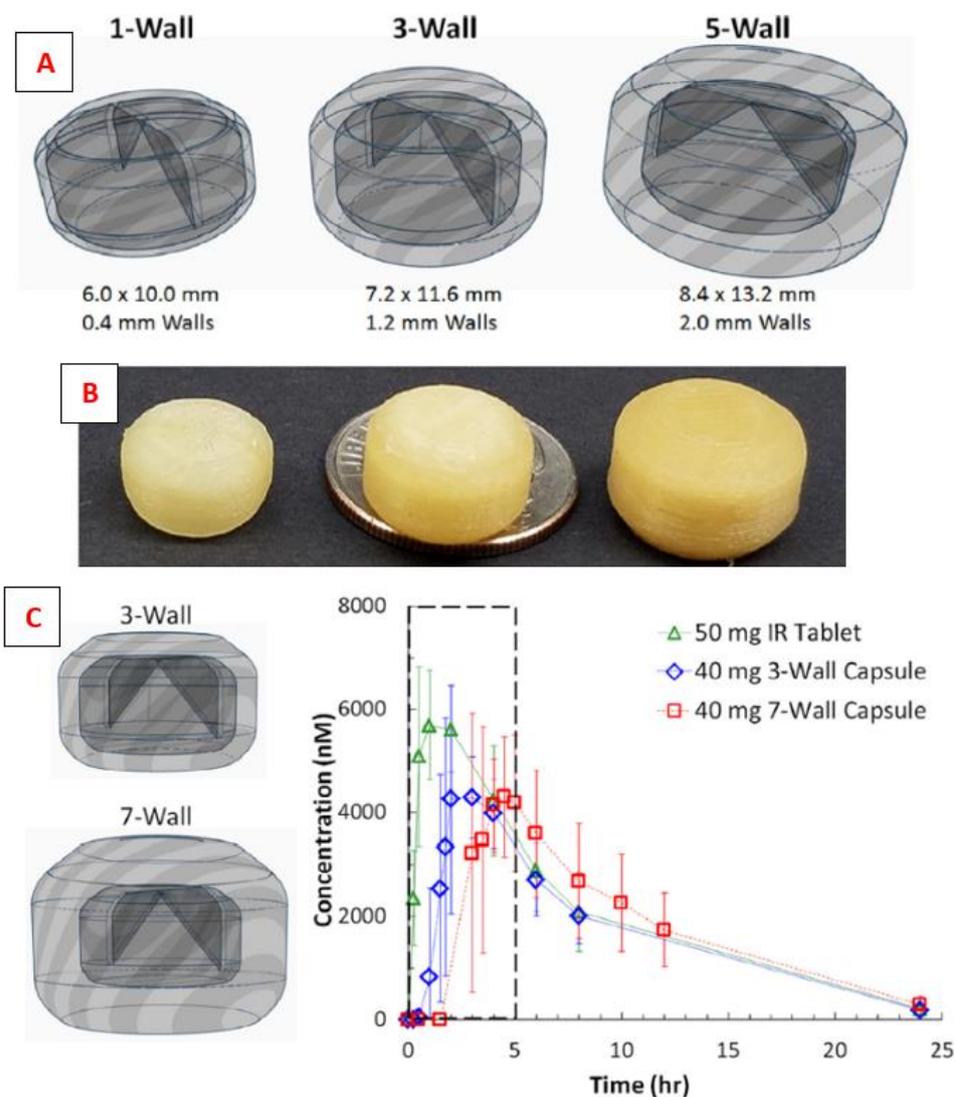


Figure 9. (A) Images of CAD drawings for 1-, 3- and 5-wall PVA capsule shells and (B) photographs of the 3D-printed PVA capsules (the 3-wall capsule on top of a U.S. dime). (C) In vivo drug release profiles in blood in Beagle dogs for the reference formulation of

lamivudine (50 mg immediate release tablet) and 40 mg 3- and 7-wall drug filled 3D printed capsules (108).

3D printing also has applications beyond small molecules towards large molecules and biologics. The growing interest in oral delivery of peptides and other biological drugs has led to the development of alternative strategies to conventional enteric coating. Targeting the upper part of the GI tract is especially challenging using enteric coatings due to the high variability that enteric coated dosage forms exhibit in the time of drug release. To overcome this challenge, one group devised 3D printed pressure sensitive capsules that were capable of breaking in a specific section of the GI tract (110). Filaments produced by extrusion of Eudragit RS powder were used to fabricate the capsules using a FDM 3D printer. The capsules were loaded with the octapeptide octreotide and the permeation enhancer sodium caprate (C10) and administered orally to beagle dogs. Paracetamol, which is completely absorbed in dogs, was also included in the formulations to help with the evaluation of the capsule performance. Moreover, drug delivery from the 3D printed capsules were compared with traditionally enteric coated gelatin capsules and enteric coated tablets. The results showed that the pressure sensitive capsules released the drug in 50% of the dogs and had a similar performance in terms of octreotide bioavailability or C_{max} compared to the enteric coated dosage forms. This study demonstrated, for the first time, a novel strategy for delivering biologics orally using 3D printing.

The combination of biomedical electronics with 3D printing represents another innovative approach to achieve advanced personalised diagnostics and therapeutic functionalities (1). Most long-term resident electronic devices need to be implanted by invasive procedures or require complex equipment for communication. However, the delivery of electronics through ingestion represents a feasible approach with myriads of functionalities, such as measuring pH or temperature or even administering medications. Using 3D printing technology, it was possible to fabricate a wireless gastro-retentive electronic device with a residence time in a porcine stomach of 36 days while maintaining *in vivo* wireless communication for at least half the time (Figure 10) (117). The device included a drug delivery module with a two-arm gastric residence architecture made of polylactic acid (PLA) and a thermoplastic polyurethane that expands to a diameter larger than the diameter of the pylorus and enables the simultaneous controlled-release of drugs.

The passive disintegration of the device allowed its passage through the pylorus and gastrointestinal tract to be finally excreted (Figure 10).

