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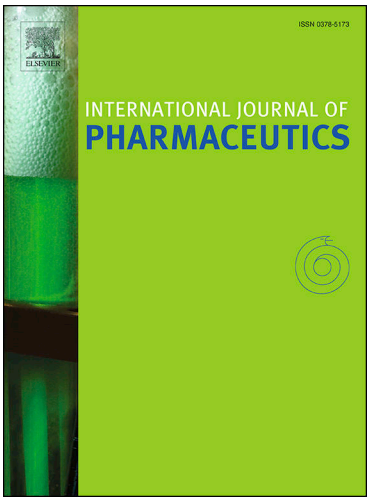

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3D Printing for Personalised Medicines: Implications for Policy and Practice

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Abstract

The current healthcare dynamic has shifted from one-size-fits-all to patient-centred care, with our increased understanding of pharmacokinetics and pharmacogenomics demanding a switch to more individualised therapies. As the pharmaceutical industry remains yet to succumb to the push of a technological paradigm shift, pharmacists lack the means to provide completely personalised medicine (PM) to their patients in a safe, affordable, and widely accessible manner. As additive manufacturing technology has already established its strength in producing pharmaceutical formulations, it is necessary to next consider methods by which this technology can create PM accessible from pharmacies. In this article, we reviewed the limitations of current pharmaceutical manufacturing methods for PMs, three-dimensional (3D) printing techniques that are most beneficial for PMs, implications of bringing this technology into pharmacy practice, and implications for policy surrounding 3D printing techniques in the manufacturing of PMs.

Keywords

3D printing; additive manufacturing; personalised medicine; pharmacy practice; policy; compounding

Abbreviations

3DP Three-dimensional printed; **APF** Australian Pharmaceutical Formulary; **API** Active pharmaceutical ingredient**; BCS** Biopharmaceutical classification system; **CAD** Computer-aided design**; DAC/NRF** Deutscher Arzneimittel-Code/ Neues Rezeptur Formularium**; DLP** Digital light processing**; FDA** Food and Drug Administration; **FDM** Fused deposition modelling; **HME** Hot melt extrusion; **INR** International normalised ratio; **NIR** Near-infrared; **PBPK** Physiologically based pharmacokinetic; **PM** Personalised medicine; **SLA** Stereolithography; **SLS** Selective laser sintering; **SSE** Semi-solid extrusion; **TGA** Therapeutic Goods Administration; **USP** United States Pharmacopeia

Contents

Introduction

It is well established that variation exists from one patient to another - enhanced knowledge in pharmacogenomics, individual pharmacokinetics, and a patient's unique anatomy and physiology has formed the understanding that not one patient is or responds the same as another (Savard, 2013). Personalised medicine (PM), as opposed to currently available conventional medicines, is underpinned by the notion of patient-centred care, as the medication is produced with drug(s), dose(s), release kinetics, and formulation completely customised to suit the individual patient's needs, as determined by the patient's personal preferences and the prescribers understanding of the patient's unique disease profile. Patient populations that most require personalisation include geriatrics , paediatrics (Bartelink et al., 2006), and overweight/obese patients (Cheymol, 2000), as often non-conventional doses are needed to account for their altered pharmacokinetic profiles, and modified dosage forms are required in cases of anatomical dysfunction, e.g. dysphagia (Aziz et al., 2022). Adverse drug reactions occur, especially in these populations, when their altered kinetics and needs are unaccounted for, with untailored therapy representing 75-85% of total adverse drug reaction cases (Alhnan et al., 2016). Currently, non-conventional doses are obtained via traditional, pharmacist-performed compounding. Many have raised the issue of poor on-site regulation and quality control, leading to increased dosing errors and cases of contamination (Drazen et al., 2012; Watson et al., 2021).

As the pharmaceutical industry remains yet to succumb to the push of a technological paradigm shift, health care professionals are left without the means to provide utterly personalised health care to their patients in a safe, affordable, and widely accessible manner. However, the three-dimensional (3D) printing of PMs offers pharmacy practice a novel solution to our current gap in patient-centred care; however, it does not come without implications. While previous reviews have explored the technical applications of 3D printing for pharmaceuticals (Afsana et al., 2018; Anwar-Fadzil et al., 2022; Chen et al., 2020; Dumpa et al., 2021; Lim et al., 2018), none have investigated the impact on policy and practice. Thus, this review aims to discuss the feasibility of introducing 3D printing methods into pharmacy practice for PMs to become readily available to patients in the community. The

study will specifically address technical methods in production, transitioning from experimentation to the consumer, and the resulting implications for practice and policy.

An initial screening of PubMed, Embase, Google Scholar, and Scopus was performed. Specific keywords included in the search were: three-dimensional printing (3d printing, 3-dimensional printing, additive manufacturing, digital manufacturing, layered manufacturing); PMs (individualised medicines, individualised therapy, personalised therapy, precision medicine); and Pharmacy Practice (clinical practice, pharmacy setting, pharmacy, chemist, compounding). The search included all types of studies and grey literature published from 2018 to 2022. Literature regarding bioprinting (e.g., 3D printing of tissues, prosthetics, and other medical implants) was excluded. Additionally, citation chaining was performed to ensure articles missed by the database searches were included.

Accessibility to PM within current pharmacy practice

The current dominating method of pharmaceutical production worldwide is batch manufacturing. Through this process, an active pharmaceutical ingredient (API) is synthesised and tested off-site. It is then shipped to a secondary location that blends the API and required excipients together to undergo various production line processes depending on the product type (Hock et al., 2021). The concept of mass-producing pharmaceuticals means that only a set of predefined commonly used doses are created per drug. These predefined doses are packaged accordingly and shipped to pharmacies and hospitals worldwide. The nature of this process is underpinned by and benefits from a lack of personalisation. It is through the production of a few discrete doses for a prescriber to choose from that large pharmaceutical companies can provide consumers with fast and cheap medicine. This quality is unarguably ideal and beneficial for patients and pharmacists. However, this does come at a cost to the overall therapeutic outcome of the patient. O'Connor and Lee (O’Connor and Lee, 2017) identified inter-patient variation of up 10-30 fold exists between patients taking the same dose. As such, prescribers will often instruct patients to modify the dose accordingly, either through tablet splitting, a method that leads to waste, uneven weight distribution and hence inaccurate dosing, or through taking multi-tablet regimens, which becomes especially dangerous and confusing for patients where multiple doses and drugs are involved (Alhnan et al., 2016). The vulnerability of mass-produced pharmaceuticals to international supply chain

issues has also been raised, as it creates dynamic availability of specific medicines to the patient (O'Connor and Lee, 2017). This concept has been exemplified in our current environment, as COVID-19 lockdown measures significantly impacted global medical supply chains, with Australia experiencing a 300% rise in drug shortages between 2019-2020 (Cameron and Bushell, 2021). Drug shortages are incredibly limiting when attempting to offer personalisation to a patient, as patients are forced to take second-line, less effective, or unsuitable medicines (Phuong et al., 2019).

As such, compounding, the most traditional method of pharmaceutical formulation, is utilised in pharmacies to provide patients with PM that is otherwise unachievable via mass production. Compounding allows for individualisation of dose and dosage form, shape, colour, and taste. It also provides a solution to patients that have reason to avoid certain excipients (e.g. allergies) (Sellers and Utian, 2012). However, Drazen et al. (Drazen et al., 2012) raise concern about the limitations compounding presents to patient safety, calling for regulations to be implemented that address the adverse drug reactions and, unfortunately, deaths occurring due to the calculated drug concentration errors and cases of contamination within compounded medicines. The Food and Drug Administration (FDA) simultaneously raised its concerns about current quality compounding guidelines following the death of 60 patients due to contaminated drugs from a pharmacy store (US Food and Drug Administration (FDA)). However, this still fails to be addressed, with Watson et al. (Watson et al., 2021) highlighting the lack of change within regulations that ensure quality control of compounded medicines.

