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TOPICAL REVIEW

Pharmacy 3D printing

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Abstract

A significant limitation of the 'one size fits all' medication approach is the lack of consideration for special population groups. 3D printing technology has revolutionised the landscape of pharmaceuticals and pharmacy practice, playing an integral role in enabling on-demand production of customised medication. Compared to traditional pharmaceutical processes, 3D printing has major advantages in producing tailored dosage forms with unique drug release mechanisms. Moreover, this technology has enabled the combination of multiple drugs in a single formulation addressing key issues of medication burden. Development of 3D printing in pharmacy applications and large-scale pharmaceutical manufacturing has substantially increased in recent years. This review focuses on the emergence of extrusion-based 3D printing, particularly semi solid extrusion, fused deposition modelling and direct powder extrusion, which are currently the most commonly studied for pharmacy practice. The concept of each technique is summarised, with examples of current and potential applications. Next, recent advancements in the 3D printer market and pharmacist perceptions are discussed. Finally, the benefits, challenges and prospects of pharmacy 3D printing technology are highlighted, emphasising its significance in changing the future of this field.

1. Introduction

In the past decade, there has been increased attention to shift away from the 'one size fits all approach', and towards the production of tailored pharmaceutics [1]. This concept emerged from common challenges encountered by high-risk patient groups such as paediatrics and geriatrics. Up to 85% of adverse drug effects stem from these populations administered therapies that are not customised to individual pharmacokinetic profiles [2]. Most commercially available medications are designed for the adult population, with single strengths and formulations. When applying such drugs towards special populations, this often results in manipulation of medications like tablet splitting and compounding to obtain required dosage strengths.

Tablet splitting is a popular practice, accounting for 25% of tablets administered in primary health care [3]. This process involves a solid dosage form that is divided into two or more parts for individualised treatment. Dividing a tablet is often advantageous in tapering or titrating doses [4], allows doses lower than manufactured strength to be achieved, ease of swallowing, and cost savings [5]. Splitting is often performed by patients, and healthcare professionals including pharmacists and nurses. Tablets can be hand split if scored, or by tablet cutters for those without score lines [6].

Despite these potential advantages, the uneven breaking of tablets may result in drug and content variation of up to 27.5% despite tablets containing score lines [7, 8]. This unintentional variation may result in adverse events, particularly clinically significant for drugs of narrow therapeutic range [9]. Further, not all tablets are suitable for splitting such as sustained release or enteric coated tablets [4].

Similarly, traditional compounding also provides individualised drug preparations in accordance with a practitioner's prescription when a commercially manufactured drug is not available. However, questions have been raised regarding extemporaneously compounded formulations, with issues of cross contamination and quality control [10, 11]. Residue from

previous batches or inadequate equipment cleaning can affect safety and lead to adverse clinical outcomes. Additionally, pharmacist errors, including drug dose miscalculations and mechanical mistakes contribute to sources of toxicity. These errors in medication management and administration can negatively impact clinical outcomes, potentially leading to patient harm [12–14].

Three-dimensional printing (3DP), an additive manufacturing (AM) technique, is an emerging technology that converts computer aided designs (CAD) into physical objects. The introduction of 3DP techniques offers a solution to the current gap of individualisation of medicines and dosage inaccuracy of traditional methods.

AM has shown revolutionary developments, yielding many benefits across numerous sections including aerospace, consumer goods, medical and pharmaceutics [15]. 3DP has fast become one of the most innovative technologies in pharmaceutics providing a platform to overcome the limitations of the 'one size fits all approach'. Unlike traditional methods, 3DP is advantageous in customisability and precision for patient specific drug delivery systems. It allows for dose flexibility, rapid prototyping, efficient printing and the creation of polypill combinations [16, 17]. The flexibility of personalising pharmaceuticals has significantly transformed the design and manufacturing of drugs, highlighting the shift towards more tailored and effective treatments.

Several studies have acknowledged the application of 3DP in large-scale manufacturing [18, 19] including 3DP of numerous active pharmaceutical ingredients (APIs) and formulations [20–24]. Currently, the main 3DP techniques that have been documented in pharmaceutical practice include binder jet-3D printing (BJ-3DP), fused deposition modelling (FDM), semi-solid extrusion (SSE), melt extrusion deposition (MED) and stereo lithography (SLA) [18]. Among these, material extrusion (ME), in particular FDM, is the most commonly used in pharmaceutical sciences, owing to the wide availability and low operational costs [25].

Although advances in 3DP have been documented with extensive trials into the suitability of 3DP in pharmaceutical manufacturing, the gap lies in differentiating pharmaceutical manufacturing from clinical pharmacy practice. Therefore, it is necessary to review the application of 3DP in clinical practice, especially at hospital and community pharmacy levels [2, 26], as past publications are limited in this area. Thus, this narrative review will present an overview of the current state of pharmacy 3DP. The study will specifically address methods of ME, the current 3D-printer market, and the resulting challenges for practice in adopting this technology.

Initial screening of Medline Ovid and Scopus databases combined with a hand search of reference lists and citation checking were performed. Combinations of key search terms were employed, including 3D printing (3D printing, AM, layered manufacturing, 3DP); pharmacy (pharmaceutics, medication, drug); and clinical (community, hospital, clinical practice). The search included all types of studies and grey literature from 2015 onwards. Included studies were required to focus on 3DP technology in clinical practice and only papers written or translated into English were included. Literature regarding large-scale drug manufacturing (e.g. mass manufacturing) and bioprinting (e.g. surgical and prostheses) were excluded.

2. 3DP techniques

The American Society for Testing and Materials has classified AM into the following categories: vat photopolymerisation (VP), material jetting (MJ), powder bed fusion (PBF), ME, binder jetting (BJ) and sheet lamination [27]. Table 1 assesses the benefits and limitations of each technology. This review will not provide extensive information on all the 3DP technologies available, as this has been covered in previous reviews [28, 29]. Rather, the review will focus on current 3DP techniques applied in pharmacy.

A general AM process involves a physical object constructed layer by layer, based on a digital model. This process is referred to as the '3Ds of 3D printing' [36], which has been illustrated in figure 1. (1) Design—digital CAD software is used to create the formulation, incorporating geometric characteristics to suit clinical requirements, e.g. paediatric or geriatric applications. The CAD design consists of the contour information for printing on an x–y plane and z-axis. The designed file is then transferred to selected 3D printer. (2) Develop—API and excipients are loaded into 3D printer. Printing parameters including temperature, printing time and nozzle size are adjusted based on API characteristics and the desired final product. (3) Dispense—the automated process begins with the printer spreading a layer of material onto the print bed, defining the x–y plane. This is followed by the ejection of binding material. Subsequent repetition of successive layers and the removal of unbound powders results in the designed 3D object [37, 38]. Since this process is automated, the potential benefit of 3DP is the decreased need for manual labour and reduction of production time and costs.

3. ME

The ME based system has accounted for over 80% of the research articles on pharmaceutical 3D printing from 2015 to 2019 [39], consisting of SSE, FDM and direct powder extrusion (DPE). The basic ME method consists of feeding heated feedstock and selectively dispensing through extruding nozzles to deposit content in layers [40]. As shown in table 2,

Table 1. Benefits and limitations of 3DP technologies.

3DP technique	Benefits	Limitations	References
VP	• High precision • Low surface roughness • Low equipment price • Versatile material options • Low material waste	• Limited resolution of projection device	[30]
MJ	• High dimensional accuracy • Good surface finish • Short printing time • Low surface roughness	• High environmental impact • High cost • Post-print processing required • Long manufacture time	[31, 32]
PBF	• Single step printing process • High resolution • No need for organic solvents • No need for post printing drying	• Active pharmaceutical ingredient (API) degradation due to melting process • Limited choice of photosensitive polymers • Unable to print hollow structures • Time consuming process • High cost • High porosity between powder and binder	[28, 31]
ME	• Simple process • Cost effective • Appropriate for prototyping • Lower volume of raw materials	• Use of organic solvents • Slow drying speeds • Less printing resolution • Affected by nozzle size	[28, 31]
BJ	• Broad range of excipients • High drug loading	• Post-print processing • Large equipment requirements	[33]
Sheet lamination	• Quick process • Low material waste • Low cost	• Low accuracy	[34, 35]

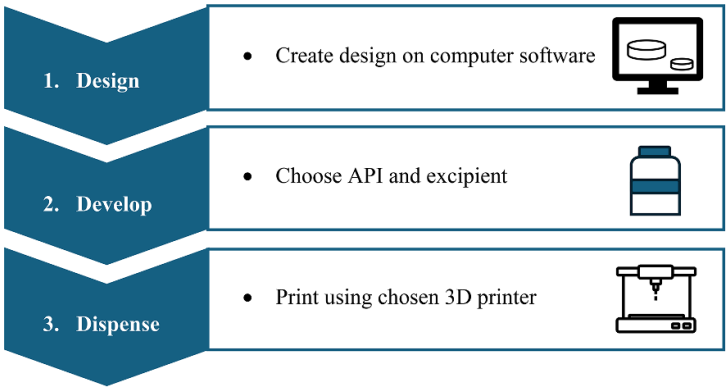

Figure 1. Schematic representation of the basic pharmacy 3DP process. Created with Microsoft Word.

the type of ME may be chosen as per its distinctive advantages and disadvantages.