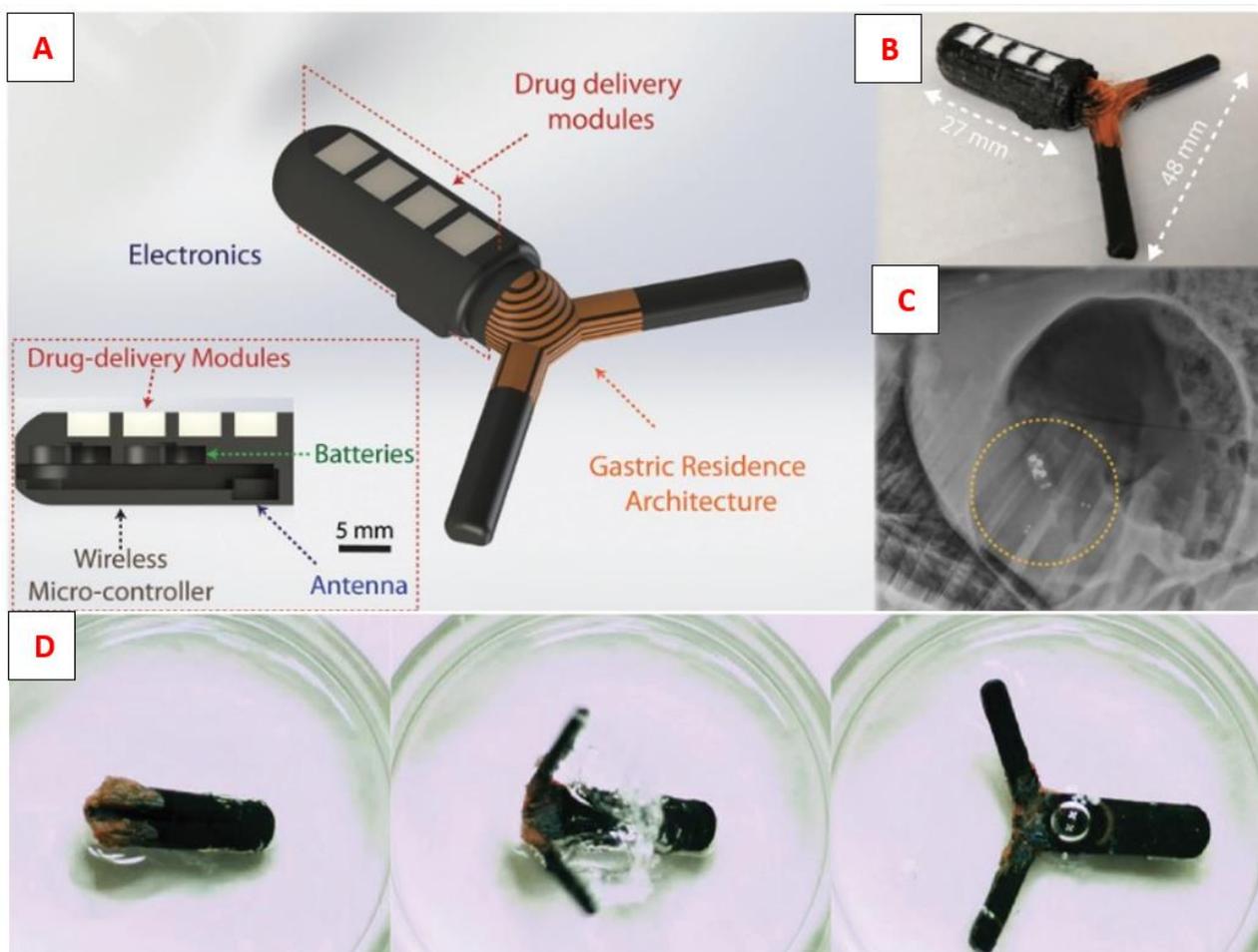


Figure 10. (A) CAD model of the gastric-resident electronic device showing a Bluetooth wireless-microcontroller, antenna, batteries, and drug delivery modules. (B) Photograph of the electronic device showing its dimensions and (C) X-ray image of the device in a porcine stomach. (D) Photographs showing the expansion of the 3D printed device before, during and after expansion (117).

3.2. Rectal Formulations

The first attempts to prepare rectal or vaginal formulations using 3DP focused mainly on creating moulds that were used to cast suppositories. Using FDM, it was possible to create moulds using different materials, such as PVA (120-122) and resins (123). However, these works did not print the suppositories themselves. More recently, a new approach to prepare self-supporting suppositories without the need for moulds has been described

(31). Using SSE technology, lipid-based suppositories loaded with the tacrolimus were successfully prepared (Figure 11A) in different sizes and with different dosages as an example of how 3DP could aid medicine personalisation. Blends of Gelucire and coconut oil were employed as excipients due to their self-emulsifying properties, which helped to solubilise the drug once the suppositories began to melt at human body temperature. As tacrolimus is an immunosuppressant drug used in a variety of conditions, such as therapy-resistant ulcerative colitis, in a subsequent study, the suppositories were adapted in size and dose for its administration to rats with experimental colitis (Figure 11B) (21). PET/CT imaging was used to monitor the evolution of the disease before and after the administration of the treatment. PET/CT images showed a remission of the disease from day 7 compared to the control group (Figure 11C), which confirmed the efficacy of this approach in ameliorating colitis.

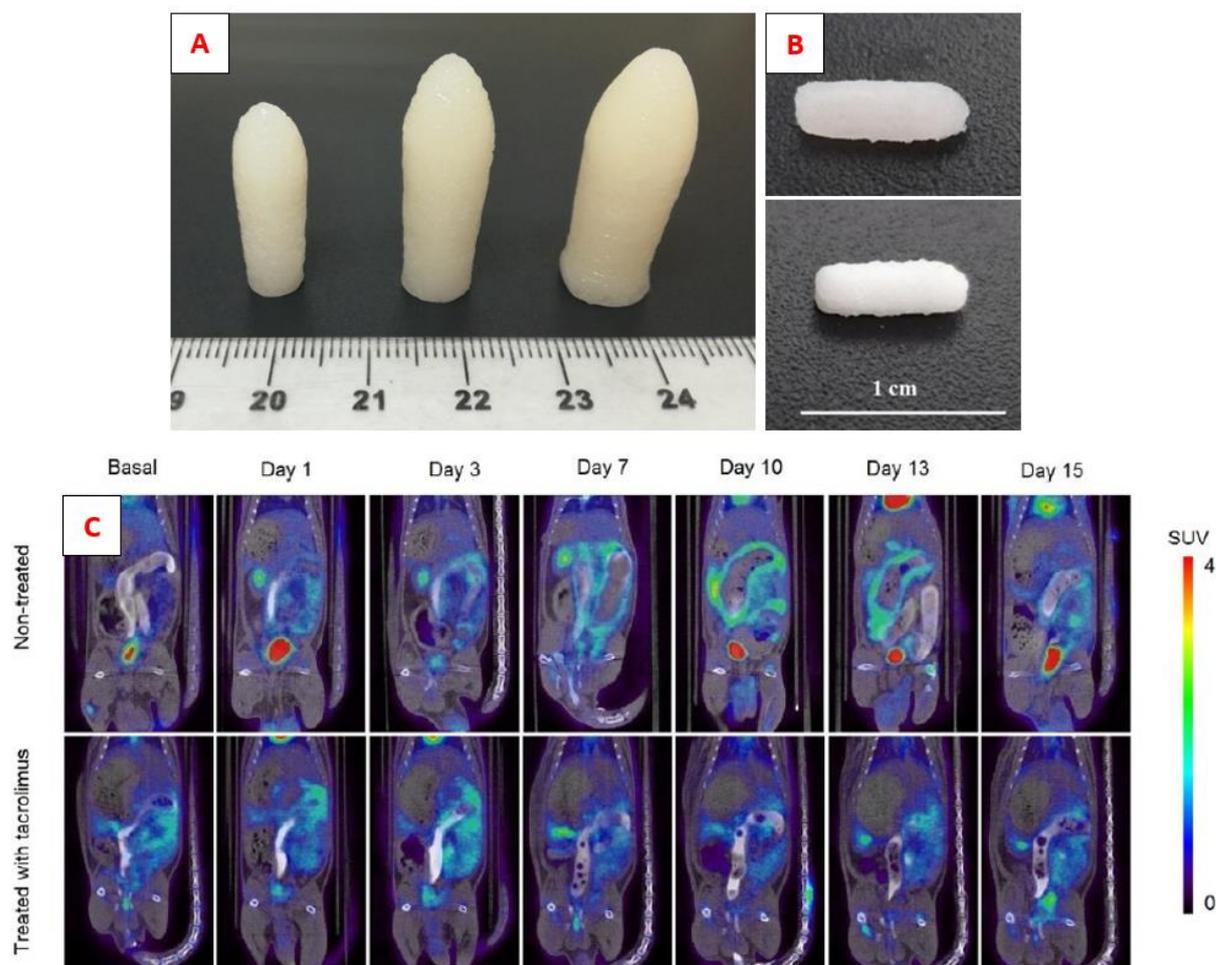


Figure 11. (A) 3D printed self-supporting suppositories in different sizes (31). (B) 3D printed suppositories adapted in size and dose for administration to rats. (C) PET/CT

images over time of rats treated with the 3D printed tacrolimus suppositories and non-treated. Experimental colitis was induced on day 3. The metabolic activity is coded on a colour scale ranging from blue (low [^{18}F]FDG uptake) to red (high [^{18}F]FDG uptake). A lower [^{18}F]FDG uptake in the colon can be observed from day 7, which means that the illness is in remission (21).

In other work, self-nanoemulsifying suppositories loaded with lidocaine were prepared for the topical pain relief in conditions such as haemorrhoids (124). The suppositories were prepared using blends of lipid excipients and surfactants (Geloil, Gelucire and Kolliphor) selected to form a nanoemulsion to provide a larger surface for drug solubilisation. This work provides another example of suppository personalisation.

3.3. Gastrointestinal Fluid Sampling

The development of technological devices capable of noninvasively sampling different locations of the GI tract could provide new insights into the relationship between the microbiome and human health. Medical analysis often relies on easily accessible samples (e.g., faeces) that are inadequate for identifying abnormal conditions, as the gut microbiome changes as intestinal contents moves through the GI tract. Recently, 3D printing has been used to fabricate a miniaturised biocompatible pill with an integrated osmotic sampler and microfluidic channels for *in vivo* capable of sampling in different locations in the gut (Figure 12) (118). The pill was composed of three main parts: top sampling head, a semipermeable membrane in the middle and a bottom salt chamber. The membrane was made of cellulose acetate and the pill casing was fabricated using a biocompatible photocurable polymer and covered with a pH-sensitive enteric coating. Also, a magnet was placed inside the salt chamber to enable the pill to sample from a targeted region of the intestine. The pill sampling head and the bottom salt chamber were manufactured using an SLA 3D printer. Briefly, a pressure differential was created across the semipermeable membrane that facilitates the flow of water from the microfluidic channels towards the salt chamber. The porosity of the membrane allowed larger particles, such as microorganisms, to get trapped in the channels. The pill was administered to pigs and non-human primates and the bacterial populations recovered from the channels closely resemble the bacterial populations present in the areas to which the pill was exposed, also demonstrating its ability to take microbiome samples from upper parts of the gut.