Technical methods of 3D printing PM

Creating a completely PM requires a dynamic manufacturing process whereby administration route, product size and shape, and drug release kinetics can be quickly and simply modified to suit the individual patient's needs and preferences. 3D printing, the process by which an object is built up in a layer-by-layer method, according to instructions from a computer-aided design (CAD) software, offers a solution to the limitations current pharmaceutical manufacturing methods impose on the development of PM. The flexibility 3D printing provides to the manufacturer, being the ability to present an automated printed build of any possible designed structure in a wide variety of material options, has already established roots

in other manufacturing industries such as agriculture, aviation, and automotive (Shahrubudin et al., 2019). However, we have seen a recent surge in interest within the realm of medicine, arising from the ability for printed products to be manufactured to a high degree of accuracy using biocompatible materials (Shahrubudin et al., 2019). As such, 3D printed (3DP) medical devices (De Maio et al., 2022; Hagan et al., 2022; Zong et al., 2022), implants (He et al., 2022; Thygesen et al., 2022; Yang et al., 2022), anatomical models (Fritz et al., 2020; Goh et al., 2021; Wake et al., 2022) and tissues for transplant (Belgheisi et al., 2022; Sharma et al., 2021; Ye et al., 2022) have already debuted their appearance on the market to be utilised in the personalisation of health care services. However, it is the ability to determine specified inner structures with intricate geometries, compartments, and infill patterns and densities via layered construction that is most attractive in overcoming obstacles of traditional pharmaceutical large-scale manufacturing and small-scale compounding.

Hot Melt Extrusion (HME)

Hot-melt extrusion describes the mixing of polymeric material in a chamber via a rotating screw under elevated temperatures. Active pharmaceutical ingredients (API) and other excipients may be added in combination with a polymer to the chamber. By heating the chamber above the polymer's melting point or glass transition temperature, molecular level mixing occurs, forming a final amorphous product. This extrudate can act as a drug-loaded filament for other techniques (Patil et al., 2016).

Fused Deposition Modelling (FDM)

A premade solid drug-loaded filament, produced mainly by HME printing, is fed through an extrusion nozzle and heated to the melting point. According to the CAD software specified XYZ coordinate, the molten filament is then deposited onto a building platform and solidified. This process is repeated in layers, building upwards until the final dosage form is produced (Dumpa et al., 2021).

Semi-Solid Extrusion (SSE)

SSE follows the same method as FDM; however, semi-solid material, such as hydrogels or pastes, is extruded through a nozzle and deposited in a layered manner according to

CAD specified coordinates. As such, high temperatures are not required, and thus it is particularly beneficial for use with thermolabile drugs (Seoane-Viaño et al., 2021).

Vat Photopolymerisation

Within a vat, ultra-violet (UV) light is applied to a thin layer of liquid photosensitive material (e.g., resin or photopolymer) that sits upon a base. The chemical reaction occurring within bonds upon exposure to UV light allows material hardening to happen in a defined shape. The base then moves downwards, with each new layer irradiated until the final dosage form is complete. There are two types of vat photopolymerisation techniques: stereolithography (SLA) and digital light processing (DLP). Both methods use UV light as their radiation source yet vary in their application: SLA uses a single laser beam that travels in time to each desired coordinate, while DLP uses multiple digital mirrors to cure an entire layer in multiple points instantaneously (Xu et al., 2021).

Ink-Jet Printing

Inkjet printing is based on a similar concept to regular office inkjet printers. Rather ink cartridges for inkjet printing contain API in solution, and this is printed onto a variety of edible material sheets (Evans et al., 2021).

Selective Laser Sintering (SLS)

SLS utilises the heat of a laser to sinter a layer of powdered particles, consisting of API and other excipients, together to form the shape of the CAD designed image. New layers of powder are applied on top, and the process is repeated until the final dosage form is complete. The print is extracted, and excess powder is brushed off to reveal the final design (Charoo et al., 2020).

Table 1.

Examples describing the benefits of 3DP pharmaceuticals for PM

No.	3D Printing Technologies	API	Benefit to Personalisation	Ref.
1	HME/FDM	Warfarin	• 3D-printed tablets with warfarin dose calculated according to specific desired patient INR outcome • Accurately titrated warfarin dose-response to suit individual patient needs as confirmed in-vivo on Sprague-Dawley rats	(Arafat et al., 2018)
2	HME/FDM	Ketoprofen	• Amorphous solid dispersion significantly improved dissolution and bioavailability of BSC II class drug • Dissolution profile manipulated by adjusting fill density of the inner core and outer shell: fastest drug release occurred with lowest fill density • Quality per US Pharmacopeia	(Hu et al., 2022)
3	HME/FDM	Humanised monoclonal antibody (mAb)	• First to achieve FDM printed mAb loaded implantable device • Homogenous amorphous solid dispersion of mAb in polymer matrix • Stable formulation with confirmed sustained-release profile over 12 weeks in-vitro designed for improved patient adherence	(Carlier et al., 2021)

4	FDM	Pramipexole, levodopa, praziquantel	• Computerised calculations developed a geometric model (cylinder based) that maintained a zero-order drug release profile over each of the 3 APIs in varying dosages • Implementing this formula means that dose titrating for personalisation can easily be achieved while maintaining release kinetics	(Windolf et al., 2022)
5	SSE	Paracetamol, ibuprofen	• Unique dosage form: chewable Lego™-like drug-loaded bricks made with soft edible gelatine-based matrix • Designed to be acceptable for the paediatric population	(Rycerz et al., 2019)
6	SSE	Phenytoin	• Unique dosage form: fast disintegrating tablets printed within a syringe to form a solution for oral administration upon drawing up liquid into the syringe • Designed for dysphagic patients to ease oral drug administration with improved dosing accuracy	(Panraksa et al., 2022)
7	SSE	Triamcinolone acetonide	• Hydrophobic drug was printed within a water-based mucoadhesive formulation • It offers a promising technique for personalising oral mucosa treatments, utilising drugs that otherwise would be unable to act via this administration route	(Schmidt et al., 2022)
8	SSE	Amikacin sulphate	• The ability to design complex microarchitectures for bone scaffolds with a locally acting sustained-release of antimicrobial	(Cui et al., 2022)

			drug offers excellent benefit for the personalisation of drug-loaded implants	
9	SSE	Levocetirizine hydrochloride	• Unique dosage form: drug-loaded oral dispersible films • Designed for simple oral administration, especially beneficial for paediatric populations and dysphagic patients	(Yan et al., 2020)
10	SSE	Captopril, nifedipine, glipizide	• Complex osmotic pump shaped multi-compartmental polypill able to deliver three active ingredients with two separate and well-defined release mechanisms • Captopril achieved zero-order release kinetics, nifedipine and glipizide followed first-order release kinetics • Showed ability to personalise drug combination and release profile within a polypill to reduce pill burden	(Khaled et al., 2015)
11	Vat Photopolymerisation	Paracetamol, caffeine, naproxen, chloramphenicol, prednisolone, aspirin	• Six-drug polypill separated into six separate drug-containing compartments with confirmed individualised release profiles. • High resolution of SLA technique meant that a six-drug containing complex designed polypill could be printed within an average pill size of roughly 1cm diameter.	(Robles-Martinez et al., 2019)
12	Vat Photopolymerisation	5-fluorouracil	• 5-fluorouracil loaded in an acrylated hyperbranched polyester showed enhanced drug release in a simulated colon environment and inhibition of premature drug release	(Chen et al., 2022)