3.1. SSE

3.1.1. SSE mechanism and printing materials

SSE is classified as a subset of ME. Unlike FDM and DPE where the printing material comprises a solid filament or powder, respectively, SSE feedstock consists of a semi-solid or semi-molten material. Firstly, the semi-solid material, which can include a combination of polymers, APIs, excipients and other additives is prepared (figure 2). The viscosity of the material may be adjusted via heating, mixing or cooling. The prepared semi-solid material is then loaded into a syringe cartridge. This chamber is usually equipped with a nozzle or multiple nozzle systems. The syringe is pushed via one of three systems: (1) pneumatic, (2) mechanical or (3) solenoid [41]. (1) A pneumatic system utilises air pressure to drive the extrusion process (figure 3(a)). In this system, a compressed air source is connected to the syringe barrel. Applying compressed air to the back of the syringe cartridge generates

Table 2. Advantages and disadvantages of three ME printing techniques.

ME 3DP	Advantages	Disadvantages	References
SSE	• Low printing temperature • Fast printing speeds • Disposable syringe and cartridge system • High drug loading • Broad range of excipients	• Post-print processing and drying • Low print accuracy • Prefabrication of semisolid materials	[41, 42]
FDM	• No solvent required • No post-printing processing • Low equipment price • High surface finish	• Prefabrication of API containing filaments • High printing temperature • Slow printing speeds • Limited number of thermoplastic polymers • Low drug loading capacity	[43]
DPE	• Small amount of feedstock material • No post-print processing	• Moderate to high printing temperature • Slow printing speeds	[44]

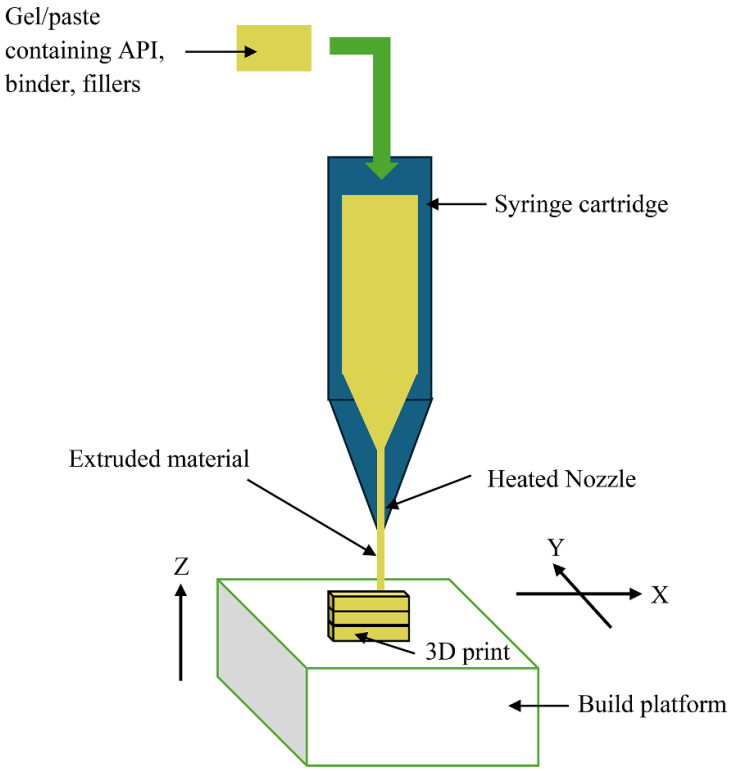

Figure 2. Basic schematic representation of the operation of an SSE system. Created with Microsoft Word.

pressure that will push the material through the nozzle. Generally, there is a high degree of precision, and a rapid extrusion process. This method is most suitable for low viscosity materials such as bioink, although gas pressure may be increased for highly viscous materials without compromising the integrity of the system [41, 45]. (2) Mechanical based systems, including piston and screw, apply mechanical force directly to the syringe to drive the material through the nozzle. (Figures 3(b) and (c)). The piston configuration provides greater control of flow, whilst the screw configuration give higher spatial control, benefiting highly viscous materials [46]. (3) In contrast, the solenoid system operates using electric pulses to disrupt a magnetic attraction between the floating ferromagnetic plunger and ferromagnetic ring. (figure 3(d)). However, this system is not currently used in pharmaceutics due to its limitation in handling sub-μl volumes of paste [41, 47]. The advantages and disadvantages of each extrusion mechanisms are summarised in table 3.

The application of SSE in pharmaceuticals offers the possibility of creating personalised dosage forms whilst avoiding the harsh conditions of other printing techniques such as FDM. SSE allows for the processing of feedstock material at relatively low temperatures, preserving the stability of sensitive APIs. Additionally, the use of pre-loaded and disposable

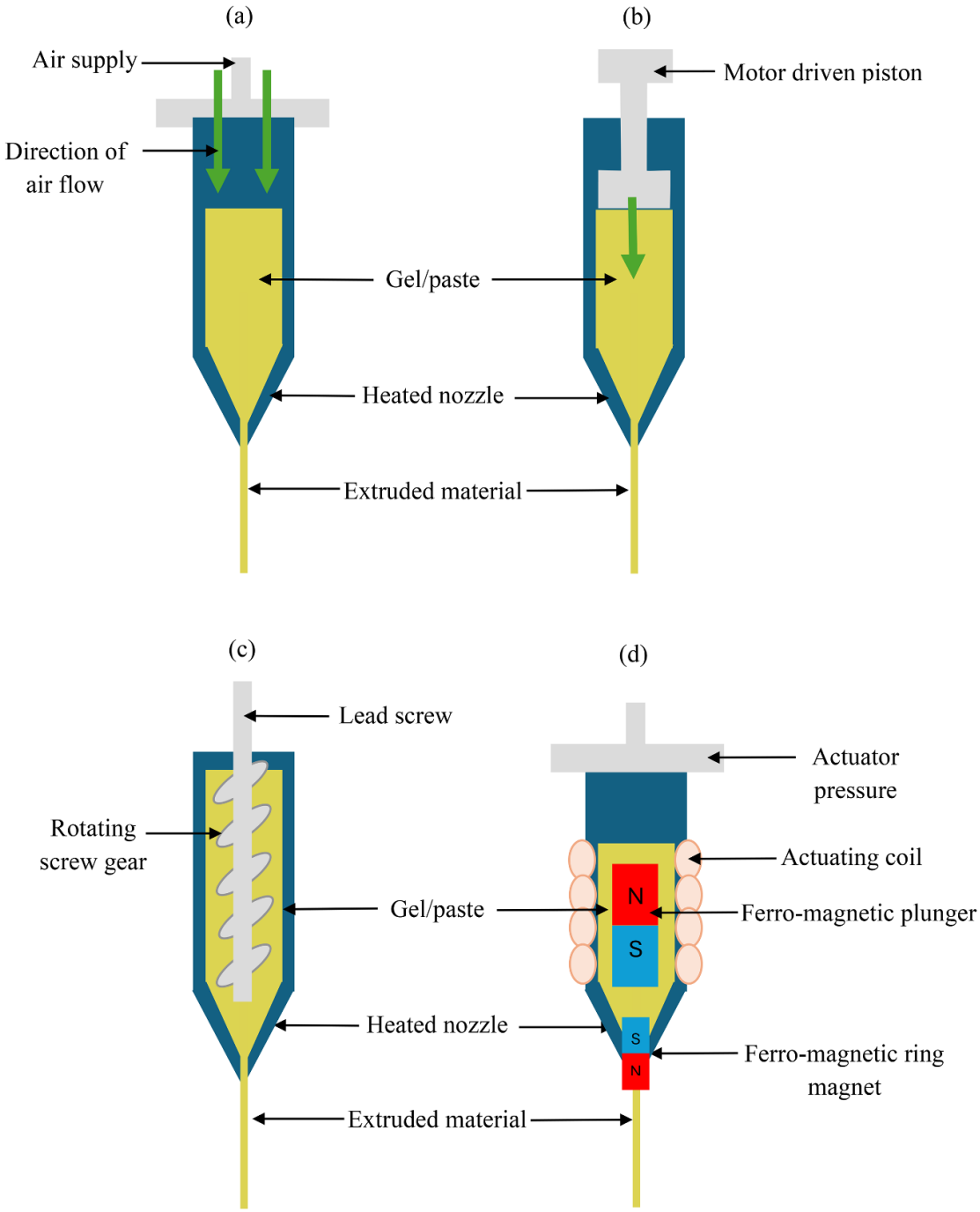

Figure 3. Schematic representation of SSE techniques (a) pneumatic (b) piston (c) screw and (d) solenoid. Created with Microsoft Word.

cartridges facilitate an efficient production process and reduces risk of cross-contamination between batches. This technology has rapidly evolved to manufacture a range of oral dosage forms and several APIs. (Table 4).

3.1.2. Current applications of SSE in pharmacy

In 2020, Zheng *et al* [57] prepared spironolactone and hydrochlorothiazide tablets for patients using pneumatic and piston SSE technology in a hospital setting. The following dosages were created: 2 mg and 4 mg spironolactone, and 5 mg hydrochlorothiazide. Physical and physicochemical properties including appearance, mass variation, drug content, and drug content uniformity of the prepared subdivided tablets were found to be superior to that of traditionally split tablets. Furthermore, the 3D printed tablets complied with European Pharmacopoeia (Ph. Eur.) and Chinese Pharmacopoeia (Ch. P2015.) specifications with no changes in API crystal structure. Following quality and safety clearance, the tablets were prescribed to clinical paediatric inpatients;

Table 3. Advantages and disadvantages of SSE techniques.