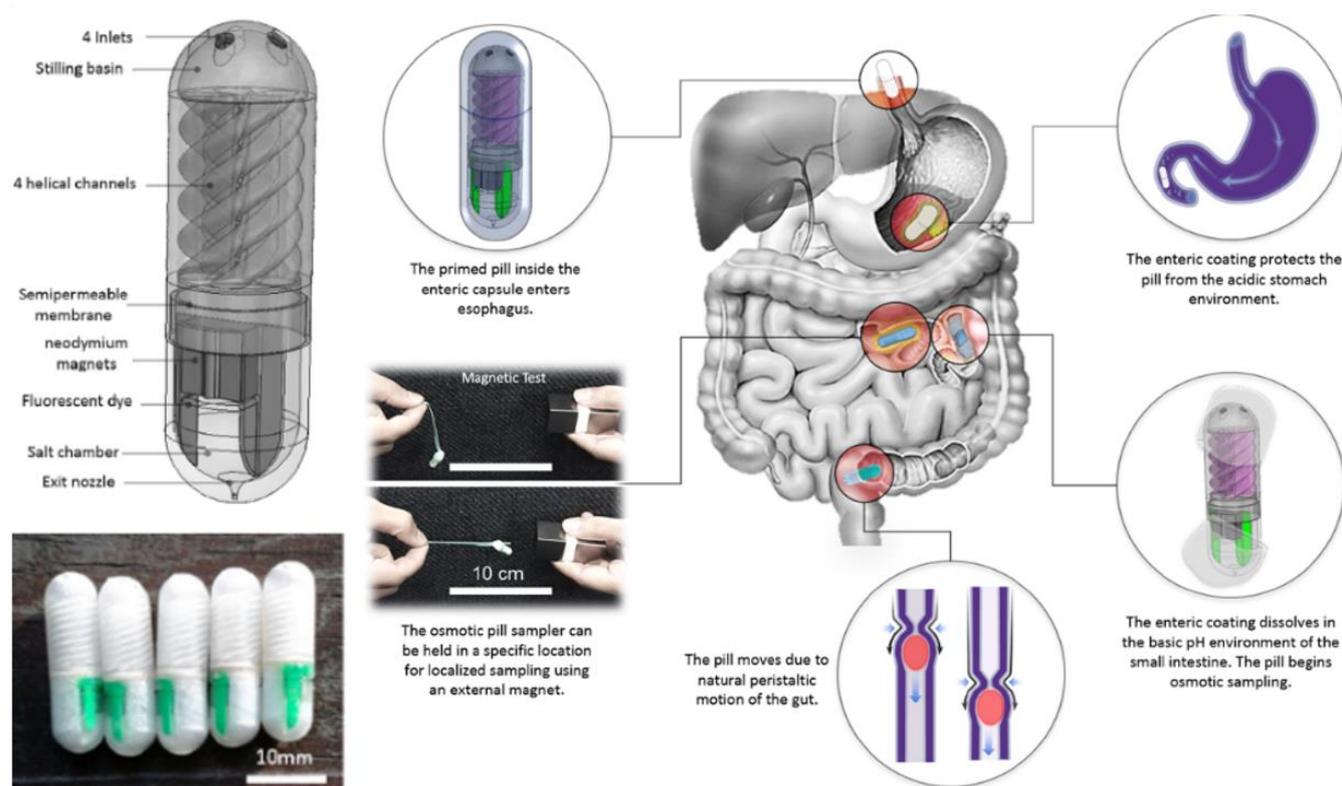


Figure 12. On the left, schematic representation and photograph of the 3D printed osmotic pill samplers. On the right, schematic hypothetical drawing of the passage of the osmotic pill in an enteric capsule through the gastrointestinal tract of a human (118).

4. Clinical Opportunities

4.1. Personalised Medicine

In recent years, several studies involving humans have been carried out to evaluate the use of 3D printing to prepare medicines tailored to each patient's needs (Table 2). 3D printing could help to drive the field of personalised medicine due to its capabilities of producing individualised printlets in small or 'one-off' batches, directly at the point of care. The dosage form could be designed to contain an appropriate dosage, drug combinations, formulation type and/or aesthetics that are tailored to suit the patient. This process could benefit a number of different situations and patient groups in the clinic, which will be discussed in turn.

Table 2. Examples of studies that used 3DP in clinical research.

Formulation	3DP technology	Drug	Aim	Ref.
Printlets	FDM	None	Investigation of the influence of the shape, size and colour of different placebo printlets on end-user acceptability.	(125)
Chewable printlets	SSE	Isoleucine	Preparation of chewable isoleucine printlets in a hospital setting with different flavours and colours to treat children with a rare metabolic disease.	(22)
Candy-like printlets	FDM	Indomethacin	Preparation of candy-like formulations for paediatric patients with enhanced palatability.	(77)
Subdivided tablets	SSE	Spiro lactone and hydrochlorothiazide	Preparation of subdivided spiro lactone tablets to be administered to patients instead of the conventional tablets subdivided by splitting.	(18)
Polypills	FDM	Lisinopril, amlodipine, indapamide and rosuvastatin	Fabrication of polypills with bespoke release patterns for multiple drugs.	(126)
Rapidly disintegrating tablets	Binder jetting	Levetiracetam	Clinical study to determine and compare drug plasma concentrations following the administration of the 3D printed tablet and the reference formulation in healthy volunteers and to evaluate the effect of food consumption on the PK profile of the 3D printed tablet.	(127)
Printlets with braille and moon patterns	SLS	Paracetamol	Preparation of orally disintegrating printlets suited for patients with visual impairment.	(60)
Mouthguards	FDM	Vanillic acid	Manufacture of a tailored oral drug delivery device in the form of a mouthguard with tuneable release rates and evaluation of its performance in human volunteers.	(128)
Orthodontic retainers	FDM	Clonidine hydrochloride	Fabrication of wearable personalized 3D printed orthodontic retainers for local sustained-release of drugs.	(129)
Printlets	DLP, SLS, SSE and FDM	None	Visual evaluation of printlets produced using different 3DP technologies by children.	(130)

A particularly promising application of 3D printed medicines is for the formulation of medicines that require exact tailoring and personalisation. For example, formulation an exact dose of narrow therapeutic index drugs (i.e. those which have a narrow gap between the therapeutic and toxic dose) is of paramount importance to ensure drug efficacy and

safety (131). Furthermore, paediatric and geriatric populations often require different dosing and formulation requirements compared with the standard adult. As an example, the elderly may have visual or swallowing impairments which may require consideration in the development of new drug products and packaging. Furthermore, children commonly require smaller and tailored dosages of medicines based on physical characteristics, for example body weight, or body surface area (132, 133). Formulation of personalised drug products with tailored dosages can be problematic due to the vast majority of medicines being commercially available as limited dose strengths and formulation types. In order to achieve the correct dosage, it is common practice for patients to manually adjust the dose by tablet splitting or crushing. This practice carries a series of risks, such as inaccurate dosing and human error (134, 135) as well as the risk of drug product failure for enteric coated tablets, leading to severe therapeutic consequences for patients (136, 137). Extemporaneous preparation (also known as compounding) can be used to prepare patient-specific drug products with tailored dosages, e.g. at facilities that hold a manufacturing license, such as within hospitals or external special manufacturing units. However, it is worth noting that preparation of these drug products can be a time-consuming and labour-intensive task.

In this instance, 3D printing has been suggested as an alternative automatic technology which is capable of formulating drug products containing an exact dosage in a flexible manner. For example, subdivided tablets of spironolactone and hydrochlorothiazide were fabricated using SSE technology as a substitute for the subdivided tablets obtained by pharmacists' splitting (Figure 13) (18). The comparison between 3D printed and splitted tablets in terms of mass variation, drug content and content uniformity yielded improved parameters for the 3D printed tablets, which were found to meet the requirements of the European Pharmacopoeia. Moreover, the 3D printed tablets had better appearance, improving the patient compliance and being especially convenient for young patients.