			• Print time was quick; significantly slower in comparison to other 3D printing techniques and conventional methods s • Benefit to personalisation is fast, simple method of creating complex dosage forms	
13	Ink-jet Printing	Propranolol	• Unique dosage form: orodispersible drug delivery systems • Designed for simple oral administration, especially beneficial for paediatric populations and dysphagic patients	(Vakili et al., 2016)
14	Ink-jet Printing	Thiamine hydrochloride	• Rapid drug release achieved • Thiamine existed in suspension and as such displayed high solubility in PVP allowing for manipulation to form a rapid dissolution profile	(Cader et al., 2019)
15	SLS	Paracetamol	• Orally disintegrating tablets were successfully printed to have disintegration times within 4 secs in water • Designed for simple oral administration, especially beneficial for paediatric populations and dysphagic patients	(Fina et al., 2018b)
16	SLS	Paracetamol	• Cylindrical, gyroid lattice, and bi-layer structures with customisable release characteristics • Customised drug release properties in simple, cost-effective manner	(Fina et al., 2018a)

17	SLS	Amlodipine, lisinopril	• Two-drug containing polypills were printed as both films and cylindrical prints • Achieved partial amorphous solid dispersion for both drugs and maintained this over a variety of concentrations, showing this technique can uphold quality dosages across concentration ranges.	(Trenfield et al., 2020)

Proposed benefits of 3D printing techniques to personalisation

Examples of the benefits each technique above presents to personalisation of medicine has been outlined in **Table 1**. All techniques displayed the ability to create unique dosage form types such as orodispersible films (Fina et al., 2018b; Vakili et al., 2016; Yan et al., 2020), tablets in syringe (Panraksa et al., 2022), gummies/chews (Rycerz et al., 2019), and drug-loaded implantable devices [40, 45] that are otherwise too difficult to achieve with current pharmaceutical manufacturing techniques, especially in the case of on-site compounding. Another notable benefit to personalisation, was the achievement of zero order release kinetics (Khaled et al., 2015; Windolf et al., 2022), whereby the application of computational calculations in CAD software to design a shape that would release a constant amount of drug over time, has been praised for its potential in maximising therapeutic outcomes for patients while limiting risk of toxicity [41]. The achievement of an amorphous solid dispersion, namely via HME, is also of great benefit to personalisation. As the molecular level mixing of poorly-water soluble drugs with molten polymer occurs, the drug exists in a higher energy state than crystalline, increasing the drug's ability to form solution and thus reach the site of action. This has been demonstrated mostly through the increased bioavailability of 3DP Biopharmaceutical Classification System (BCS) II drugs compared to conventional dosage forms (Carlier et al., 2021; Hu et al., 2022; Trenfield et al., 2020), proving the benefit of this technique in optimising drugs via simple methods to comply with any administration route and dosage form, size, and shape that the patient desires.

There are also proposed benefits to see in the future once these techniques are established within pharmacy practice. Arafat et al. (Arafat et al., 2018) raised the idea of a dynamic warfarin dosing system, whereby patients could wear international normalised ratio (INR) sensors that generate real-time data regarding coagulation levels to feed to a 3D printing database, to then be translated into 3DP warfarin doses, demonstrating the potential for these systems to work alongside therapeutic drug monitoring methods. Li et al. (Li et al., 2021) also introduced the notion of integrating established physiologically based pharmacokinetic (PBPK) models with 3D printing technology to further provide a means of personalising patient dosing, as the dose can be estimated according to input patient defined parameters and then translated into the appropriate 3DP dosage form.

Personalised medicine would have more implications for compounds with a narrow therapeutic index, where individualising the dosage and release profile of the compound may significantly reduce the risk of toxicity for certain patients while enhancing the therapeutic effect. There is still value in the current 'one size fits all' or 'few sizes fit almost all' method of pharmaceutical production when it comes to wide therapeutic index drugs. However, it should also be mentioned that for certain patients, even wide therapeutic index drugs may require personalisation.

Apart from the considerations of pharmacokinetics and pharmacodynamics, the need for dose adjustment at different stages of treatment is also a factor to consider. For example, during dose reduction of medications, some patients may require a much slower tapering process than others to minimise the risk of serious withdrawal effects. However, this may not be feasible with the current production system. E.g., in Australia, the antidepressant Venlafaxine is available in three strengths: 37.5mg, 75mg and 150mg and is only available as a sustained-release formulation meaning the capsule cannot be modified and crushed for smaller doses. Prescribers are forced to reduce the dose by half each time for every patient when tapering which increases the risk of the patient getting withdrawal effects. With 3D printing, medication could be customised for different patient needs.

This paper does not call for pharmaceutical companies to change the entire pharmaceutical production. Instead, it raises the possibility of applying 3DP as part of the production process to fill the current gap in personalised medicine, especially for special patient populations. As the concept of PM is increasingly recognised in the healthcare system to be an imperative part of patient-centred care, the pharmaceutical industry should also recognise the demand for adopting new technology such as 3D printing in the drug development process to accommodate different patient needs.

Implications of 3DP PM for pharmacy practice

PMs need to be developed within the framework of manufacturing at a community or hospital pharmacy level. As the ability for 3D printing to create PMs is already well established,

moving forward involves assessing the feasibility of introducing this technology into the community.

Doctor acceptability

For 3D printed personalised medicine to be introduced in the community, doctors, i.e., prescribers, must first understand and see the therapeutic benefit of this novel technology in clinical practice. In general, many doctors hold a positive view towards the applications of 3D printing in the pharmaceutical sector. In a small cross-sectional study conducted by Goh et al. in 2022, 55 healthcare professionals in Singapore were surveyed of which 22 are doctors and 33 are pharmacists (Goh et al., 2022). More than 60% of healthcare professionals were willing to prescribe 3D printed tablets. Another study by Rautamo et al. in 2020, also interviewed health professionals including physicians on the potential for 3D printing as a manufacturing method in paediatric medicines (Rautamo et al., 2020). Many see the great benefit of 3D printing in providing patient-specific dosing, improving drug acceptance and producing new drugs on-demand in the hospital setting. Some doctors also suggested the use of 3D printing in personalising drug combinations and doses for HIV and organ transplant patients as a polypill to minimise polypharmacy and improve adherence. However, concerns regarding medication safety, administration, cost, stability, bioequivalence, and drug interactions were also expressed. These concerns must be addressed for physicians to change their current practice and include 3D printed drug products as part of their treatment options.

It is worth noting that many of the concerns were due to the lack of knowledge towards the capability and function of this new technology. For example, regarding the concerns about drug interactions between the different active ingredients in a polypill, 3D printing may have the advantage of preventing some harmful drug interactions (Goh et al., 2022). 3D printing has the flexibility in tablet design, where blank layers can be printed to physically separate 2 or more ingredients in a pill and adjust their release profile. This allows one drug to be released before another to minimise the risk of drug interactions.

Another major issue in the implementation of 3D printed PM in practice is the lack of clinical resources and guidelines for prescribers to follow. Currently, the health system evolves around evidence-based practice. It involves physicians making clinical decisions based on the best available evidence to ensure the quality use of medicine and patient safety. Therefore,

having 3D printed PM included in the guidelines would allow doctors to see it as a possible option for patient treatment. This is not a near future, as the first FDA-approved 3D printed drug Spritam® became available on the market in 2015 for the treatment of epilepsy, it has been included in widely used evidence-based prescribing guidelines such as UpToDate in the US. In the guidelines, its formulation (tablets for oral suspension/soluble disintegrating tablet), available strengths (250mg, 500mg, 750mg, 1000mg), flavour (spearmint) as well as administration directions (Tablet disintegrates in a mean time of 11 seconds (ranging from 2 to 27 seconds) in the mouth when taken with a sip of liquid) are outlined giving physicians an option to prescribe it for patients with swallowing difficulties (UpToDate, 2023).