Subtype	Advantages	Disadvantages	References
Pneumatic	• Simple utilisation process • High degree of precision • Significant pressures can be used for high viscosity materials	• Delay due to compression of gas volume • Flow rate cannot be controlled directly	[41, 48]
Piston	• Flow rate directly correlated to movement of piston and cartridge dimensions • Control over extrusion flow • Lower cost that pneumatic and solenoid • Easy turnover of syringe apparatus	• High loss of material	[41, 48]
Screw based	• Better spatial control • Suitable for high viscosity materials • Lower cost than pneumatic and solenoid • Easy turnover of syringe apparatus	• High shear force • High loss of material	[41]
Solenoid	• Most suitable for materials with ionic or UV irradiation based linking mechanisms	• Unsuitable for viscous materials • Many factors affect accuracy of printing: deflection time, variables in temperature, time of valve opening	[41]

however, this study presented limitations in the lack of therapeutic assessment, hence was unable to establish the efficacy of 3D printed tablets.

Several studies have looked at the application of 3DP in paediatric populations. Liu *et al* [58] formulated 3D printed subdivided levothyroxine sodium tablets as an alternative method for the manual division of tablets. As a first line drug with a narrow therapeutic index, individual dosage needs must be fulfilled with absolute accuracy. Levothyroxine is commercially available in 25 μg, 50 μg, and 100 μg tablets. This study looked to produce 3D printed tablets ranging from 1/10 to 1/4 of the conventional 50 μg doses. Similar to that of Zheng *et al* physicochemical properties were determined, meeting the quality requirements of the Ph. Eur., Ch. P2015., and FDA's Industry Guidance. The tablets were then administered to 91 preterm infants in two hospitals in Guangdong, China, with hypothyroxinaemia. Results proved that 3D printed levothyroxine sodium tablets significantly elevated free thyroxine (FT4) levels of infants, subsequently decreasing thyroid stimulating hormone to reduce damage to the immature thyroid.

Another study conducted at the Clinic University Hospital in Spain highlighted the practicality of SSE in paediatric hospital patients aged 3–16 years, focusing on cases of maple syrup urine disease [59]. Personalised chewable isoleucine formulations using SSE incorporated six different flavours and colours, which were positively accepted by paediatric patients. Particularly in paediatric populations, the study recognised that children take special regard of flavour and colour, suggesting that catering to these preferences has the potential to improve acceptability and compliance. Furthermore, the mean isoleucine blood levels observed were within an optimal range of 200–400 μM, indicating effective control of the condition. The authors observed the SSE technique could potentially reduce formulation contamination, as printing occurred inside the enclosed print space, with the use of disposable build platforms and ink cartridges.

Finally, to address the challenge of patients' perceptions about medications, including taste, colour and flavour, Karavasili *et al* [60] developed cereal based dosage forms. Utilising cereal as a carrier for ibuprofen and paracetamol, hydrophobic and hydrophilic drugs respectively, the researchers aimed to enhance medication acceptability in paediatric and geriatric settings. The loaded ink pastes of 1:3 cereal powder to water ratio were loaded into a pneumatic system, facilitating the creation of diverse designs and shapes, notably 3D printed numbers and letters. Although not yet administered to patients, evaluation of physicochemical characterisation of the cereal inks yielded promising results. Integration of this design into breakfast enhances patient acceptance and adherence, potentially improving therapeutic outcomes.

3.1.3. Potential clinical applications of SSE

The gastro-floating system has become a method to prolong the gastric retention time of pharmaceutical formulations. SSE technology has evolved in creating such dosage forms to remain in the stomach for an extended period. For instance, Yang and Kim [21] introduced this system for famotidine, a commonly prescribed H_2 antagonist used in the treatment of dyspepsia and gastroesophageal reflux. In their study, tablets were successfully printed using the SSE system (figures 4(a) and (b)). Scanning electron microscopy was used to analyse the surface and internal

Table 4. Summary of oral formulations produced by SSE.

Formulation type	API (theoretical % w/w in filament)	Materials composition (theoretical % w/w in filament)	References
Immediate release	Aspirin (10%)	HPMC[a] 2910 (5%–15%), PEG[b] (75%–85%)	[49]
Immediate release	Carbamazepine (24%)	β-cyclodextrin[c] (72.1%), HPMC F4M (3.9%)	[50]
Immediate release	Ibuprofen (10%)	Gelatin[d], glycerine[e], MCC[f], mannitol[g], lactose[h], HPMC (%'s unknown)	[51]
Sustained release	Aspirin (10%)	HPMC 2208 (10%–20%), PEG (65%–75%), PAA[i] (5%)	[49]
Sustained release	Glipizide (1.7%, 2%, 2.3%)	HMPC (10%–30%), lactose (22.7%–43.3%), MCC (25%), PVP[j] (5%)	[52]
Sustained release	Efavirenz (25.5%), tenofovir (12.8%), emtricitabine (8.52)	Humic acid[k] (38.3%), polyquaternium 10[l] (12.8%), cellulose acetate phthalate[m] (2.04%)	[53]
Sustained release	Levetiracetam (23.4%)	PVA–PVP copolymer (15.9%–25.9%), HPMC (5%–15%), SiO_2[n] (10%)	[54]
Orodispersible	Carbamazepine (24%)	β-cyclodextrin (72.1%), HPMC F4M (1.4%), Ac-Di-Sol[o] (2.5%)	[50]
Orodispersible	Hydrochlorothiazide (40.4%)	Lactose monohydrate (18.2%), PVP 30 K (8.1%), Ac-Di-Sol (30.3%), banana flavouring essence (3.05%)	[55]
Orodispersible	Levocetirizine (10%)	HPMC (64%), pregelatinised starch[p] (10%), maltitol[q] (15%), sucralose[r] (1%)	[56]

[a] HPMC, hydroxypropyl methylcellulose (binder).
[b] PEG, polyethylene glycol (binder, plasticiser).
[c] Beta-cyclodextrin (complexing agent).
[d] Gelatin (binder).
[e] Glycerine (moisturiser).
[f] MCC, microcrystalline cellulose (filler).
[g] Mannitol (filler. diluent).
[h] Lactose (binder, diluent).
[i] PAA, polyacrylic acid (thickener).
[j] PVP, polyvinylpyrrolidone (hydrophilic polymer, binder).
[k] Humic acid (polyelectrolyte).
[l] Polyquaternium (polyelectrolyte).
[m] Cellulose acetate phthalate (binder).
[n] SiO_2, silicon dioxide (anti-caking agent).
[o] Ac-Di-Sol (disintegrating agent).
[p] Pregelatinised starch (filling agent).
[q] Maltitol (flavouring agent).
[r] Sucralose (flavouring agent).

structures of the tablets, particularly emphasising the layer-by-layer approach of 3DP (figures 4(c) and (d)). Interestingly, it was observed that the actual height of the printed layers was lower than the height layer set in the print parameters. This discrepancy can be attributed to the contraction of the hydroxypropyl methylcellulose gel during the drying process, therefore contributing to the shrinkage of tablet size. This finding highlights the importance of understanding material behaviour that can significantly influence the characteristics of the dosage form.

Orodispersible dosage forms address the issue of swallowing problems commonly encountered with paediatric and geriatric patients. Upon contact with saliva, the orodispersible film (ODF) is designed to dissolve or disperse. As the film disintegrates, the APIs embedded within are released, which can be absorbed through the mucosal membranes in the mouth. The conventional methods to produce ODFs include solvent casting, electrospinning, hot melt extrusion (HME) and most recently, SSE.

A feasibility study by Oblom *et al* [61] investigated 3D printed warfarin ODFs and oral powders in unit dose sachets. The prepared printing solutions consisted of warfarin sodium in hydroxypropyl cellulose (HPC) solution, with drug concentrations controlled by adjustment of film size. The ODFs were found thin and flexible, aligning with acceptable ODF properties. The accuracy of ODFs were shown to be superior to oral powders in the uniformity of content, proving the accuracy of this technique. It is noted that both forms have an advantage for hospital settings and are suitable for administration via nasogastric tubes. Additionally, the incorporation of a QR code printed onto the surface of the ODFs, containing dosage information, could help reduce the risk