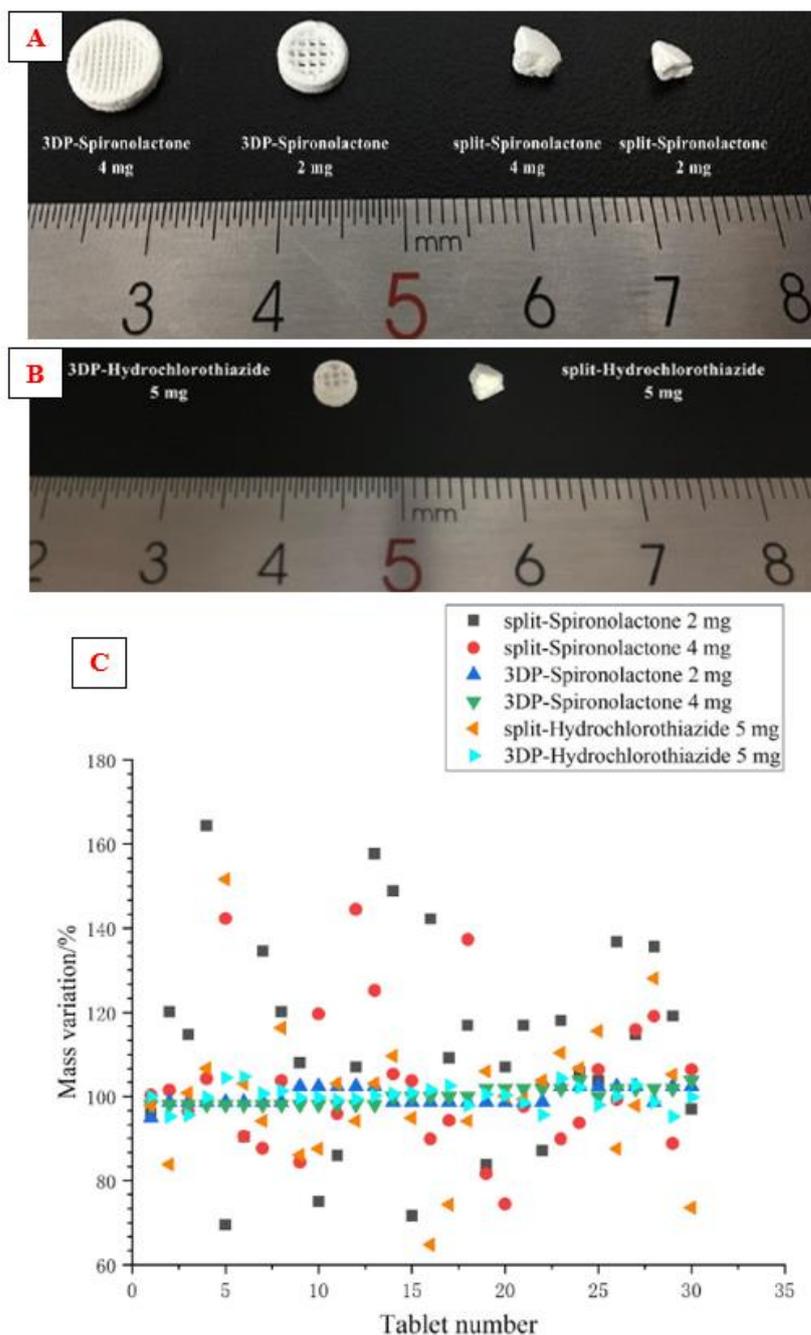


Figure 13. Photographs of 3D printed spironolactone tablets (2 and 4 mg) (A) and hydrochlorothiazide tablets (5 mg) (B) compared to tablets with the same dose obtained by splitting commercial tablets. (C) Mass variation for subdivided tablets obtained by 3D printing and by splitting commercial tablets (18).

The first clinical study that used 3D printing for the preparation of personalised therapies in a hospital pharmacy setting was published in 2019 (22). Chewable isoleucine printlets with different flavours (22) and colours were prepared by SSE to treat children with a severe metabolic disease; maple syrup urine disease (MSUD) (Figure 14A). The printed

formulations were compared with the conventional capsules prepared by manual compounding in terms of isoleucine blood levels and medicine acceptability after six months of treatment. Isoleucine printlets showed mean drug concentration levels closer to the target value and with less variability, which was attributed to the consistency in formulation compared with manually filled capsules, which were often opened onto food-stuff for administration into children (Figure 14B and C). Moreover, all of the different flavours and colours of the printlets were in general well accepted by patients, although each patient had different preferences. Research is also ongoing at Alder Hey Hospital in Liverpool for the production of personalised 3D printed hydrocortisone preparations for paediatrics (138).

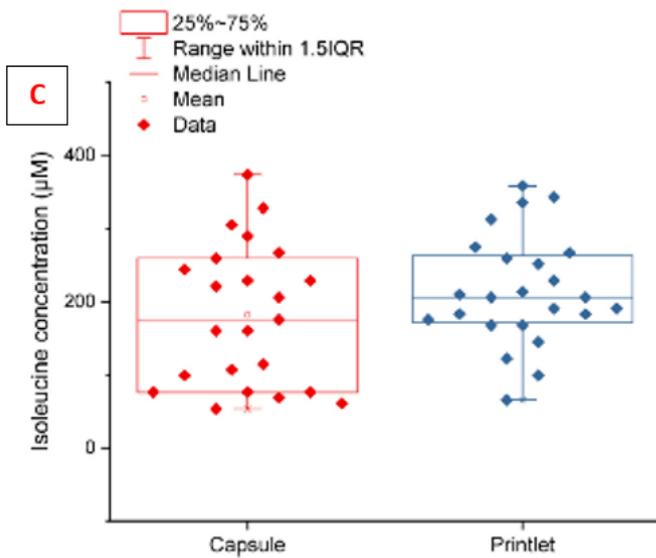
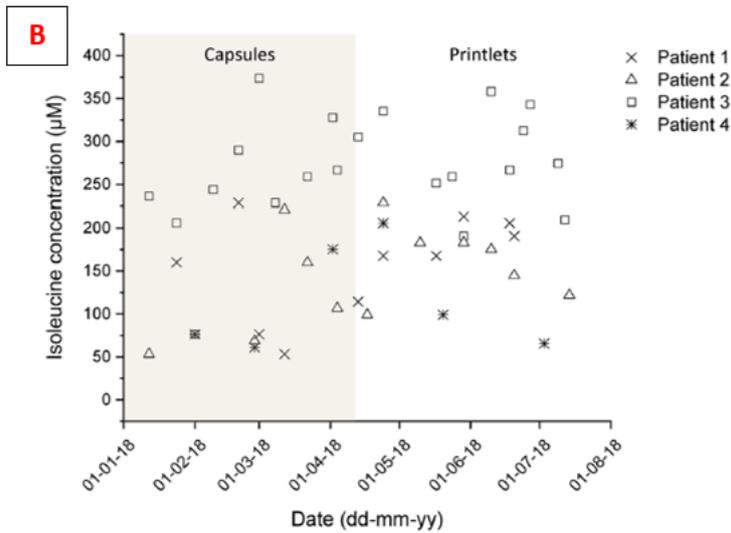


Figure 14. (A) Chewable printlets in different flavours, colours and with different doses of isoleucine. (B) Isoleucine blood levels of the patients during the study and (C), isoleucine blood levels and mean values for printlets and capsules during the study (22).

Personalised medicine has been especially linked to genetic testing, whereby drugs are selected based on the genetic makeup of an individual patient. It can be envisioned that, in the future, 3DP is used as a small-scale personalised drug manufacturing tool which is linked to enable the patient's medicine and dosage to be produced directly at the point of care, which would be a current challenge for centralised manufacturing processes.

In addition to the production of oral dosage forms, 3D printing has also been used to manufacture drug delivery devices with customised designs and drug release rates. For example, in one study it was possible to fabricate a customisable oral delivery device in the form of a mouthguard, which was loaded with vanillic acid for human release studies (Figure 15) (128). A sustained release of vanillic acid was achieved through the duration of use. However, the release rate was faster compared with *in vitro* release, perhaps due to disturbances generated by tongue movements and salivation. Volunteers only reported some minor discomfort due to imperfect fitting and speech impediment, problems that could be partially overcome with the use of a 3D printer with better resolution to obtain mouthguards with well-defined walls. In another study, personalised orthodontic retainers loaded with clonidine hydrochloride (CH) were prepared for the local sustained-release of the drug (129). The PK profiles of CH after dosing were simulated using pharmacokinetic modelling (Gastroplus®). The simulated release profiles showed a burst release followed by a sustained-release for more than 3 days, but when the retainers were washed to remove the CH present on the surface of the device, the burst release and also the possible adverse effects derived from the burst release were avoided.



Figure 15. Photograph of the 3D printed mouthguard comprising a clobetasol propionate (CBS) free zone (red) and a CBS-containing zone (off-white). On the left, another

mouthguard comprising a drug laden area (off-white) and a drug-free area (white) where CBS was substituted by vanillic acid for human testing (128).