Pharmacist acceptance

The current role of a pharmacist involves the custody, preparation, dispensing, and provision of medicines ((PSA), 2019). As such, pharmacists lie at the forefront of introducing 3DP PMs to the community. However, it is crucial to recognise that graduate pharmacists currently are not taught and thus, in the absence of additional study, lack the skills to navigate CAD software and 3D printing technology. A questionnaire performed in Saudi Arabia aimed to investigate the current knowledge of pharmacists regarding 3D printing technology. Only 53.2% of participating pharmacists communicated they were even aware of the general concept of 3D printing, with even less, 22.4%, aware of its use in the pharmaceutical industry. Although this raises concern for pharmacist acceptance of 3DP PM, 75% of pharmacists agreed there is a requirement to introduce PMs to address non-conventional patient needs, with 60% of pharmacists responding that they would be willing to learn how to 3D print PMs to do so (Algahtani, 2021).

A survey performed in the Netherlands, a country with a strong foundation in traditional compounding, further engaged with pharmacists to understand their opinions on the matter. Pharmacists within the study identified PMs, especially via 3D printing techniques, to be too specialised for all community pharmacies to partake in, and thus would be better suited for university hospitals and existing specialised compounding pharmacies. Interestingly they also raised the fact that pharmacy is a business. As such if 3D printing and its associated training and equipment were a financially attractive option that suited their business model, then, they would be very willing to engage (Beer et al., 2021). While further international studies would

be required, these initial surveys highlight the potential acceptability of pharmacist engagement in learning how to implement 3D printing PMs into their practice in a way that is commercially advantageous.

Economic viability

Economic gain is an essential factor that contributes largely to the decision-making process a business will undertake when looking to adopt new methods. In the case of pharmacy, it is considered a business, and as such, pharmacy owners have responded in surveys that they will consider the financial benefit of 3D printing PMs carefully before introducing this service to the community (Algahtani, 2021; Beer et al., 2021).

There are many factors to be considered when assessing the economic viability of 3D printing PMs within pharmacy practice. The initial cost of installing a 3D printer in a pharmacy varies widely based on the type of printer introduced and how technical the pharmacist desires the settings. FDM is the cheapest, most accessible option, with basic hobbyist models available from USD$180 and industry-grade models starting at USD$2500 (Chen et al., 2021). As FDM usually prints with low resolution compared to other techniques and has a long print time (hours) (Dumpa et al., 2021), pharmacists do have the option to try other quick, high-resolution techniques near a similar price point; for example, industry-grade SLA printers exist from USD$3500. For all techniques, this price quickly reaches anything above USD$15,000 for larger and more complex models (Chen et al., 2021). This introduces a limitation to pharmacy practice, as pharmacy business owners will have to carefully consider the benefit an additional cost for increased print speed would provide to allow this production method to keep up with the fast-paced, demanding environment of community pharmacy. However, compounding pharmacies already allow for longer production time of traditional compounding techniques, often requesting patients to pick up their medicines a few days later. Hence, this limitation already exists in the realm of providing PMs.

However, the cost of start-up is not only limited to the machine. Other costs identified include CAD software prescription, cost of computers that can run software with higher system requirements, cost of materials used for printing, and cost of pharmacist training, which is currently not easily defined.

This system poses a cost to the pharmacy owner, but it will likely also introduce costs to the patient. Issues of the price of patient tests that can be performed to optimise the personalisation of medicine have been raised, as pharmacogenetic testing is regarded as an expensive practice (Amekyeh et al., 2021). In many countries, patients also have their health care and treatment partly subsidised by the government (Beer et al., 2021), so with the uncertainty of where 3DP PMs fit within current guidelines, there is no way to predict whether the costs of PMs will need to be entirely covered by the patient or not.

Taken together, many have raised concerns around the cost-effectiveness of 3D printed drugs compared to conventional drugs. As shown in Table 1, patients taking warfarin may benefit from 3D printed PM to achieve precise dosage titration based on INR to suit their needs. However, current conventional warfarin tablets are already available in many different strengths including 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg and 10 mg and the cost is extremely low ranging from USD $0.10 to $0.88 per unit (Drugs.com, 2023). From an economic perspective, 3D printed warfarin tablets may not have an advantage over the current generic brands available, due to the cost of a 3D printer, active ingredients and fibre/filament required in the production process. However, cost-effectiveness analysis not only compares costs but also the outcome of the treatment. From a clinical and patient perspective, 3D-printed tablets may offer a greater benefit. With the current warfarin dosing titration, patients may need to take multiple tablets and multiple strengths to make up for their dose. This raises the issue of administration error and adherence. With 3D printing, it is possible to customize doses into one tablet, which is more convenient for the patient and reduces the risk of an incorrect dose being administered. During the dose titration period, 3D printing also allows small batch production to minimise wastage.

Moreover, since doctors are prescribing PM through compounding in current practice, using conventional compounding approach. Compounding pharmacies need to invest in the equipment and devices required to manufacture extemporaneous products. This includes capsule machines, fume hoods, measuring devices, containers etc., as well as the cost of a clean room and labour. With the current method, pharmacists often need to spend 30 minutes to over an hour making just one product. On the other hand, for 3D printed drugs, the cost involves the initial investment in a 3D printer and the recurring cost of ‘ink’, i.e., the active ingredient and filament. This is not much different from the current compounding production process (Beer et al., 2021). As a result, 3D printing may prove more cost-effective for

compounding pharmacies in the long run, since it requires less floor space, less labour, and is less prone to human error.

As researchers Gilbert (Thomas and Gilbert, 2015) interestingly applied the notion of economies of scale to this current situation, they proposed that as 3D printing techniques become a more widely adopted practice in community pharmacy, then price would follow, allowing 3DP PM to become a cheaper service to introduce and maintain in a community setting.

Safety and quality

The most outstanding issue associated with traditional compounding is the lack of implementation of quality testing methods that assure the patient is receiving correctly dosed and safe medicine. (Drazen et al., 2012; Watson et al., 2021). Many have similar concerns for 3D printing of PMs.

The computerised nature of 3D printing PM overcomes the risk of human error affecting dose calculations and the mechanical weighing of individual materials when a pharmacist is manufacturing on-site. This is because computational calculations can quickly and accurately determine the number of layers and final print weight as a function of the input dose without pharmacist involvement.

Stability and shelf life are also factors that must be assessed for 3D prints. Patients taking home any medication trust that the product is effective following a reasonable amount of time stored. Aita et al. (Aita et al., 2020) observed the dissolution behaviour of and dose contained within SSE printed tablets to remain unchanged following a storage period of 5 days; however, this study presented limitations in its short duration, hence was unable to establish a reasonable conclusion regarding the stability of the printlets beyond this time. Other prints containing complex release profiles have also been assessed, with zero-order kinetics of a binder jet printed controlled released pseudoephedrine tablet showing unchanged release kinetics following a month of open container exposure to room temperature of normal humidity (Wang et al., 2006). Although the data available shows no concern for degradation and instability following storage, much further testing is required to ensure that the stability and shelf life of 3D printing PMs is reasonable to be stored in a patient's home over time.

Methods for on-site quality control of 3D printing PMs have already been proposed, offering a benefit to PM that has yet to be addressed in traditional compounding. Vakili et al. (Vakili et al., 2016) implemented colourimetry to identify the specific dose of propranolol present on an orodispersible film. Colourimetry is an analytical technique whereby a colour's saturation is quantified (Gilchrist and Nobbs, 2017). By dying propranolol ink red and assessing via colourimetry the saturation of the printed coloured dye compared to the base material, colourimetry proved to distinguish between the amount of colour present and translate this to drug concentration accurately ($R^2 > 0.9758$), allowing for quick drug concentration testing in a non-destructive manner (Vakili et al., 2016). Trenfield et al. (Trenfield et al., 2018; Trenfield et al., 2020) proposed an alternate method called the 'point-and-shoot' approach. Their study involved the development of amlodipine and lisinopril specific calibrated models based on the near infra-red (NIR) spectroscopy results of each of those drugs. NIR is a non-destructive analytic technique used to determine organic structural compositions by how the examined sample absorbs or emits radiated light of known varied wavelengths (O'Sullivan and Kerry, 2013). The NIR calibrated model determined drug and concentration by matching tested values to the predetermined absorbance value from the calibrated graph, with model data applied over a range of geometries displaying excellent linearity, accuracy, and specificity (Trenfield et al., 2018; Trenfield et al., 2020). The advantage of NIR is that it can be applied to a community pharmacy setting, as NIR devices are available in a portable desktop form, a more accessible option than traditional bulky lab based analytical machines (Eady et al., 2021).