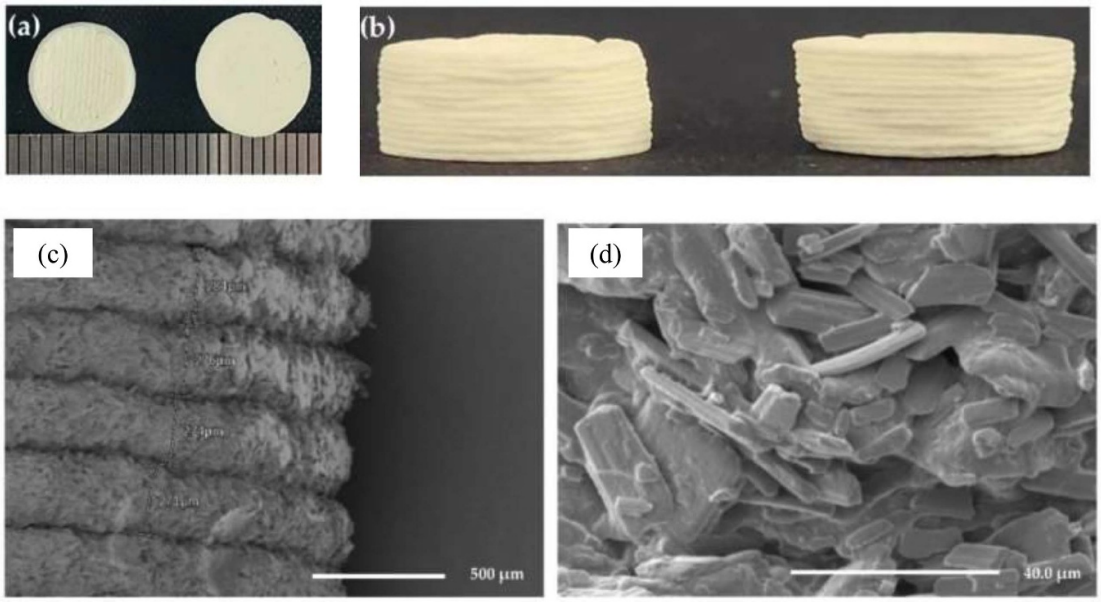

Figure 4. 3D printed famotidine tablets using SSE: (a) top view (b) side view (c), (d) scanning electron microscopy image of the tablets surface. Reproduced from [21]. CC BY 4.0.

of medication errors. Similarly, Sjöholm and Sandler [62] also developed ODFs infused with warfarin. A low standard deviation in drug content indicated that this method is suitable for narrow therapeutic index drugs. However, a drawback of this dosage form is the limited capability in delivering dosages with high drug strengths and delayed release behaviour, indicating a need for further research and development.

Local delivery systems have been developed to enhance drug delivery, particularly in conventional chemotherapy. Yi *et al* [63] introduced 3D printed patches, composed of poly(lactide-co-glycolide), polycaprolactone and 5-fluorouracil for the prolonged delivery of anti-cancer drugs. The patches were fabricated via pneumatic extruder at 600 kPa and 140 °C. Designed to release the drug over four weeks, the patches demonstrated promising therapeutic effects with significant tumour size decrease in *in-vivo* mouse models. This advancement has the potential to enhance or complement existing anti-cancer treatment options.

3.2. FDM

3.2.1. FDM mechanism and printing materials

FDM operates on the principle of ME and has been extensively documented across numerous industries [64–66]. FDM represents the most widely reported technique in pharmaceutical literature [67], gaining popularity from its simplistic and affordable process.

FDM involves pre-made thermoplastic filaments as feedstock [68]. The filament is loaded and pushed into a heated liquefier to a pinch roller mechanism for melting [69], where the printhead nozzle moves in three degrees of freedom to deposit molten filament. A physical object is constructed through successive layers as defined by the CAD model onto the fabrication platform. The reduction of its temperature allows for the solidification process. Once the first layer is deposited, subsequent layers can be extruded, until the 3D object is complete [69]. The principle of FDM is illustrated in figure 5. Whilst the regular FDM machine consists of a single nozzle, a subdivision of FDM is the dual-nozzle FDM system, enabling simultaneous printing of two filaments. Although the increased complexity of this system remains to be explored, there is the potential to increase the versatility of drug design and employ different drug release kinetics [70].

In pharmacy practice, there are currently three ways to incorporate an API into the filaments. (1) Impregnation: the filament is placed in an API containing solution or dispersion, allowing for passive diffusion of drug into filament [71]. (2) Print and fill: an empty shell is manufactured, followed by subsequently filling the shell with powder or liquid API and the continuation to encapsulate the shell to close the structure. (3) HME with FDM: API and excipients are added to a conveyor to be extruded through a hot orifice into a filament containing the API [25].

Compared to the other methods, the key advantage of HME is higher drug quantity and control of loaded filaments [72]. Further, HME has demonstrated the ability to increase water solubility of drugs by distributing low water-soluble APIs in hydrophilic polymers [73].

One major challenge of FDM in clinical practice is the need for high temperatures, which can degrade drugs and polymers. The HME with FDM process

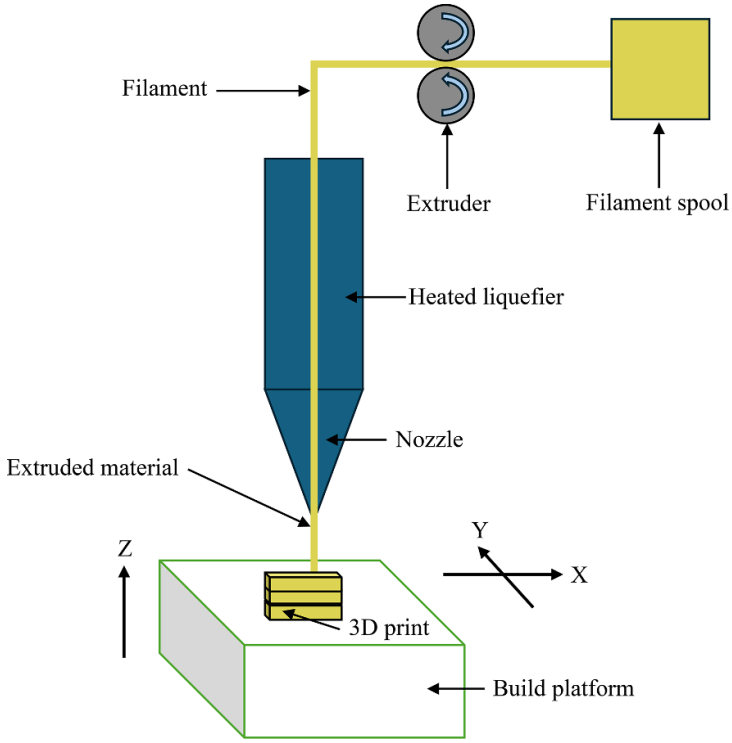

Figure 5. Basic schematic representation of the operation of a FDM system. Created with Microsoft Word.

has two temperature events, one during the HME filament production, and another during the 3DP process [74]. This can be problematic for thermally sensitive drugs. A survey by Cailleaux *et al* [25] noted that of 52 FDM 3D-printed tablets reviewed in the literature, 41 were extruded at temperatures ranging from 120 °C to 210 °C, while 43 were printed between 130 °C to 250 °C. Thermogravimetric analysis (TGA) of common excipients such as HPMC and PEG 400 showed that the decomposition of HPMC started at 250 °C, thus withstanding the typical HME temperatures. Conversely, PEG 400 began to lose weight at approximately 130 °C, indicating it may not be suitable for higher temperature processes [73]. In terms of APIs, take for example, ramipril, which has a melting point of 109 °C, demonstrated a mass loss at temperatures of 130 °C. This suggests the importance of choosing and testing thermally stable materials to be suitable for printing which is crucial for advancing FDM in drug product development and manufacturing [75]. Table 5 provides a summary of recent successful FDM-printed APIs using the HME method of drug loading.

3.2.2. Current applications of FDM in pharmacy

Based on the principles of 3DP, FDM has the potential to overcome conventional delivery forms. Despite its status as the technique most frequently documented in pharmaceutical literature, only one recent application in pharmacy practice has been recorded. Tagami *et al* [86] reported the development of suppositories, a common hospital practice for localised administration. The 3D printed hollow suppository shells could be loaded with model drugs, utilising a matrix of PVA and a biocompatible water-soluble polymer. Selecting ibuprofen as the model drug, this was injected into a half suppository shell via a syringe, before adhesive was used to close the suppository cap. A dissolution test was performed at 37 °C, where thickness and inner structure of the suppository shell correlated with rate of drug release. The authors also explored the potential for multiple shelled compartments to accommodate for poly-suppository formulations using ibuprofen and domperidone. The study highlights the high efficiency of on-demand printing, particularly beneficial in paediatric treatments in hospital settings. Despite the success of initial testing, *in-vivo* experiments are necessary to evaluate efficacy.

3.2.3. Potential clinical applications of FDM

While the application of FDM in pharmacy is currently limited, it still holds significant potential for clinical use. A polypill is a drug delivery system which contains multiple drugs. The polypill formulation offers two key benefits: the potential for customised formulations, and to address the problem of polypharmacy and pill burden. Pereira *et al* [84] offered a novel solution to create a polypill containing four model drugs: lisinopril, indapamide, rosuvastatin and amlodipine. This formulation aimed to improve medication adherence, particularly for patients who require single daily doses of cardiovascular medications, by reducing the need to take four separate tablets. The polypills were printed using

Table 5. Summary of material compositions produced by HME-FDM.