4.2. Improved Medicine Acceptability

3D printing has demonstrated the potential to produce medicines with a desirable geometry or formulation characteristics, enabling an improvement in medicine acceptability. To date, a number of different patient-friendly formulations have been developed, including rapidly dispersing tablets (139, 140), chewable formulations and rapidly dissolving oro-dispersible films (67, 141). In all cases, these formulations could ease administration in patients with dysphagia, commonly demonstrated in paediatric and geriatric populations.

4.2.1. Paediatrics

One of the benefits of implementing 3D printing in healthcare and early human studies is the possibility to produce dosage forms with personalised colours and flavours, which paediatric patients could especially benefit from. Among these patients, the main reason for refusal of medication is taste adversity (142). Thus, the development of dosage forms using taste-masking strategies and with attractive shapes and colours could improve patient compliance and treatment adherence. In this regard, a study used FDM to prepare candy-like chewable printlets with enhanced palatability that can be easily consumed by children (Figure 16) (77). Indomethacin was used as model drug and hypromellose acetate succinate (HPMCAS) and polyethylene glycol (PEG) were used as the thermoplastic carrier and plasticiser, respectively. The preparation of drug filaments using HME helped to improve the taste due to the drug-polymer interactions during the HME process. Printlets imitating Starmix® sweets were printed in the form of a heart, bottle ring, bear, ring, and lion. The taste masking ability of the Starmix® printlets was evaluated by giving the formulations to healthy volunteers. The printlets showed adequate taste masking and the volunteers did not report any bitterness or aftertaste, which is of the utmost importance in paediatric medicine. Other works have proposed interesting approaches taking advantage of the versatility of 3D printing, such as the manufacture of chocolate-based dosage forms with customised designs (143) and chewable gelatin-based Lego™-like bricks (144).

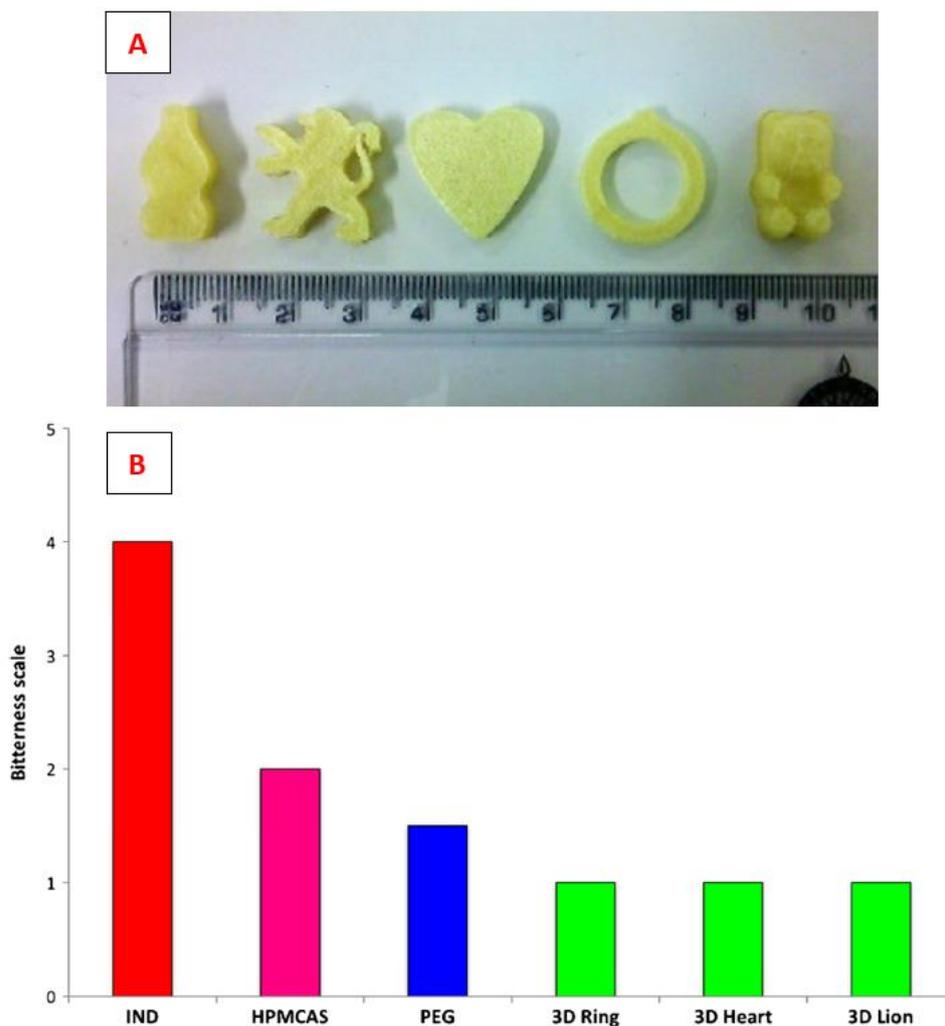


Figure 16. (A) Photograph of 3D printed tablets in different shapes loaded with indomethacin. (B) Taste masking evaluation of indomethacin (IND), hypromellose acetate succinate (HPMCAS), polyethylene glycol (PEG) and Starmix[®] designs (77).

In another study, the preference of children aged 4-11 years for different printlets was assessed based on visual inspection of the printlets (130). Placebo printlets were prepared using four different 3D printing technologies: DLP, SLS, SSE and FDM (Figure 17A). The results of the survey showed that 61.7% of children consider DLP printlets to be the most visually appealing, followed by SLS printlets, and with both FDM and SSE printlets scoring the lowest (Figure 17B). However, when the children were informed that the SSE printlet is chewable, most of them changed their original choice highlighting children's preference for chewable dosage forms.

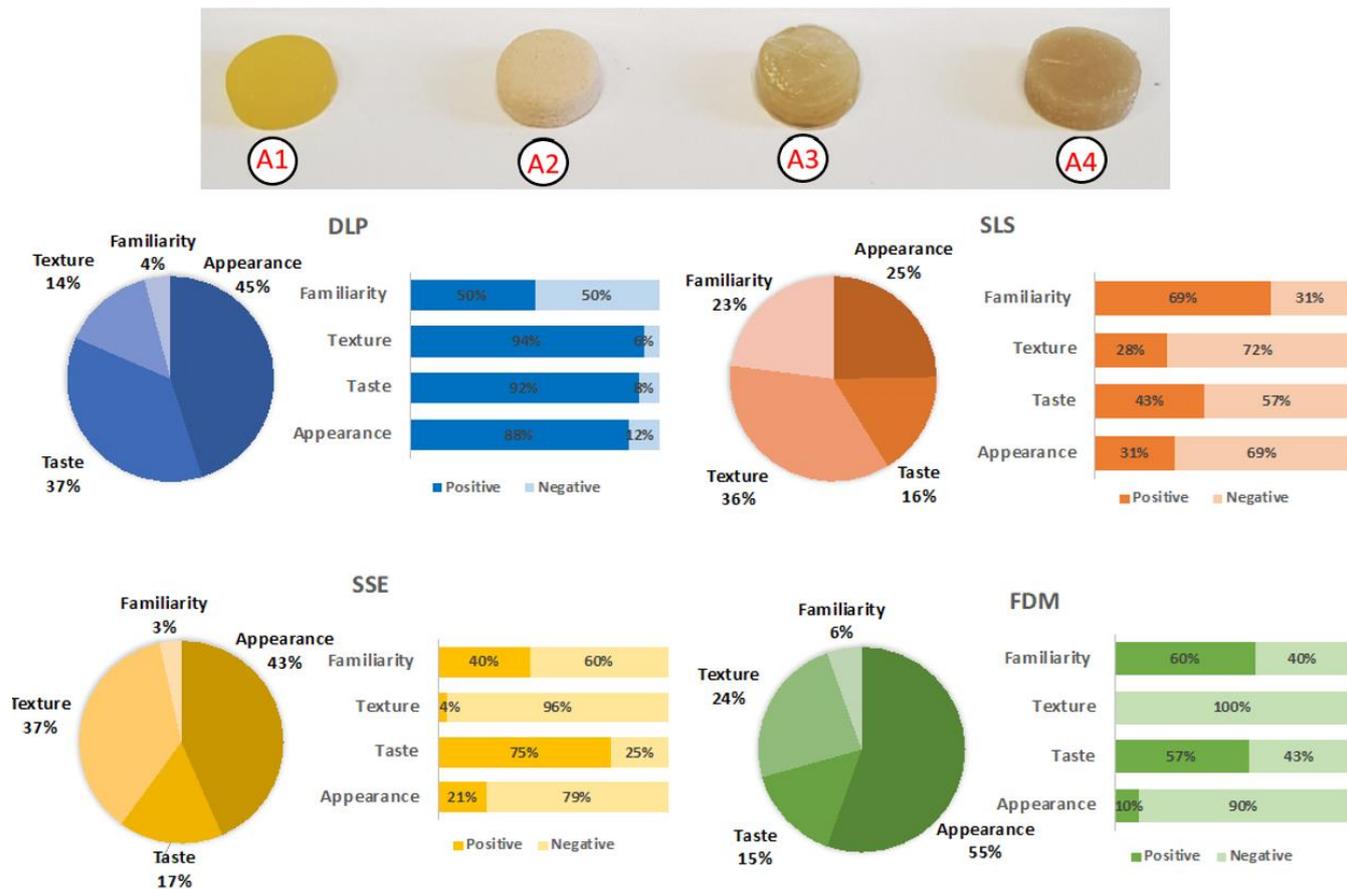


Figure 17. Above, placebo printlets fabricated with (A1) digital light processing (DLP), (A2) selective laser sintering (SLS), (A3) semi-solid extrusion (SSE) and (A4) fused deposition modelling (FDM). Below, summary of visual description data for the printlets manufactured by the different 3DP technologies based on their familiarity, appearance, perceived taste and texture (DLP, n = 244; SLS, n = 170; SSE, n = 125; FDM, n = 92) (130).