Community pharmacists have also suggested the benefit of having mass-produced filaments as this not only incorporates large-scale pharmaceutical companies as critical stakeholders in the provision of PM but also allows for additional safeguards to be implemented, such as off-site quality testing of drug-loaded cartridges/filaments and the use of traceable barcodes to minimise drug error (Beer et al., 2021). However, the issue with mass-produced filaments is that it would limit the flexibility of 3D printing in the personalisation of treatment. The manipulations to the dosage forms and the release profiles of different drugs through 3D printing would be constrained as it would have been pre-defined in the mass-production process. For patients who may be allergic to the ingredients in the filaments, pharmacies would need another production system in place to accommodate their needs. This will likely incur a whole new set of costs for the pharmacy and may not be economically feasible for

them. Therefore, it could be argued that at the current stage, the implementation of 3D printing in the pharmaceutical industry would likely evolve around two pathways: compounding small batches of extemporaneous preparations in pharmacies to fill the gap in personalised medicine and large-scale production in pharmaceutical companies to aid drug development.

Patient acceptability

Patients must accept this type of medicine in order for it to be viable in practice. Most studies have investigated paediatric acceptability of 3DP medicines, as children are usually the most critical assessors of how well the feel and taste of medicine is tolerated. Paediatrics also make up a large portion of PM requirements, with 37% of all paediatric scripts requiring some form of manipulation prior to administration, including tablet splitting, tablet crushing, and pharmacist compounding (Lafeber et al., 2022). Studies have illustrated that following the administration of a personalised 3DP medication, a large majority, 77%, of children would be happy to continue to take the medication daily if they were told to do so. An 83% overall paediatric acceptability of the dosage form, with 93% of children enjoying the taste (Bracken et al., 2022), shows that unique paediatric dosage forms such as 3DP chews and gummies provide an enjoyable alternative to "bad tasting oral liquids" (Lafeber et al., 2022). Limited studies extend beyond paediatric patient acceptability; hence, it is imperative that further research is performed in older populations.

Implications of 3DP PM for policy

Internationally, no current policies or guidelines exist that specifically outline the role of and provide a framework for the use of 3D printing techniques in the manufacturing of PM. Pharmacists do, however, have access to frameworks that outline how on-site extemporaneous production of medicines may be performed, which can be referred to when looking for ways to apply 3D printing methods as a means of doing so. Hence, we have outlined in Table 2. the regulatory frameworks of international compounding guidelines, discussing further their implementability within the scope of 3D printing PM.

All international compounding frameworks included criteria whereby a compounded formulation was exempt from requiring approval from that country's respective governing pharmaceutical or manufactured goods agency. The following criteria were consistent with all assessed guidelines: the preparation must be performed by a registered pharmacist or pharmacy technician; the product must comply with the specified form of quality assessment guideline, e.g. quality testing as outlined by the United States Pharmacopeia (USP) must be confirmed for medicines compounded in the United States (US); and the compounding formulation must resonate with the drug, dose, and dosage form that has been prescribed by the practitioner (Brazil Ministry of Health (BMOH), 2012; Committee of Ministers (COM), 2016; General Pharmaceutical Council (GPC), 2018; National Association of Pharmacy Regulatory Authorities (NAPRA), 2018; Pharmacy Board of Australia (PBA), 2017; US Food and Drug Administration (FDA), 2016). In some cases, such as the US, a written note from the practitioner identifying the need for compounding is additionally required (US Food and Drug Administration (FDA), 2016).

Points of difference arose regarding whether a defined need for compounding was necessary. For example, Australian compounding guidelines only approve of compounding methods in the circumstance that commercially available medicines are unavailable or unsuitable (e.g., in the case of allergy to excipient) (Pharmacy Board of Australia (PBA), 2017); however, this is contrary to Brazil, where pharmacists can compound any medicine, regardless of the product's commercial availability (Brazil Ministry of Health (BMOH), 2012). Another defining point of difference was which formulations may be used in the case of compounding, with Germany allowing only the use of specific methods outlined in the Deutscher Arzneimittel-Code/ Neues Rezeptur Formularium (DAC/NRF) (Deutsche Arzneimittel-Codes/Neues Rezeptur Formularium (DAC/NRF), 2022), whereas other countries such as Brazil and Australia provide reputable formularies to follow, such as the Australian Pharmaceutical Formulary (APF) (Pharmaceutical Society of Australia (PSA), 2022), however, additionally allow for the use of other formulations whereby quality, safety, efficacy, stability, and rationale can be confirmed (Brazil Ministry of Health (BMOH), 2012; Pharmacy Board of Australia (PBA), 2017). This is notable when discussing the use of 3D printing techniques as a method of compounding, as the future development of confirmed formulations that adhere to the criteria mentioned above would allow for the implementation of 3DP PMs into pharmacy practice.

Interestingly, Brazil has shown to have a much more developed system of compounding PMs compared to other countries, with compounding pharmacies as the predominating pharmacy type and compounded formulations accounting for annual revenue of $1.5B USD in 2017 (World Congress of Compounding (WCOC), 2018). As such, their additional guidelines surrounding physical spaces that must be available in all compounding pharmacies are of benefit to consider if other international policies are to be revisited to accommodate for 3D printing methods, as the requirement of an on-site quality control lab for all compounding pharmacies addresses key safety concerns discussed prior in implications for practice (Brazil Ministry of Health (BMOH), 2012).

Although it is evident that 3D printing could be considered a method of compounding and as such has compounding frameworks available to follow in pharmacy practice, there is a need for these written regulations to be adapted to include guidelines and terminology for 3D printing specifically, as well as the development of confirmed 3D printing formulations to follow that have defined quality assurance measures. An example of guidelines being amended to accommodate the use of 3D printing techniques is the recent US FDA and Australian Therapeutic Goods Administration (TGA) guidelines for manufacturing personalised medical devices, produced in 2017 and 2021, respectively (Therapeutic Goods Administration (TGA), 2021; US Food and Drug Administration (FDA), 2017). These guidelines followed a similar rationale regarding the requirements for considering personalisation, allowing for personalised devices to be 3DP if the device: is personalised prior to manufacturing; comes from a written request by a practitioner, has no commercially suitable alternative, and is suited to the individual's specific anatamo-physiology. These updates, as well as the statement released by the FDA outlining that "3D printing also has medical applications for FDA-regulated drugs and biologics" (US Food and Drug Administration (FDA), 2020), provide precedence that further amendments to current guidelines will allow for the future of 3D printing techniques for PM being utilised in pharmacy practice.

Table 2.

International compounding guidelines and a summary of the criteria whereby on-site extemporaneous manufacturing is exempt from requiring governing agency approval.