API (theoretical % w/w in filament)	Materials composition (theoretical % w/w in filament)	HME temperature (°C)	3DP temperature (°C)	References
Allopurinol (10%)	PVA[a] (75%), glycerol[b] (15%)	175	200	[76]
Caffeine (5%)	Kollidon[c] (28.5%), PCL[d] (57%), PEO[e] (9.5%)	140	150	[77]
Carvedilol (20%)	HPMC Affinisol 15LV (60%), Eudragit[f] RS PO (15%), Kolliphor[g] TPGS (5%)	110	180	[78]
Ciprofloxacin (10%–35%)	PVA, dibutyl sebacate[h] (%'s unknown)	175	195	[79]
Griseofulvin (30%)	HPC[i] (70%)	140	170	[80]
Haloperidol (15%)	Kollidon (74.5%), glutaric acid[j] (10.5%)	115	120	[81]
Isoniazid (30%)	HPC, HPMC, PEO, Eudragit, Kolliphor, TEC[k] (% vary)	120–155	165–195	[82]
Itraconazole (20%)	HPC (65%), PVP (15%)	135	185	[83]
Lisinopril (20%)	PVA (56%), sorbitol[l] (30%), TiO_2[m] (1%)	90	150	[84]
Theophylline (50%)	HPC (45%), triacetin[n] (5%)	120	120	[85]

[a] PVA, polyvinyl alcohol (polymer).
[b] Glycerol (plasticiser).
[c] Kollidon (hydrophilic polymer).
[d] PCL, polycaprolactone (use undetermined).
[e] PEO, poly-ethylene oxide (binder, plasticiser).
[f] Eudragit (polymer).
[g] Kolliphor (solubiliser).
[h] Dibutyl sebacate (plasticiser).
[i] HPC, hydroxypropyl cellulose (hydrophilic polymer).
[j] Glutaric acid (solubiliser).
[k] TEC, triethyl citrate (plasticiser).
[l] Sorbitol (plasticiser).
[m] Titanium dioxide (use undetermined).
[n] Triacetin (plasticiser).

multilayer structures. It was found that drugs on the outer layer released quicker than the two inner drugs, and as such, future research was proposed to refine the release profiles. In another example, McDonagh *et al* [87] engineered multilayer pills that support complex oral dosage forms with multiple release profiles. These dual-drug designs shown in figure 6(a), inspired by the polypills, enable both simultaneous and delayed release. The drug release profile in figure 6(b) concludes that the design of polypill layers and infill density can effectively control the release of API. This feature can potentially be adapted for tailored regimens where one drug layer is released once daily and another in a twice-daily schedule. Like the study by Pereira *et al* McDonagh *et al* also faced the challenge of generating specific profiles due to the design of a layered polypill.

Another study looked into the feasibility of hermetic capsule closure systems for creating enteric capsules [88]. Enteric capsules are less commonly compounded due to the time-consuming process; however, 3DP offers a more time efficient method of production. The work of Krause *et al* [89] explored the feasibility of a pressure controlled drug delivery system. The study used Eudragit® RS filaments to print empty capsule shells, which were subsequently filled with paracetamol as the model drug. The pressure sensitive system releases drugs directly into the small intestine due to the high pressure of the duodenum region. Another novel technique is the introduction of floatable tablets, with gastro-retentive floating systems to prolong the drugs release profile. For example, Windolf *et al* [90] combined the two techniques of polypill and gastro floating, creating the first floatable polypill with extended release of pramipexole, levodopa and benserazide for Parkinson's disease. The floatable tablets were designed to remain in the gastrointestinal tract longer, thereby reducing dosing frequencies.

3.3. DPE

3.3.1. DPE mechanism and printing materials

One of the main limitations of FDM is the need for filament preparation using HME. The use of HME increases the likelihood of chemical degradation, triggered by conditions such as elevated temperature, moisture, and excipient incompatibility [91, 92].

Attempts have therefore been undertaken to counter the need for filament preparation. Liu *et al*

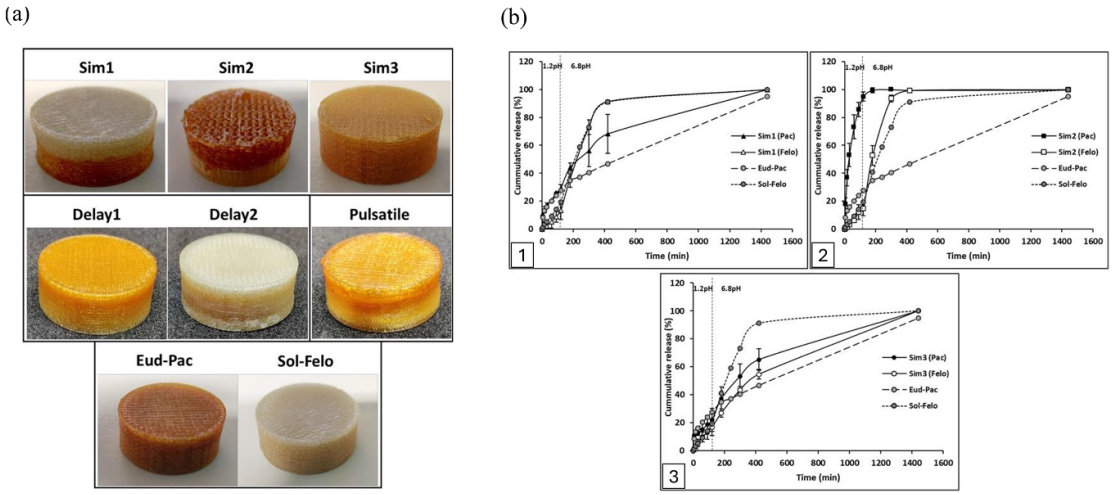

Figure 6. Images of multilayer pill profiles: (a) visual appearance of printed tablets and (b) *in vitro* drug release of immediate release dual-drug tablets. Reproduced from [87]. CC BY 4.0.

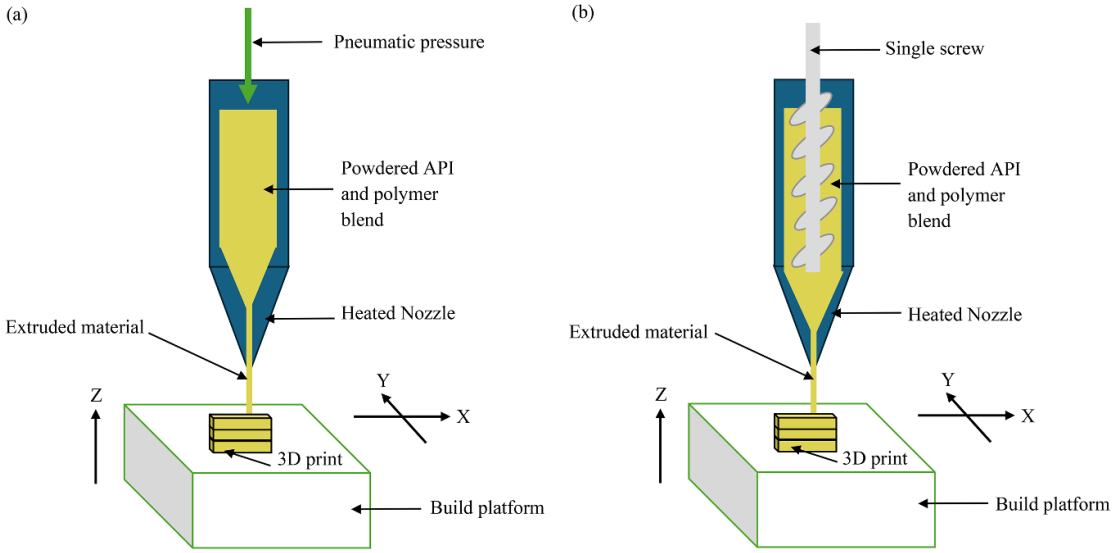

Figure 7. Basic schematic representation of the operation of a DPE system (a) pneumatically activated syringe (b) single screw extruder. Created with Microsoft Word.

[93] introduced a new 3DP system for the casting industry. This study was successful in producing large plastic moulds, starting from polymer pellet feedstock, and using a screw extrusion device. One of the main advantages observed was that the amount of processing equipment used was greatly reduced [94].

This technique, known as DPE is schematically illustrated in figure 7. A pellet or powder mixture containing the API and polymers are fed through (a) a pneumatically activated syringe or (b) the die of a single-screw extruder. This creates and deposits a fused extrudate onto the build platform [44]. The ability to directly print materials in powdered form overcomes the mechanical limitations of FDM filaments, increasing the number of excipients suitable for extrusion printing. However, the material's mechanical properties, including the powder flow significantly impacts the printing process, posing a challenge for hospital and community pharmacies to acquire granulated powders [95].

Goyanes *et al* [96] successfully demonstrated DPE to directly print tablets, using itraconazole as a model drug. The study emphasised the advantage of eliminating the preliminary HME step of FDM and the reduction of material wastage. Since material was directly printed from powder or pellet form, approximately 8 g of drug and excipients was needed, hence suitable for preclinical studies. TGA indicated that the API and excipients were stable, and there was no degradation of the drug at printing temperature.