4.2.2. Adult and Geriatric Populations

To date, several studies have evaluated the potential for 3D printing to create patient-friendly formulations that would be otherwise impossible to produce with conventional mass manufacturing processes. Goyanes. et al. (125) published the first study which evaluated acceptability of 3D printed medicines. A wide variety of printlets were produced using FDM printing, with differing geometries and colours, which were evaluated for ease of swallowing and picking (Figure 18). It was noted that printlets with a similar physical appearance to conventional formulations (e.g., caplets and discs) were favoured. Interestingly, and somewhat unexpectedly, and that the formulation the formulation that scored the highest in ease of swallowing and picking were the torus-shaped printlets, which highlights the need to consider alternative shapes and sizes despite conventional practice.



Figure 18. (A) Capsule-shaped printlets in different colours and printlets with different geometries (disc, torus, sphere, titled diamond, capsule, pentagon, heart, diamond, triangle and cube) presented in four different sizes (125).

In another interesting study, SLS 3D printing was employed to prepare orally disintegrating printlets (ODPs) with Braille and Moon patterns to enable visually impaired patients to identify medications (Figure 19A and B) (60). The printlets were also produced in different shapes to offer additional information, such as the dosing regimen, and their readability was verified by a blind person. Using FDM, it was also possible to fabricate intraoral films with Braille dots of 0.2 mm height to comply with the Marburg Medium spacing convention for pharmaceutical Braille on packaging (Figure 19C). The films were subjected to a haptic evaluation by visually impaired volunteers, which reported an excellent readability of the Braille texts. Moreover, the intensive handling derived from the haptic evaluation did not affect the height of the dot, a crucial factor to guarantee the readability and safety of the films (145).

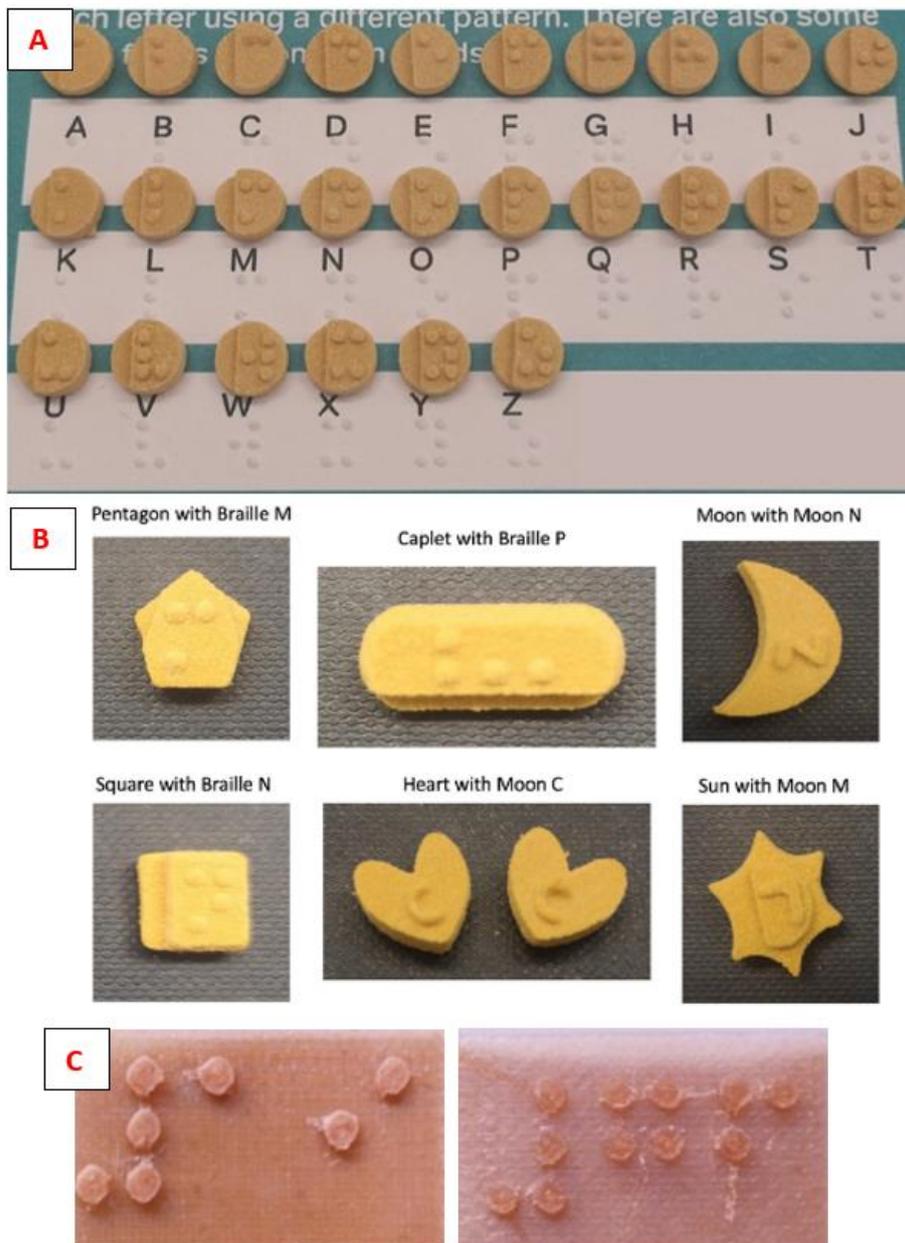


Figure 19. (A) Photograph of printlets containing the Braille alphabet and below and (B), printlets with Braille and Moon patterns printed in different shapes (60). (C) Images of the Braille dots onto the surface of films with different dosage strengths (145).

Although not tested in humans, orodispersible warfarin films were prepared using SSE (23) as an alternative to oral powders in unit dose sachets prepared by manual compounding used to treat the patients. Moreover, a QR code was printed onto them by inkjet printing to avoid medication errors. The administration of the films through a nasogastric tube was mimicked to ensure that the formulations could be administered to the hospital patients. The films displayed improved drug content compared to the conventional formulation with the

added advantage of easier administration, as they are intended to be administered directly into the patient's mouth without the need of water.

Polypharmacy, which involves the use of more than one medicine at a time is an increasing reality in geriatric populations that can cause challenges in medication adherence (146). For example, patients who have multiple co-morbidities (for examples those with heart disease, diabetes, or HIV) are often affected by a high tablet burden which requires patients to have a good understanding of and discipline with their treatment regime to ensure treatment efficacy and safety(147). To overcome a high tablet burden and reduce complexity in the treatment pathway, pharmaceutical companies have developed polypills, which combine multiple drugs and/or dosages into a single formulation. It is worth noting that the conventional production of polypills does not currently support personalisation, and instead uses mass production to produce fixed-dose combinations. Whilst this can reduce the pill burden for patients who are on maintenance (and unchanging dosages) it does not support the ability to individualise dosages based on the changing needs of the patient.

As an alternative solution, a number of papers have demonstrated the potential for 3D printing to produce 3D printed polypills (termed polyprintlets) using a range of printing technologies due to its ability to flexibly adapt dosages and drug combinations on demand (4, 11, 148). A previous study prepared highly modular 3D printed polyprintlet capsules using FDM printing combined with hot-fill technology (126). The multi-drug systems contained four drugs used in the management of cardiovascular diseases (lisinopril, amlodipine, indapamide and rosuvastatin) separated into four different compartments with two different spatial distributions; concentric and parallel. The parallel format was intended to obtain an immediate release profile, whereas the concentric format was designed to achieve a more delayed release of the drug. Drug release control was achieved by manipulating shell thickness and pore sizes in the concentric and parallel formats, respectively. In silico simulation of pharmacokinetics was performed using Gastroplus® to provide an approximate in vitro plasma profile that could help to design a polypill suited to individual patient needs.