No.	Country	Criteria for exemption from required governing agency approval	Ref
1	Australia	• Prescription can act as the instruction for compounding • Appropriate circumstance: commercial product unavailable, commercial product unsuitable (e.g., allergy), undertaking research sanctioned by an ethics committee • Products compounded according to formulations published in a reputable source or using formulations with confirmed quality, stability, safety, efficacy, and rationality • Complex compounding (sterile preparations, hormones, cytotoxics, micro-dose dosage forms with less than 25mg of API, modified-release preparations) requires developing a professional practice profile and evidence of the appropriate training. • Pharmacists should document the preparation of compounded products	(Pharmacy Board of Australia (PBA), 2017)
2	Europe	• The physician must identify on the prescription that it is for in-pharmacy preparation • Appropriate circumstance: commercial product unavailable, commercial product unsuitable (e.g., allergy) • Products should be prepared following appropriate quality assurance systems, e.g. The European Pharmacopeia or other national	(Committee of Ministers (COM), 2016)

		• Documentation is recommended but not necessary unless in the case of stock preparations. Documentation includes demonstrating the need for pharmacy preparation, demonstrating all ingredients meet relevant requirements, a record of preparation process and testing (where required).	
3	USA	• The practitioner must note on valid prescription the need for compounding • The product is compounded with the United States Pharmacopeia (USP) chapters on pharmacy compounding • All ingredients used must be FDA approved • The compounded medicine must not be a copy of commercially available products • The product does not contain drugs that are on the difficult to compound list (still being developed with the Pharmacy Compounding Advisory Committee	(US Food and Drug Administration (FDA), 2016)

4	Brazil	• A pharmacist may compound any valid prescription
		• The compounding methods are performed per those outlined in the Brazilian Pharmacopeia National Form or where quality, efficacy, and stability can be confirmed
		• The quality guarantee must be followed:
		  ○ Prepare appropriate documentation for procedures, compounding orders, materials, conditions and cleaning of workspace, storage methods, a record of personnel training, a record of auditing and inspections, and records of maintenance
		  ○ Provide necessary subsidies to the pharmacist to maintain the safety and efficiency of products and keep conditions hygienic and sanitary.
		  ○ There must be an assigned area for quality control
			(Brazil Ministry of Health (BMOH), 2012)

5	Canada	• There must be a demonstrated patient-healthcare professional relationship • There must not be third party reselling of the product outside of the pharmacy setting • A pharmacist may compound a valid prescription where necessary (not available commercially or commercial options are not suitable for the patient) • Pharmacist must receive proper orientation, training, and a skills assessment before compounding • Compounding must be performed in a separate space designated explicitly for compounding • The methods of compounding must follow the Master Formulation Record, and where changes are made, there must be documented rationale and references to ensure quality and safety	(National Association of Pharmacy Regulatory Authorities (NAPRA), 2018)
6	United Kingdom	• Preparation must be in accordance with a prescription • Record of the premises (temperature, moisture, etc.), a record of staff training, documentation of methods for each preparation, and record of equipment and facilities maintenance must be kept and ready in the case of an audit. • The formula for compounding used must be documented complete including the methods uses and the source of the formula (The British Pharmacopeia or any other reputable, traceable source)	(General Pharmaceutical Council (GPC), 2018)

Conclusion

3D printing techniques have proved the ability to create complex PMs in a way that is simple, fast, and potentially more accessible to pharmacy practice in the future. Although further research must be performed, this technology seems acceptable for both pharmacists and patients, seeming most feasible to be initiated within specialized pharmacy settings such as hospitals and compounding facilities. There is also demonstrated potential for its use following existing polices and frameworks. As 3D printing of PM becomes a reality for pharmacy, careful consideration must be made for the technical and clinical implications and the impact this has on current practice and policy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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References

(PSA), P.S.o.A., 2019. Pharmacists in 2023: Roles and Remuneration. Pharmaceutical Society of Australia (PSA).

Afsana, Jain, V., Haider, N., Jain, K., 2018. 3D Printing in Personalized Drug Delivery. Curr. Pharm. Des. 24, 5062-5071.

Aita, I.E., Breitkreutz, J., Quodbach, J., 2020. Investigation of semi-solid formulations for 3D printing of drugs after prolonged storage to mimic real-life applications. Eur. J. Pharm. Sci. 146, 105266.

Algahtani, M.S., 2021. Assessment of Pharmacist's Knowledge and Perception toward 3D Printing Technology as a Dispensing Method for Personalized Medicine and the Readiness for Implementation. Pharmacy (Basel) 9.

Alhnan, M.A., Okwuosa, T.C., Sadia, M., Wan, K.W., Ahmed, W., Arafat, B., 2016. Emergence of 3D Printed Dosage Forms: Opportunities and Challenges. Pharm. Res. 33, 1817-1832.

Amekyeh, H., Tarlochan, F., Billa, N., 2021. Practicality of 3D Printed Personalized Medicines in Therapeutics. Front. Pharmacol. 12, 646836-646836.

Anwar-Fadzil, A.F.B., Yuan, Y., Wang, L., Kochhar, J.S., Kachouie, N.N., Kang, L., 2022. Recent progress in three-dimensionally-printed dosage forms from a pharmacist perspective. J. Pharm. Pharmacol.

Arafat, B., Qinna, N., Cieszynska, M., Forbes, R.T., Alhnan, M.A., 2018. Tailored on demand anti-coagulant dosing: An in vitro and in vivo evaluation of 3D printed purpose-designed oral dosage forms. Eur. J. Pharm. Biopharm. 128, 282-289.

Aziz, Z.H.A., Katas, H., Omar, M.S., Mohamed Shah, N., Mohamad Yusop, S., Shafiee, M.N., Mohd Tarmizi, S.F., 2022. Preference, Perception, and Acceptability of Fluid Gels as a Potential Age-Appropriate Dosage Form for Elderly Patients with Dysphagia. Gels 8, 218.

Bartelink, I.H., Rademaker, C.M.A., Schobben, A.F.A.M., van den Anker, J.N., 2006. Guidelines on Paediatric Dosing on the Basis of Developmental Physiology and Pharmacokinetic Considerations. Clin. Pharmacokinet. 45, 1077-1097.

Beer, N., Hegger, I., Kaae, S., De Bruin, M.L., Genina, N., Alves, T.L., Hoebert, J., Kälvemark Sporrong, S., 2021. Scenarios for 3D printing of personalized medicines - A case study. Exploratory Research in Clinical and Social Pharmacy 4, 100073.

Belgheisi, G., Haghbin Nazarpak, M., Solati-Hashjin, M., 2022. Fabrication and evaluation of combined 3D printed/pamidronate-layered double hydroxides enriched electrospun scaffolds for bone tissue engineering applications. Applied Clay Science 225, 106538.

Bracken, L., Habashy, R., McDonough, E., Wilson, F., Shakeshaft, J., Ohia, U., Garcia-Sorribes, T., Isreb, A., Alhnan, M.A., Peak, M., 2022. Creating Acceptable Tablets 3D (CAT 3D): A Feasibility Study to Evaluate the Acceptability of 3D Printed Tablets in Children and Young People. Pharmaceutics 14.

Brazil Ministry of Health (BMOH), 2012. Brazilian Pharmacopeia National Form. Brazil Ministry of Health (BMOH).

Cader, H.K., Rance, G.A., Alexander, M.R., Gonçalves, A.D., Roberts, C.J., Tuck, C.J., Wildman, R.D., 2019. Water-based 3D inkjet printing of an oral pharmaceutical dosage form. Int. J. Pharm. 564, 359-368.

Cameron, E.E., Bushell, M.-J.A., 2021. Analysis of drug shortages across two countries during pre-pandemic and pandemic times. Research in Social and Administrative Pharmacy 17, 1570-1573.

Carlier, E., Marquette, S., Peerboom, C., Amighi, K., Goole, J., 2021. Development of mAb-loaded 3D-printed (FDM) implantable devices based on PLGA. Int. J. Pharm. 597, 120337.

Charoo, N.A., Barakh Ali, S.F., Mohamed, E.M., Kuttolamadom, M.A., Ozkan, T., Khan, M.A., Rahman, Z., 2020. Selective laser sintering 3D printing – an overview of the technology and pharmaceutical applications. Drug Dev. Ind. Pharm. 46, 869-877.

Chen, G., Xu, Y., Chi Lip Kwok, P., Kang, L., 2020. Pharmaceutical Applications of 3D Printing. Additive Manufacturing 34, 101209.

Chen, J.V., Dang, A.B.C., Dang, A., 2021. Comparing cost and print time estimates for six commercially-available 3D printers obtained through slicing software for clinically relevant anatomical models. 3D Print Med 7, 1.