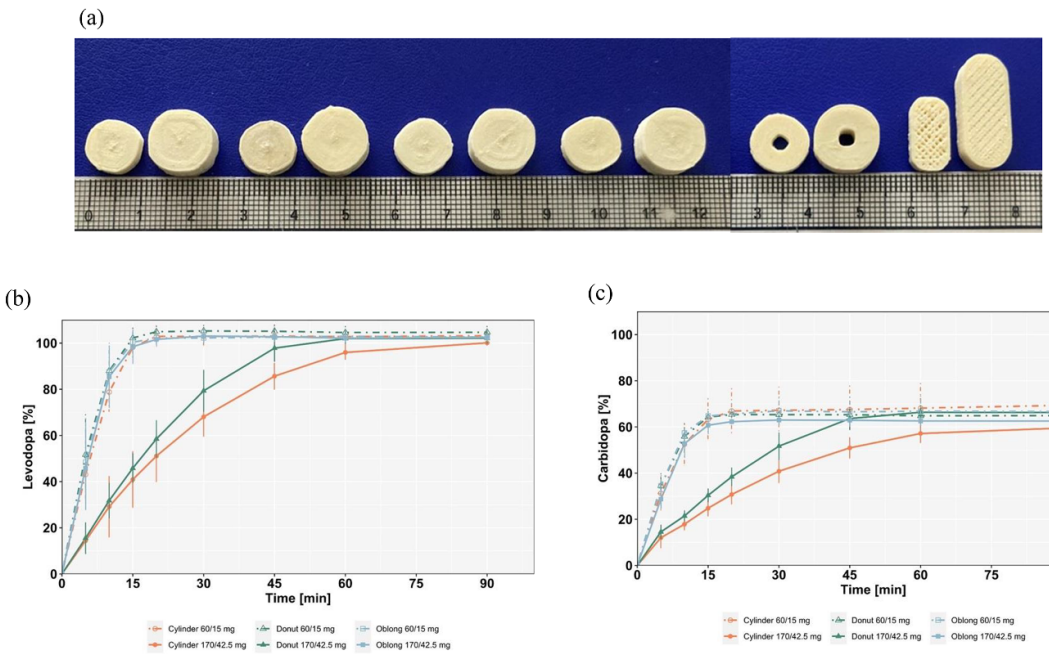

Figure 8. (a) Immediate release levodopa and carbidopa tablets of various shapes and sizes; dissolution profiles of (b) levodopa and (c) carbidopa. Reproduced from [97]. CC BY 4.0.

3.3.2. Current applications of DPE in pharmacy

Adopting the single screw DPE technique, Rosch *et al* [97] was the first to develop formulation and optimal printing processes for levodopa and carbidopa in a hospital setting. Arising from the need of variable dosing, patients with Parkinson's disease often require levodopa/carbidopa doses compiled from a combination of commercial drug products. 3DP provided the versatility of individualised doses whilst eliminating the necessity of fragmented split tablets. DPE was specifically chosen, to overcome the challenges of timely extemporaneous formulations. The powdered formulations consisted of levodopa, carbidopa, Kollidon®, Kollicoat®, and a plasticiser. The authors found this process to be cost efficient, using 50–100 g of powder blend for each batch, noting that small batches could be as low as 10 g. Figure 8(a) shows visual representation of the DPE printed tablets, including cylinder, donut and oblong shapes. Drug release tests concluded that more than 80% of levodopa could be released in 10 min (figure 8(b)). However, the major issue faced was the printing temperature. Levodopa was able to tolerate DPE temperatures of 180 °C, yet degradation of carbidopa was present even at 150 °C, thus the latter could not be printed, with only 60%–70% recovered after 90 min (figure 8(c)). Despite the feasibility of DPE printing in a hospital setting, *in-vivo* experiments remain to be explored to evaluate efficacy.

3.3.3. Potential clinical applications of DPE

Similar to the pharmaceutical developments of SSE, ODFs have also been produced by the DPE method. In 2023, Racaniello *et al* [98] created oral mucoadhesive films to deliver clobetasol propionate in the treatment of Oral Lichen Planus. Designed for the target population of paediatric patients, the printed films eliminate the need to swallow tablets. The DPE technique was chosen for the ability to use powdered feedstocks, which avoids the complications associated with filament-based printing methods. The *ex vivo* dissolution studies demonstrated gradual release of the drug, and exhibited high mucoadhesive properties that enhance adhesion to mucosal surfaces. The authors concluded that this technique offers a promising solution for paediatric therapies to improve patient compliance and treatment outcomes.

Wang *et al* [99] experimented with various core–shell geometries, to control the drug release behaviour. Although this experiment only used paracetamol as the model drug, the printing of the core–shell structure can be expanded to numerous other excipients. When compared to FDM filaments, drug loading was far greater in DPE, producing 40% high drug loaded tablets. The tablets were also found to consistently show zero order control release indicating the potential to prolong the therapeutic effect and avoid side effects.

Another novel innovation involved the creation of opioid medicines with abuse deterrent properties [100]. This study explored the potential of DPE to mitigate the challenges of opioid abuse, by developing tramadol formulations with alcohol resistant and abuse deterrent characteristics. The incorporation of HPC polymers enabled the print-lets (the proprietary name of 3D printed medicines) to achieve alcohol resistant properties in ethanol. Further, the study assessed the abuse potential by stimulating

intravenous administration, finding that approximately 20% of the drug could be extracted via dissolving in boiling water. This level of extractability suggested that the print-lets were moderately abuse resistant. Overall, the results of this study are promising, with abuse deterrent properties otherwise unachievable with conventional products. There is a possibility that this technique can be applied to other drugs with high potential for abuse including stimulants and depressants.

Drug delivery platforms are not only limited to oral forms. A recent study highlights that 3DP implants can provide localised and efficient controlled release of raloxifene [92]. Implants are typically manufactured using solvent casting, compression or injection moulding. DPE has proven to be equally as successful, enabling precise control of raloxifene through alteration of implant shape. This approach facilitates the personalisation of raloxifene patches for individual dosage requirements. Given the success of converting raloxifene into an implant, there is potential for other APIs to be delivered into similar patch-based systems. Although further research if required, engineering controlled release for these drugs could reduce the frequency of dosing and improve patient compliance.

4. Pharmaceutical 3D printers

Currently, the 3DP drug market is still at its developmental stage, with many printers and instrumentation not explicitly developed for pharmaceutical purposes. There is a need to design 3DP equipment specifically for pharmaceutical practice, taking into consideration quality control, precision, and good manufacturing practice (GMP) compliance.

4.1. FabRx

Established in 2014 by academics from the University College London (UCL), FabRx Ltd (UK) has revolutionised the manufacturing of medicines. In 2023, FabRx Ltd launched the M3DIMAKER 2 GMP printer, a multi-printhead system, expanding upon the single printhead M3DIMAKER 1 in 2020. The original printer was designed for small batch production of drug products for clinical trials, having currently been used in paediatric clinical studies [101].

The M3DIMAKER printers utilise ME, with an exchangeable printhead system to enable users to work with SSE, FDM, and DPE. Hence at the user's discretion, one head can be used for SSE, extrusion of a gel or paste under pneumatic pressure; the second head is switched for FDM, where API and excipients are combined in the extruder to produce a filament and placed into the printer; and the final head allows for the single stepped DPE process printing of powder mixes. Further, the M3DIMAKER system is equipped with online quality control procedures and camera monitoring, to detect progress of printing and faults during manufacturing. Most notably, the preparation of 28 print-lets can be carried out in approximately eight minutes using SSE, suggesting a quick turnover is achievable, particularly applicable in a fast-paced pharmacy practice environment [102].

4.2. Triastek

Triastek Inc. founded in 2015, is a pharmaceutical company based in Nanjing, China, credited with the MED® platform. Use of their novel MED® device has been implemented in clinical trials. Triastek received approval from the FDA for 3D printed 'T19', designed to treat rheumatoid arthritis [103]. The novel 'T19' design functions as a chronotherapeutic delivery system to maximise therapeutic effect according to the circadian cycle. A second product, 'T20', was approved for treatment of cardiovascular and clotting disorders [104]. Most recently in 2022, the company announced clearance of a third drug, 'T21', for colon targeted treatment of ulcerative colitis [105, 106]. Although still in its trial phase, this first in human study has promising findings, with 'T21' tablets demonstrating controlled and accurate delivery of drugs [107].

Other companies, including Exentis (Germany), MB Therapeutics (France) and Merck (USA) are working towards pharmaceutical printing; however, research findings have yet to be published, to the best of our knowledge.

5. Stakeholder reviews

Despite the extensive trials of different 3DP techniques, investigation into the acceptability and feasibility of implementing this technology into pharmacy practice remains scarce. Previous studies have emphasised the importance of stakeholders, particularly the significance of patient, doctor, and pharmacist views [2].

It is known that pharmacists have driven the advancement of 3DP in pharmaceutics, stemming from academics at UCL School of Pharmacy [108]. A survey conducted in the Netherlands revealed a shift towards a reduction in the number of compounding pharmacies because of higher costs and lack of space for compounding activities. Pharmacists expressed the lack of ability to sustain quality standards, with great emphasis in avoiding compounding unless necessary. When given the option of 3DP, pharmacists identified children and older individuals as the main population groups to benefit, for the tailoring of APIs and excipients. It was suggested by participants that the automated process of printing would be less laborious and time consuming, reducing the need to train staff on compounding processes. Despite the positive feedback, some respondents argued that the preparation of printing mixtures

and cleaning processes were time consuming, with a lack of evidence in operating processes [109].

The main concerns of 3DP in both pharmaceuticals and pharmacy practice centre on medication safety. Ensuring patient safety is the prime objective of healthcare professionals, with pharmacotherapy the most common therapeutic intervention to improve health outcomes [110]. In a qualitative study conducted by Rautamo *et al* in 2020 [111], 19 participants comprising physicians, nurses and pharmacists were interviewed through focus group discussions. The main concerns raised were surrounding the accuracy of printed materials, and whether the dosage forms would reach optimal therapeutic effects. Since the selection of materials and APIs suitable for printing is limited, coupled with a trial-and-error approach, the true impact of effectiveness and safety remains unknown. Although numerous experiments have concluded the accuracy of doses would meet standard pharmacopeia guidelines [112, 113], scepticism persists among healthcare professions, possibly due to the lack of *in vivo* studies [114].