4.3. Mass Manufacture

3D printing has also been explored as an alternative tool for mass production. Indeed, in 2016, the world's first 3D printed oral drug product received regulatory approval from the FDA (Spritam[®], Aprelia Pharmaceuticals) and was commercialised for patient use (42). The Spritam[®] manufacturing system involves a scaled-up binder jet printing system enabling tablets containing the anti-epileptic drug, levetiracetam, to be mass produced in a fixed dose. The ability of binder jet 3D printing to produce highly porous and rapidly disintegrating oral formulations was exploited to produce high drug-loaded (1000 mg) rapidly disintegrating tablets. This product was approved following a study in 2016 which tested the first 3D printed medications in humans (127). The study aimed to compare drug plasma concentrations following the administration of the 3D printed tablet and the reference formulation (an immediate-release tablet) in healthy volunteers. In addition, the effect of food consumption on the pharmacokinetic profile of levetiracetam 3D printed tablet was also evaluated. The results showed that the rate and extent of drug absorption obtained with the 3D printed tablet was equivalent to the conventional immediate-release tablet. A delay and a reduced absorption profile were only observed in volunteers under fed conditions, and most participants agreed that the 3D printed tablet was acceptable and easy to take and swallow (Figure 20).

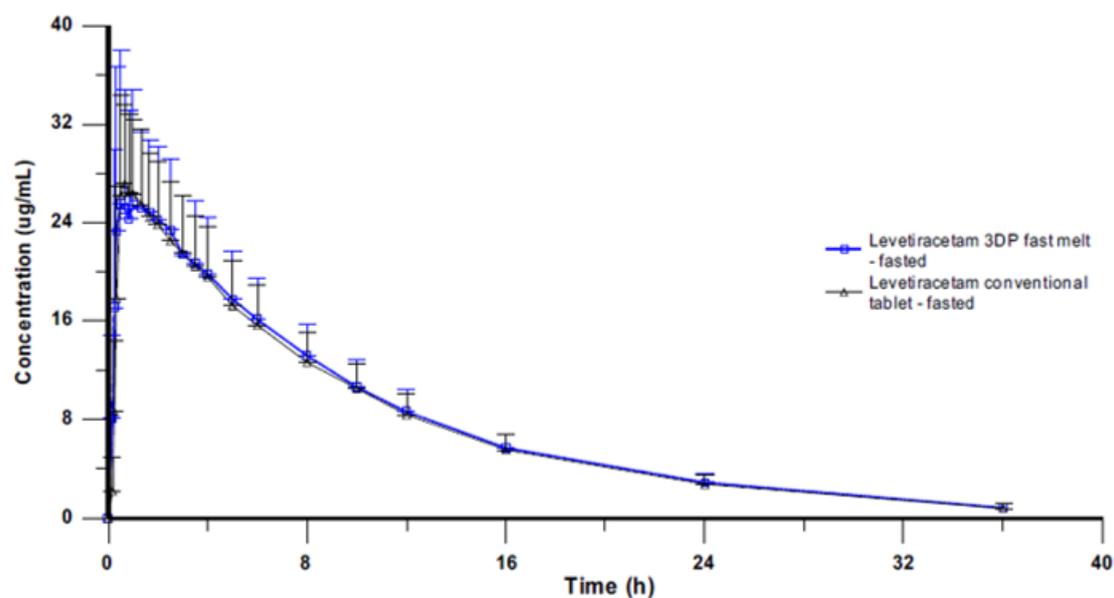


Figure 20. *In vivo* levetiracetam plasma concentration profiles after oral administration in participants of a 1000 mg dose of the reference formulation and a 1000 mg dose of the 3D printed tablet under fasted conditions (127).

4.4. On-demand Printing in Hard-to-Reach Areas

Due to the potential for portable and decentralised manufacture, 3D printing could have numerous benefits for hard-to-reach locations to improve medicines access, such as within low- and middle-income countries (149), disaster zones or even in space. In 2017, the very first medical supplies were 3D printed in space, whereby custom-fitted hand splint models were both designed and printed in orbit (150). In 2019, NASA funded the evaluation of 3D printed prosthetics for treating space injuries such as mallet finger (151). In-space 3D printed manufacturing could also be applied to oral medicines and medical devices, enabling astronauts to better design and produce medicines on demand based on the unexpected clinical needs of crew members within deep space-crewed missions.

4.5. Veterinary Applications

As demonstrated in Section 3, due to the potential for 3D printing to produce animal-appropriate medicines in a wide range of dosages, there is a natural extension of this technology into the veterinary medicine sector. Domestic animals, such as dogs, cats, guinea pigs and rabbits, typically require dosing by age or body weight, depending on the drug and indication. Conventionally, this requires the owners to split commercially available dosage forms or administer an appropriate dosage via a syringe directly onto the animal's food or into their mouth. Such practices come with a high risk of human error, as well as a risk of the animal rejecting the medicine if the formulation is not palatable. Dogs, for example, have an acute sense of smell and hence if the formulation is not desirable or palatable, there is a risk that the drug may not be administered or rejected. Owners typically attempt to overcome this issue via masking the medicine in the animal's food, however there is a risk of drug-food interactions, or the animal eating only a small part of the food and not gaining the appropriate dosage (152, 153).

It could be envisioned that, in the future, personalised animal formulations with a suitable dose and palatability could be 3D printed in the veterinary clinic or at home, to ensure pet safety in medicines administration (154).

5. Challenges and Future Directions of 3D Printing in Pharmaceuticals

The integration of 3D printing, alongside other innovative technologies, into pharmaceuticals has been forecast to give rise to a new digital pharmacy era (Figure 21). With the integration of non-invasive diagnostics or drug monitoring strategies (e.g., via artificial intelligence and point-of-care testing) and electronic prescriptions, 3D printing could provide a digital and decentralised platform for the production of tailored medicines in response to these monitored outputs (155). Indeed, numerous researchers around the world hold this vision for 3D printing, with new research papers being published every day to further evidence the potential of 3D printing technologies in formulation development and patient care. However, as discussed in the previous sections, only a limited number of studies have been performed in pre-clinical and clinical settings. This hesitation around testing formulations *in vivo* is likely due to a combination of reasons, ranging from regulatory, quality and technical concerns through to a need for a shift in mindset and culture for the acceptance of digital technologies in Pharma.