Chen, K.-Y., Zeng, J.-J., Lin, G.-T., 2022. Fabrication of 5-fluorouracil-loaded tablets with hyperbranched polyester by digital light processing 3D printing technology. European Polymer Journal 171, 111190.

Cheymol, G., 2000. Effects of Obesity on Pharmacokinetics. Clin. Pharmacokinet. 39, 215-231.

Committee of Ministers (COM), 2016. Resolution CM/Res on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients Council of Europe (COE).

Cui, M., Pan, H., Fang, D., Sun, H., Pan, W., 2022. 3D printed personalized amikacin sulfate local drug delivery system for bone defect therapy. Journal of Drug Delivery Science and Technology 70, 103208.

De Maio, F., Rosa, E., Perini, G., Augello, A., Niccolini, B., Ciaiola, F., Santarelli, G., Sciandra, F., Bozzi, M., Sanguinetti, M., Sali, M., De Spirito, M., Delogu, G., Palmieri, V., Papi, M., 2022. 3D-printed graphene polylactic acid devices resistant to SARS-CoV-2: Sunlight-mediated sterilization of additive manufactured objects. Carbon 194, 34-41.

Deutsche Arzneimittel-Codes/Neues Rezeptur Formularium (DAC/NRF), 2022. DAC/NRF Guidelines for Compounding. Avoxa – Mediengruppe Deutscher Apotheker GmbH.

Drazen, J.M., Curfman, G.D., Baden, L.R., Morrissey, S., 2012. Compounding Errors. N. Engl. J. Med. 367, 2436-2437.

Drugs.com, 2023. Warfarin Prices, Coupons and Patient Assistance Programs. .

Dumpa, N., Butreddy, A., Wang, H., Komanduri, N., Bandari, S., Repka, M.A., 2021. 3D printing in personalized drug delivery: An overview of hot-melt extrusion-based fused deposition modeling. Int. J. Pharm. 600, 120501.

Eady, M., Payne, M., Sortijas, S., Bethea, E., Jenkins, D., 2021. A low-cost and portable near-infrared spectrometer using open-source multivariate data analysis software for rapid discriminatory quality assessment of medroxyprogesterone acetate injectables. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 259, 119917.

ELDesoky, E.S., 2007. Pharmacokinetic-Pharmacodynamic Crisis in the Elderly. Am. J. Ther. 14, 488-498.

Evans, S.E., Harrington, T., Rodriguez Rivero, M.C., Rognin, E., Tuladhar, T., Daly, R., 2021. 2D and 3D inkjet printing of biopharmaceuticals – A review of trends and future perspectives in research and manufacturing. Int. J. Pharm. 599, 120443.

Fina, F., Goyanes, A., Madla, C.M., Awad, A., Trenfield, S.J., Kuek, J.M., Patel, P., Gaisford, S., Basit, A.W., 2018a. 3D printing of drug-loaded gyroid lattices using selective laser sintering. Int. J. Pharm. 547, 44-52.

Fina, F., Madla, C.M., Goyanes, A., Zhang, J., Gaisford, S., Basit, A.W., 2018b. Fabricating 3D printed orally disintegrating printlets using selective laser sintering. Int. J. Pharm. 541, 101-107.

Fritz, B., Fucentese, S.F., Zimmermann, S.M., Tscholl, P.M., Sutter, R., Pfirrmann, C.W.A., 2020. 3D-printed anatomic models of the knee for evaluation of patellofemoral dysplasia in comparison to standard radiographs and computed tomography. Eur. J. Radiol. 127, 109011.

General Pharmaceutical Council (GPC), 2018. Guidance for registered pharmacies preparing unlicensed medicines. General Pharmaceutical Council (GPC).

Gilchrist, A., Nobbs, J., 2017. Colorimetry, Theory, in: Lindon, J.C., Tranter, G.E., Koppenaal, D.W. (Eds.), Encyclopedia of Spectroscopy and Spectrometry (Third Edition). Academic Press, Oxford, pp. 328-333.

Goh, G.D., Sing, S.L., Lim, Y.F., Thong, J.L.J., Peh, Z.K., Mogali, S.R., Yeong, W.Y., 2021. Machine learning for 3D printed multi-materials tissue-mimicking anatomical models. Materials & Design 211, 110125.

Goh, O., Goh, W.J., Lim, S.H., Hoo, G.S., Liew, R., Ng, T.M., 2022. Preferences of Healthcare Professionals on 3D-Printed Tablets: A Pilot Study. Pharmaceutics 14.

Hagan, C.T., Bloomquist, C., Warner, S., Knape, N.M., Kim, I., Foley, H., Wagner, K.T., Mecham, S., DeSimone, J., Wang, A.Z., 2022. 3D printed drug-loaded implantable devices for intraoperative treatment of cancer. J. Control. Release 344, 147-156.

He, B., Wang, J., Xie, M., Xu, M., Zhang, Y., Hao, H., Xing, X., Lu, W., Han, Q., Liu, W., 2022. 3D printed biomimetic epithelium/stroma bilayer hydrogel implant for corneal regeneration. Bioactive Materials 17, 234-247.

Hock, S.C., Siang, T.K., Wah, C.L., 2021. Continuous manufacturing versus batch manufacturing: benefits, opportunities and challenges for manufacturers and regulators. Generics and Biosimilars Initiative journal 10, 44-56.

Hu, Z., Xu, P., Zhang, J., Bandari, S., Repka, M.A., 2022. Development of controlled release oral dosages by density gradient modification via three-dimensional (3D) printing and hot-melt extrusion (HME) technology. Journal of Drug Delivery Science and Technology 71, 103355.

Khaled, S.A., Burley, J.C., Alexander, M.R., Yang, J., Roberts, C.J., 2015. 3D printing of tablets containing multiple drugs with defined release profiles. Int. J. Pharm. 494, 643-650.

Lafeber, I., Ruijgrok, E.J., Guchelaar, H.J., Schimmel, K.J.M., 2022. 3D Printing of Pediatric Medication: The End of Bad Tasting Oral Liquids?—A Scoping Review. Pharmaceutics 14.

Li, X., Liang, E., Hong, X., Han, X., Li, C., Wang, Y., Wang, Z., Zheng, A., 2021. In Vitro and In Vivo Bioequivalence Study of 3D-Printed Instant-Dissolving Levetiracetam Tablets and Subsequent Personalized Dosing for Chinese Children Based on Physiological Pharmacokinetic Modeling. Pharmaceutics 14.

Lim, S.H., Kathuria, H., Tan, J.J.Y., Kang, L., 2018. 3D printed drug delivery and testing systems — a passing fad or the future? Advanced Drug Delivery Reviews 132, 139-168.

National Association of Pharmacy Regulatory Authorities (NAPRA), 2018. Guidance Document for Pharmacy Compounding of Non-sterile Preparations —Companion to the Model Standards for Pharmacy Compounding of Non-sterile Preparations. National Association of Pharmacy Regulatory Authorities' (NAPRA).

O'Connor, T., Lee, S., 2017. Chapter 37 - Emerging Technology for Modernizing Pharmaceutical Production: Continuous Manufacturing, in: Qiu, Y., Chen, Y., Zhang, G.G.Z., Yu, L., Mantri, R.V. (Eds.), Developing Solid Oral Dosage Forms (Second Edition). Academic Press, Boston, pp. 1031-1046.

O'Sullivan, M.G., Kerry, J.P., 2013. 12 - Instrumental assessment of the sensory quality of meat, poultry and fish, in: Kilcast, D. (Ed.), Instrumental Assessment of Food Sensory Quality. Woodhead Publishing, pp. 355-373.