Concerns about contamination and antimicrobial activity are particularly critical in drug production. Organic solvents, commonly used in preparing feedstock materials, are susceptible to microbial growth [115]. Take for example the impregnation method of incorporating an API into a filament for FDM—the filament is submerged in a solution or dispersion of an API and solvent mixture. Choices of solvents include, but are not limited to, ethanol, acetone and methanol [25]. The extended period during which the filament is submerged in the solvent mixture increases the risk of fostering microbial growth if proper sterilisation measures are not implemented. Further research is thus required to test and ensure that the final printed products are free from contamination.

6. Current trends and challenges of ME

The general trend established in the application of 3DP technology into healthcare practice identified four studies utilising SSE, while FDM and DPE were used in one study. Such interest in SSE was attributed to the advantages of this technology, particularly its simplicity in incorporating APIs directed with excipients for printing purposes. SSE operates at lower temperatures compared to FDM and DPE, making it more suitable for thermally sensitive APIs, given most pharmaceutical drugs degrade at the operating temperatures typical of 3D printers. The ability to operate printer speeds of up to 20 mm s^{-1}, surpasses other forms of 3DP resulting in time and cost savings [48, 116]. Additionally, use of disposable syringe and pre-filled cartridges eliminates chance of cross contamination [41]. Consequently, there exists the potential for small-batch manufacturing utilising SSE for pharmacy 3DP.

Whilst the benefits are evident, achieving an optimal printing process with SSE still requires careful consideration. Low resolution may compromise tablet accuracy, in exchange for the advantageous faster printing speeds [117]. Further, due to the semi solid nature of feedstock, the necessity of post print drying is required for structural stability, noting the direct correlation between viscosity of material and drying time. Less viscous material generally requires longer drying time, increasing the risk of structural collapse [22].

7. Advantages of pharmacy 3DP in personalised dosing

3DP holds the potential to personalise medication therapies, providing opportunities to patients and healthcare providers. This technology can significantly impact healthcare by producing small batches for personalised dosing. Owing to the portable size of 3D printers, these can be conveniently installed in community hospitals and pharmacies, nursing homes, and other point of care locations to facilitate on-site manufacturing.

3DP can enable the ability to titrate doses of medicines, particularly for drugs with a narrow therapeutic index, and those prone to adverse events on initiation and dosage increases. For instance, patients taking oral anticoagulants such as warfarin require careful monitoring of their international normalized ratio (INR) levels to manage thrombotic and bleeding risks [118]. Conventionally available in fixed-dose tablets (1 mg, 2 mg, 3 mg, and 5 mg), the introduction of 3D-printed tablets allows for precise calculation of warfarin doses tailored to achieve specific INR targets for individual patients. This fine-tuning of dosing is particularly critical for medications with narrow therapeutic indices like warfarin, where small changes in dose can significantly affect clinical outcomes [119].

Additionally, personalised titration of medicines can be applied on serotonin and noradrenaline reuptake inhibitors. These medications commonly cause serotonergic effects upon initiation. Starting doses can be initiated at lower than conventionally available strengths, with subsequent increases tailored to individual patient tolerance and therapeutic response. This approach allows for careful adjustment of dosage increments, ensuring optimal management of both efficacy and side effects throughout the treatment course [120]. Such personalised dosing strategies offer substantial benefits, particularly for certain populations such as paediatric and geriatric patients where precise dosing can significantly impact treatment efficacy and safety.

7.1. Paediatrics

The safety and efficacy of medications in paediatric populations continue to be critical areas of study

and concern [121]. Children are often more sensitive to pharmacotherapy, with physiological changes during childhood impacting the pharmacodynamics and pharmacokinetics of a compound [122]. A number of paediatric groups require individualised medication, including those necessitating high or low doses, patients with dysphagia, allergies, and multi-dosing regimens [121]. Several studies have focused on child-friendly formulations, including chewable isoleucine formulations and medications masked as cereal [59, 60]. However, due to the unavailability of paediatric dosages, existing commercial formulations are ground up and dispensed to meet the needs of children. Recently, Zhu *et al* [123] addressed this issue using SSE technology to meet this clinical demand. Commercially available propranolol tablets typically start at a minimum strength of 10 mg, with children needing 1/2–1/10 of a dose to meet their individual needs. This study showed favourable results to create 1, 2, 2.5 and 5 mg propranolol hydrochloride gummy chewable tablets. The gummy tablets were favoured by children due to different cartoon shapes, and drug content were within the range of 90 %–110%. Hence the authors expressed the clinical benefits of 3DP technology in achieving personalised medicine in paediatrics.

Children often show a preference for chewable tablets for several reasons that enhance their medication experience including appealing taste, convenience and sensory satisfaction. A visual preference study involving children aged 4–11 years compared placebo print-lets created using 3D printing technology. These print-lets were judged on visual appearance, texture, familiarity and taste. The study revealed a substantial majority (79%) of participants selecting the chewable SSE print-lets over non chewable print-lets. This preference solidifies children's strong preference for chewable forms of medication delivery, which can contribute to better adherence among young patients [124].

7.2. Geriatrics

For patients who have trouble swallowing, such as older adults or those with conditions like Parkinson's disease, orodispersible tablets produced by 3D printing offer a significant advantage. These tablets are designed to dissolve quickly in the mouth without the need for water, facilitating easier administration.

For example, FDM technology was found to be suitable in preparing oral dispersible aripiprazole films [125]. This study compared 3D printed HPC containing aripiprazole films and conventional solvent-cast films. It was found that the 3D printed HPC film fully disintegrated within 45 s, compared to 63 s for solvent-cast films. The faster disintegration time observed for the 3D printed HPC films may be attributed to the higher surface roughness, allowing for greater exposure of the film to the disintegration medium. This characteristic underscores the potential advantages of 3D printing in pharmaceutical film production, particularly in optimizing dissolution rates for improved medication delivery and patient compliance.

7.3. Polypill

The presence of comorbidities and multimorbidity is common, especially in geriatric populations [126, 127]. The use of 3DP is not limited to customised dosages and dosage systems, but also polypill combinations. Polypill formulations, containing multiple layers of APIs have emerged in recent years. The SLA process was utilised to fabricate a six-layered tablet containing a combination of paracetamol, caffeine, naproxen, chloramphenicol, prednisolone, and aspirin [128]. This study demonstrated the potential for manufacturing polypharmacy therapies to improve the probability of adherence. The authors demonstrated the efficiency of this method in fabricating high-resolution polypills without the risk of thermal degradation. Recently, this concept has been applied to FDM. Anaya *et al* [129] engineered a three-layered polypill consisting of nifedipine, simvastatin and gliclazide. However, further research is required to facilitate transition from experimental use to clinical practice. It is crucial to ensure that such combinations do not result in adverse reactions. Nevertheless, by combining multiple drugs, it is possible to reduce the impact of polypharmacy, lessening the burden of managing multiple medications whilst maintaining treatment efficacy.

7.4. Braille encoded dosage formulations

Individuals who are blind and visually impaired (BVI) are often subject to an increased risk of medication errors, particularly the inability to differentiate various types of medications following removal from packaging [130]. 3DP provides the necessary means to navigate the complexity of medication taking, by printing characters onto tablet surfaces.

Awad *et al* [131] integrated a novel approach, incorporating Braille and moon patterns on the surface of 3D orally disintegrating print-lets using selective laser sintering (SLS). The freedom in customisability offers the benefit of different shapes, as well as patterns inferring a medications name, dosage instructions or drug indication as per patient needs. A similar technique was applied to intraoral films using the HME with FDM approach. Participants of this study reported the clarity of Braille-encoded text in this approach exceeded that of the current standard of Braille text on pharmaceutical packaging [132]. This concept can aid the treatment of visually impaired patients in improving adherence and minimising medication errors.

Alternatively, 3DP can also be used to print three-dimensional medication labels for BVI individuals. Yijun and colleagues studied FDM methods in producing 3D medication labels to ease the drug

administration for BVI individuals [133]. Prototype designs were created using acrylonitrile butadiene styrene as the filament. The text was formatted in uppercase, using a regular font, with a letter spacing of 5 mm from centre to centre. The letters' elevation heights varied between 1 mm and 1.5 mm. A half sphere symbolized the medication dose unit, while vertical lines and a horizontal centre line with alternating arrowhead elevations indicated the frequency of administration and the timing of medication in relation to food. Medication identifiers were represented by symbols corresponding to target organs. Both healthy volunteers and BVI suffers have tested the medication labels.

8. Challenges and limitations of pharmacy 3DP

8.1. Lack of regulatory guidelines

As an emerging manufacturing technology, 3DP faces challenges for integration into the healthcare sector, particularly within the most strictly regulated pharmaceutical industry.

To date, the Food and Drug Administration (FDA) has issued guidance on the technical considerations of medical devices and prosthetics using AM [134]. However, comprehensive regulatory frameworks for 3D printed products intended for drug delivery have yet to be developed and are expected to be addressed in the foreseeable future. This regulatory gap poses challenges despite trials of 3D printed dosage forms in selected clinical practices. Unlike traditional pharmaceutical manufacturing methods, which adhere to established guidelines, 3DP introduces questions of material quality, printing accuracy and incorporation of APIs. Notably, while the FDA has approved the first 3D printed tablet, specific regulations or guidelines for 3D printed drug delivery systems have yet to be established.