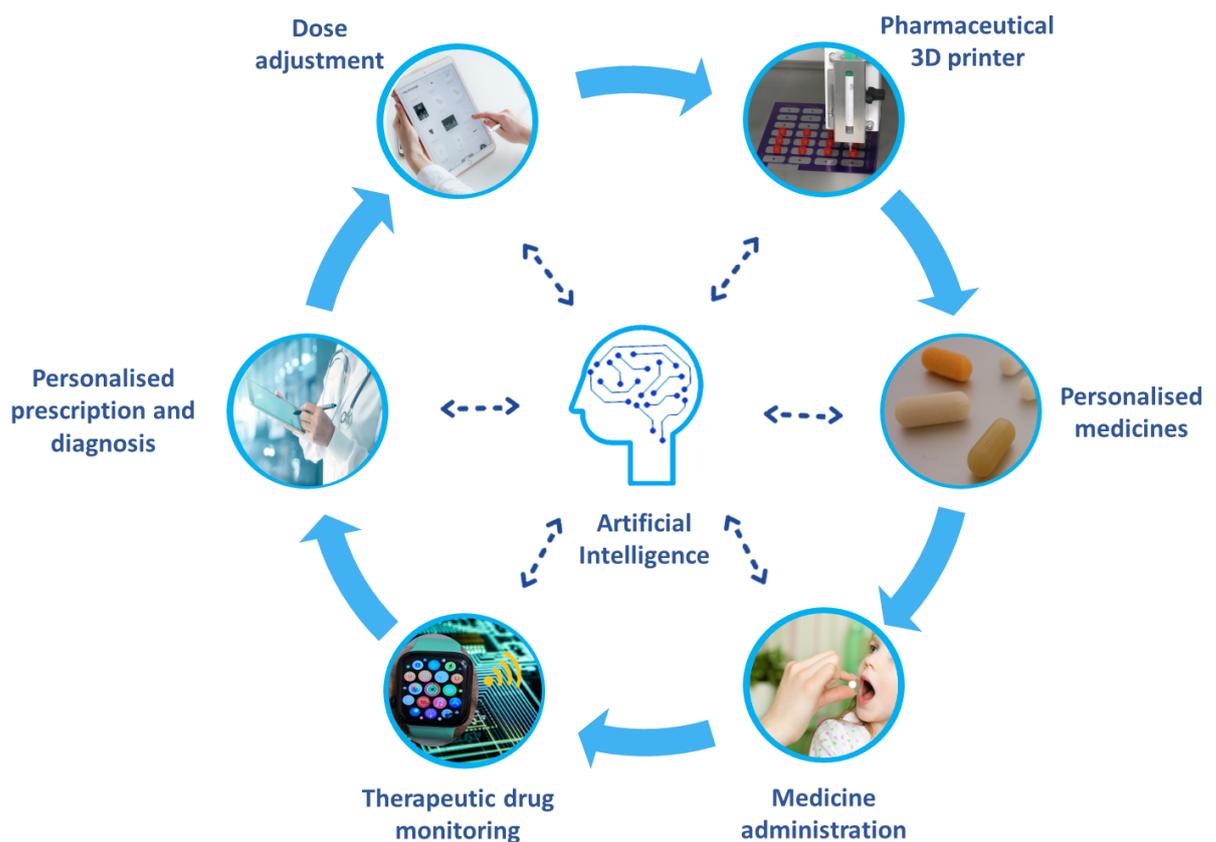


Figure 21. The virtuous cycle of personalised medicine.

It is widely regarded that the most pressing obstacle for the integration of 3D printing in pharmaceuticals is the lack of clear regulatory guidance and advice from regulatory agencies. In 2017, the Food and Drug Administration (FDA) published a technical guidance on 3D printed medical devices and prosthetics (156), however, although the FDA has already approved some additively manufactured medical devices, none of these have a drug delivery function (157). To date, the only 3D printed drug product approved for commercialisation is Spritam[®], by Aprelia Pharmaceuticals, which is an alternative scaled-up manufacturing process and hence falls under the standard regulations for dosage form production. For the on-demand production of personalised medicines using 3D printing, standard regulations could not apply due to the need for flexible and adaptative manufacture based on real-time market demands.

The long-standing debate of whether 3D printing should be considered a manufacturing process or extemporaneous production (compounding) is still ongoing, with strong arguments in favour of the latter. Extemporaneous compounding involves the preparation of an unlicensed medicine for an individual patient in response to an identified need. Conventionally, extemporaneous formulations are produced in hospital pharmacies, community pharmacies, and specials manufacturing units, with the pharmacist producing a personalised drug product for the patient. Indeed, on the one hand, 3D printing technologies can be viewed as ‘automatic compounders’, whereby a drug-loaded feedstock is inserted into the printer and the dosage controlled via the amount of material deposited onto the build plate. This vision is similar in concept to an automatic liquid dispenser, whereby the correct dose is automatically calculated and dispensed by the machine.

Two potential implementation models could be applied here. One strategy could involve a ‘Nespresso’ style system, whereby the 3D printer is analogous to the coffee machine and the drug-loaded feedstock is analogous to the interchangeable coffee pods. This model would involve the drug-loaded feedstock cartridges being premade by a facility holding a manufacturing license, involving the feedstock being manufactured, quality and safety approved and delivered to local pharmacies for on-demand dispensing. Alternatively, another strategy could involve the feedstock being prepared in the hospital or pharmacy via extemporaneous preparation (pharmaceutical compounding); whereby the pharmacist could either mix the required drug and excipient powders or crush

commercialised preparations and mix with additional excipients. The potential to use marketed formulations would avoid the risk of patent infringement as it would follow the general process of extemporaneous preparation.

However, depending on the 3D printing technology used, external factors such as the application of heat or light may be required and hence it would be important to ensure the quality of the formulation post-printing. It is clear that for the application of 3D printing within personalised medicines and drug development, it is vital that regulatory guidance and support is developed to best guide and support stakeholders looking to innovate the sector and to aid the integration of this technology into the pharma space.

Another key consideration for the application of 3D printing into clinical trials involves ensuring the quality of the dosage forms produced to ensure participant safety. Conventional quality control (QC) tests used within large-scale manufacturing processes are inherently destructive, laborious and expensive, which would be unsuitable for on-demand production at the trial site using 3D printing. Several studies have described the implementation of reliable and non-destructive analytical techniques for real time drug quantification (158). In this sense, near infrared (NIR) and Raman spectroscopy have shown to be capable of performing QC measures of 3D printed medicines in a non-destructive manner in studies performed by University College London in collaboration with Pfizer (159, 160). Other studies have suggested using track-and-trace measures by including QR codes and data matrices on formulations to ensure drug product quality and safety (161, 162). Such innovative strategies could provide a real-time assurance of drug product quality, facilitating the use of the technology in the clinic.

Aside from regulatory and QC issues, commercially available 3D printers were previously not standardised or fit-for-purpose (pertaining to Good Manufacturing Practice; GMP) for the production of pharmaceutical products. As discussed previously, there are a wide range of different 3D printing technologies available, many of which have been explored for the production of pharmaceuticals in academic research papers. However, certain technologies are more amenable to pharmaceutical production than others. Vat photopolymerization methods, for example, have widely recognised technical challenges surrounding the use of non-GRAS certified materials with potential cytotoxic effects *in vivo*. Indeed, the ideal 3D printer for pharmaceuticals will be compact, low cost,

easy-to-use, produce medicines safely and with a high quality, and have an acceptable production speed. With the aim of attaining this goal, companies have been focussed on developing pharmaceutical 3D printers that meet GMP and QC requirements. For example, FabRx Ltd., a company specialised in the manufacture of 3D printed drug products, has recently developed the M3DIMAKER™ 3D printer which has multiple exchangeable extrusion-based nozzles that is intended for use in hospital pharmacies, special manufacturing units or clinical trial settings (163). This is the first 3D printer especially developed for the production of personalised medicines that can be fully validated to GMP regulations, achieving a significant milestone in the history of 3D printed pharmaceuticals.

From a Big Pharma business perspective, one concern around digitalised 3D printing technologies for decentralised production may be the need for protection of formulation and process details which are widely regarded as business-critical trade secrets. Due to the requirement for digital transfer of computer aided designs and printing conditions, issues surrounding data security and accessibility needs to be well controlled and maintained. Another technical challenge for pharmaceuticals during drug development and clinical trials is the potential for scale-up of 3D printing processes. Phase II and III clinical trials generally recruit a higher number of participants compared to first-in-human (FIH) trials and hence pose a higher demand on dosage form production. Strategies to enable the effective scale up for Phase II and III trials could involve use of multiple 3D printers running in tandem or using a 3D printer with multiple nozzles enabling a higher throughput.

A final, and somewhat harder to tackle, challenge hindering the adoption of 3D printing is the need for a mindset and culture shift within the pharmaceutical industry. Indeed, the industry has well established manufacturing procedures that were developed over 200 years ago to enable the safe and effective production of medicines. However, with the increasing demand for personalised oral therapies, it is likely that the adoption of alternative flexible manufacturing technologies may be needed in order to meet these changing market and patient needs. Whilst the evidence-base for the benefits of 3D printing in pharmaceuticals is extensive, it is clear that there is still more work to be done before all stakeholders will have full confidence in the technology. To date, the majority of published research in the area has had limited involvement from more than one key

stakeholder. To increase receptiveness in the community, it will be critical to move towards a more multidisciplinary approach to 3D printing research, inviting other major stakeholders (including clinicians, patients, and Big Pharma) to come together to discuss a way forward for this technology in the sector and to evaluate more streamlined routes into animal and human studies. By taking these initiatives, 3D printing will be translated from a theoretical prospect to a realistic and revolutionary manufacturing tool to benefit the pharmaceutical industry and patients alike.

6. Conclusions

This review article summarises the existent investigations on the applications of 3D printing technology in the field of preclinical and clinical research. Both preclinical studies and FIH trials require a platform that enables rapid, on demand manufacturing of dosage forms with flexible doses; requirements that conventional manufacturing techniques cannot meet. It is in this sense that 3D printing can revolutionise the way medicines are designed and produced, expediting the drug development process. This innovative technology is capable of producing dosage forms of virtually any shape and size and with the exact dose necessary to meet the requirements of the preclinical or clinical study. The affordable cost of 3D printers makes it possible to implement them in research laboratories and hospital settings, where small batches of printlets can be produced on demand with flavours, colours and shapes customised to the patients. The continued advances within the research community will enable the translation of 3D printing technologies towards a revolutionary manufacturing tool within preclinical and clinical drug development.

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