Panraksa, P., Zhang, B., Rachtanapun, P., Jantanasakulwong, K., Qi, S., Jantrawut, P., 2022. 'Tablet-in-Syringe': A Novel Dosing Mechanism for Dysphagic Patients Containing Fast-Disintegrating Tablets Fabricated Using Semisolid Extrusion 3D Printing. Pharmaceutics 14.

Patil, H., Tiwari, R.V., Repka, M.A., 2016. Hot-Melt Extrusion: from Theory to Application in Pharmaceutical Formulation. AAPS PharmSciTech 17, 20-42.

Pharmaceutical Society of Australia (PSA), 2022. Australian Pharmaceutical Formulary (APF) Handbook Pharmaceutical Society of Australia.

Pharmacy Board of Australia (PBA), 2017. Guidelines on Compounding of Medicines Pharmacy Board of Australia

Phuong, J.M., Penm, J., Chaar, B., Oldfield, L.D., Moles, R., 2019. The impacts of medication shortages on patient outcomes: A scoping review. PLoS One 14, e0215837.

Rautamo, M., Kvarnstrom, K., Siven, M., Airaksinen, M., Lahdenne, P., Sandler, N., 2020. Benefits and Prerequisites Associated with the Adoption of Oral 3D-Printed Medicines for Pediatric Patients: A Focus Group Study among Healthcare Professionals. Pharmaceutics 12.

Robles-Martinez, P., Xu, X., Trenfield, S.J., Awad, A., Goyanes, A., Telford, R., Basit, A.W., Gaisford, S., 2019. 3D Printing of a Multi-Layered Polypill Containing Six Drugs Using a Novel Stereolithographic Method. Pharmaceutics 11, 274.

Rycerz, K., Stepien, K.A., Czapiewska, M., Arafat, B.T., Habashy, R., Isreb, A., Peak, M., Alhnan, M.A., 2019. Embedded 3D Printing of Novel Bespoke Soft Dosage Form Concept for Pediatrics. Pharmaceutics 11.

Savard, J., 2013. Personalised Medicine: A Critique on the Future of Health Care. J. Bioeth. Inq. 10, 197-203.

Schmidt, L.M., Dos Santos, J., de Oliveira, T.V., Funk, N.L., Petzhold, C.L., Benvenutti, E.V., Deon, M., Beck, R.C.R., 2022. Drug-loaded mesoporous silica on carboxymethyl cellulose hydrogel: Development of innovative 3D printed hydrophilic films. Int. J. Pharm. 620, 121750.

Sellers, S., Utian, W.H., 2012. Pharmacy Compounding Primer for Physicians. Drugs 72, 2043-2050.

Seoane-Viaño, I., Januskaite, P., Alvarez-Lorenzo, C., Basit, A.W., Goyanes, A., 2021. Semi-solid extrusion 3D printing in drug delivery and biomedicine: Personalised solutions for healthcare challenges. J. Control. Release 332, 367-389.

Shahrubudin, N., Lee, T.C., Ramlan, R., 2019. An Overview on 3D Printing Technology: Technological, Materials, and Applications. Procedia Manufacturing 35, 1286-1296.

Sharma, A., Gupta, S., Sampathkumar, T.S., Verma, R.S., 2021. Modified graphene oxide nanoplates reinforced 3D printed multifunctional scaffold for bone tissue engineering. Materials Science and Engineering: C, 112587.

Therapeutic Goods Administration (TGA), 2021. Personalised medical devices (including 3D-printed devices): Regulatory changes for custom-made medical devices. Australian Government: Department of Health

Thomas, D., Gilbert, S., 2015. Costs and cost effectiveness of additive manufacturing: A literature review and discussion.

Thygesen, T., Slots, C., Jensen, M.B., Ditzel, N., Kassem, M., Langhorn, L., Andersen, M.Ø., 2022. Comparison of off-the-shelf β-tricalcium phosphate implants with novel resorbable 3D printed implants in mandible ramus of pigs. Bone 159, 116370.

Trenfield, S.J., Goyanes, A., Telford, R., Wilsdon, D., Rowland, M., Gaisford, S., Basit, A.W., 2018. 3D printed drug products: Non-destructive dose verification using a rapid point-and-shoot approach. Int. J. Pharm. 549, 283-292.

Trenfield, S.J., Tan, H.X., Goyanes, A., Wilsdon, D., Rowland, M., Gaisford, S., Basit, A.W., 2020. Non-destructive dose verification of two drugs within 3D printed polyprintlets. Int. J. Pharm. 577, 119066.

UpToDate, 2023. Levetiracetam: Drug Information.

US Food and Drug Administration (FDA), Compounding Laws and Policies, in: (FDA), U.S.F.a.D.A. (Ed.). U.S. Food and Drug Administration (FDA).

US Food and Drug Administration (FDA), 2016. Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act: Guidance. U.S. Department of Health and Human Services.

US Food and Drug Administration (FDA), 2017. Technical Considerations for Additive Manufactured Medical Devices: Guidance for Industry and Food and Drug Administration Staff. U.S. Department of Health and Human Services

US Food and Drug Administration (FDA), 2020. 3D Printing of Medical Devices.

Vakili, H., Nyman, J.O., Genina, N., Preis, M., Sandler, N., 2016. Application of a colorimetric technique in quality control for printed pediatric orodispersible drug delivery systems containing propranolol hydrochloride. Int. J. Pharm. 511, 606-618.

Wake, N., Vincent, J., Robb, F., 2022. Chapter 2 - Medical Imaging Technologies and Imaging Considerations for 3D Printed Anatomic Models, in: Wake, N. (Ed.), 3D Printing for the Radiologist. Elsevier, pp. 11-29.

Wang, C.C., Tejwani Motwani, M.R., Roach, W.J., Kay, J.L., Yoo, J., Surprenant, H.L., Monkhouse, D.C., Pryor, T.J., 2006. Development of near zero-order release dosage forms using three-dimensional printing (3-DP) technology. Drug Dev. Ind. Pharm. 32, 367-376.

Watson, C.J., Whitledge, J.D., Siani, A.M., Burns, M.M., 2021. Pharmaceutical Compounding: a History, Regulatory Overview, and Systematic Review of Compounding Errors. J. Med. Toxicol. 17, 197-217.

Windolf, H., Chamberlain, R., Quodbach, J., 2022. Dose-independent drug release from 3D printed oral medicines for patient-specific dosing to improve therapy safety. Int. J. Pharm. 616, 121555.

World Congress of Compounding (WCOC), 2018. Emerging Markets Panel: Compounding around the World. World Congress of Compounding (WCOC).

Xu, X., Awad, A., Robles-Martinez, P., Gaisford, S., Goyanes, A., Basit, A.W., 2021. Vat photopolymerization 3D printing for advanced drug delivery and medical device applications. J. Control. Release 329, 743-757.

Yan, T.T., Lv, Z.F., Tian, P., Lin, M.M., Lin, W., Huang, S.Y., Chen, Y.Z., 2020. Semi-solid extrusion 3D printing ODFs: an individual drug delivery system for small scale pharmacy. Drug Dev. Ind. Pharm. 46, 531-538.

Yang, Y., Wu, H., Fu, Q., Xie, X., Song, Y., Xu, M., Li, J., 2022. 3D-printed polycaprolactone-chitosan based drug delivery implants for personalized administration. Materials & Design 214, 110394.

Ye, X., Zhang, Y., Liu, T., Chen, Z., Chen, W., Wu, Z., Wang, Y., Li, J., Li, C., Jiang, T., Zhang, Y., Wu, H., Xu, X., 2022. Beta-tricalcium phosphate enhanced mechanical and biological properties of 3D-printed polyhydroxyalkanoates scaffold for bone tissue engineering. Int. J. Biol. Macromol. 209, 1553-1561.

Zong, W., Ouyang, Y., Miao, Y.-E., Liu, T., Lai, F., 2022. Recent advances and perspectives of 3D printed micro-supercapacitors: from design to smart integrated devices. Chemical Communications 58, 2075-2095.