Recently, the FDA formed the Emerging Technology Team (ETT) consisting of industry representatives including quality review and inspections programs to discuss and identify regulatory issues surrounding novel technology [135]. The ETT has provided a framework and objectives to sponsors developing new technologies. If their technology is accepted by the ETT, members will work to discuss, identify, and resolve technical and regulatory issues related to the development and implementation of the novel technology. The course of collaboration with the ETT, includes meetings between sponsors and ETT members, site visits, and integrated quality assessments and pre-license inspections. As of writing, 3D printing manufacturing is included as an example of accepted emerging technologies for small molecules [136].

8.2. Quality control

Another aspect of implementation is that qualification standards for 3D printer manufacturers do not currently meet GMP requirements. The safety of drugs is a crucial area of concern, primarily in maintaining quality control throughout the manufacturing process.

A study conducted by Bendicho-Lavilla *et al* [137] implemented an in-line analytical balance for automated mass uniformity testing. This integrated balance mechanism was compared with an external balance, and no significant differences were recorded. However, mass uniformity is only one aspect of quality control testing. Other critical parameters such as stability, dissolution rate, and content uniformity also play crucial roles in efficacy and safety. Integrating automated technologies within the printer can streamline the testing process, but comprehensive quality control measures must encompass all relevant factors to meet regulatory standards and ensure consistent product quality.

In a study by Diaz-Torres *et al* [48], an SSE 3D printer was configured with pressure sensors for material characterisation. The sensor was able to determine rheological properties of inks, temperature-dependent flow properties and viscoelastic behaviour, making it possible to identify the most suitable printing conditions. Therefore, the potential to control feedstock materials could facilitate an advanced 3D printing process for the future of personalized medicine.

8.3. Printing methods

One of the primary hurdles of 3D printers is that the ideal printer should be cost-effective and meet the clinical needs of various dosage forms. However, standard 3D printed products are not without their drawbacks. These methods experience issues such as void formation between successive layers, and defects in the shape and cracks in the final product, which can be attributed to inadequate processing conditions [43, 121]. To ensure precise and accurate printing, the printer's components, including the printhead, nozzle and liner, must be adapted to the characteristics of the drugs being produced.

For instance, in the FDM printing process, application of heat can cause structural damage to heat-sensitive drug formations. FDM commonly utilises temperatures of up to 220 °C [138]. Indeed, in many cases recorded, temperatures exceeding 120 °C have been observed to cause drug degradation, deterioration of mechanical properties, reduced physical stability, filament ageing and relatively low resolution of the 3D printed objects [139]. Methods that use filaments such as FDM are most likely to be subjected to formation of voids or incomplete layer bonding,

undermining the mechanical strength of the printed drug products. This method also faces challenges with filament flow consistency. Printing nozzle clogging has an undesirable effect in HME, which can disrupt the printing process and lead to inconsistent drug products. The term 'clogging' refers to the accumulation of a highly viscous polymer melt within the extrusion channel, blocking the flow of the polymer. Unfortunately, this process often occurs in HME, where low-viscosity polymer melt moves towards the top of the channel instead of the nozzle [140].

Moreover, despite the broad application of 3D printing technology across many fields, most machines currently used are not customized for pharmacy, causing functions to be unsuitable for medical use [121]. Owing to these drawbacks, 3D printing is still at a competitive disadvantage compared to traditional methods used in large-scale drug manufacturing.

8.4. Lack of personnel training

The current application of 3DP in the pharmacy field is still in developmental stages and operation of this technology requires a certain degree of specialisation. Across the medical field, it is acknowledged that the use of 3D printing, whether in medical equipment or bioprinting, requires professionals to maintain a high level of training and competence before effectively operating associated software and hardware [141]. This training extends beyond that for the operator of the machine, but also clinicians and other healthcare personnel who may be involved in the process. Despite the advancements in 3D printing technology, many clinicians and pharmacists lack experience in 3D printing drugs [2]. When 3D printed drugs enter mainstream use, there is the need for incorporation into university degree programs for the relevant healthcare personnel [120].

In the context of hospital settings, the integration of 3D printing technology for drug preparation and delivery introduces logistical challenges that must be addressed. There will need to be well-defined methods and protocols for managing the logistics of 3D printed medications, including considerations for efficient and timely delivery to ensure that patients receive their medications accurately and in a timely manner without unnecessary delay. This includes the establishment of effective systems for the coordination of production schedules, transportation, and inventory management to meet patient needs and maintain the quality of the medications produced.

Moving forward, stakeholders in the pharmaceutical industry, in conjunction with regulatory authorities and researchers, must collaborate to establish strong frameworks that facilitate the adoption of 3D printing in drug development and manufacturing. This collaborative effort will be pivotal in navigating technical and legal considerations to ensure patient safety and compliance. Figure 9 illustrates the most common 3D printing challenges in pharmacy practice.

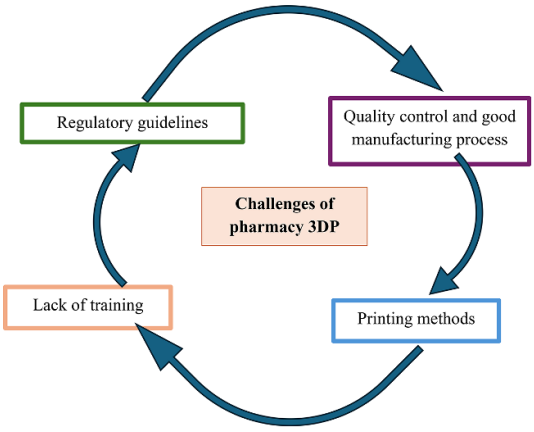

Figure 9. Challenges of pharmacy 3DP. Created with Microsoft Word.

9. Future directions

Although only three techniques of ME have thus far been implemented into pharmacy practice, other large-scale manufacturing technologies including BJ-3DP, SLS and SLA have demonstrated potential. In 2015, the FDA approved the first 3D printed drug, Spritam (levetiracetam), an orodispersible tablet created by inkjet printing [142], proving to be a significant step in industrial advancement of pharmaceutical manufacturing.

However, these technologies remain limited due to great costs of machinery and impracticality of large equipment for pharmacy practice. Taking binder jet printing as an example, machinery comprises several key components including build platform, print head, powder bed, powder feeding system, and binder supply system [33]. The extent of large components results in lack of portable equipment, posing a challenge for implementation in community and hospital pharmacies due to limited space.

With the prospect of introducing 3DP into hospitals and pharmacies becoming a reality in the near future, the training and education of healthcare providers, including pharmacists, physicians and nurses are necessary to deliver 3DP technology in a safe and efficient manner [111]. Moreover, the question remains surrounding the economic benefits of 3DP to the pharmaceutical industry. The cost associated with implementation of 3DP poses a significant barrier. While the economic benefits in large-scale manufacturing are evident, initial investment and ongoing maintenance expenses for small scale manufacturing can be substantial. Additionally, logistical costs, such as transportation and storage are unexplored. These factors require careful consideration of financial implications for the application of this technology.

Four-dimensional printing (4DP) has also begun to emerge, representing an advanced extension of 3DP technologies. 4DP builds on 3DP by incorporating the dimension of time. It involves the use of smart materials programmed to change shape, properties or function over time, in response to environmental stimuli such as temperature, humidity or pH. For example, a drug loaded device might release its medication only when a specific pH level is reached, or the release rate is adjusted based on patient specific data. In theory, all 3D printers could be adapted for 4DP [143]. The use of 4DP is still in its early stages, and the exploration of its delivery approaches is limited. However, there is significant potential for advancements in targeting temporal and spatial control of release.

10. Conclusion

3DP technology, particularly ME, has the potential to revolutionise pharmacy practice. The shift from mass manufacturing to producing flexible and personalised dosage forms has clear advantages for paediatric and geriatric populations. Indeed, SSE, FDM and DPE techniques have been demonstrated in preliminary studies, particularly in hospital pharmacy settings, to overcome challenges of tablet splitting, compounding and pharmacist errors. The ability to produce a wide range of delivery systems, from tablets to polypills and patches, 3DP can improve the effectiveness and adherence of medication use. As AM 3DP continues to evolve over the next decade, the capability to develop excipient compositions, customisable drug delivery forms and versatility in manufacturing requires pharmacy-based printers tailored to the requirements of GMP. With the continued emergence of 3DP processes for pharmacy practice, further studies should prioritise policies and guidelines to provide a framework of quality and safety policy as the technology transitions from theory to practical application.

11. Expert opinion

The ideal parameters for a 3D printer in pharmacy practice should align with specific requirements of GMP and be easy to use. For each ME printer, there will be varying degrees of optimal parameters. In general, the size of machinery should have an exterior size of less than 600 × 600 × 600 mm, and an interior working field ranging from 200 to 250 mm. Temperature control features are essential to prevent material degradation and ensure the stability of printed medications, ideally around 100 °C for SSE whilst up to 250 °C for FDM and DPE. An optimal syringe cartridge for SSE should accommodate up to 20 mL. For SSE, FDM and DPE, nozzle heads ranging from 0.4 to 0.8 mm in diameter are suitable, depending on print speed. The SSE process is most suited for blister packing, since up to 28 print-lets can be produced in 8 min, equivalent to a four-week supply of daily dosing. The needs of community pharmacies differ from those of hospital settings due to varying turnover rates and resource availability. Particularly for hospitals, the use of disposable syringe cartridge systems in SSE will help minimise cross contamination risks.

Data availability statement

The data of this study are available from the corresponding author upon request.

All data that support the findings of this study are included within the article (and any supplementary files).

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Conflict of interest

The authors declare no conflict of interest.

Authorship contribution statement

Jessica Cheng: Writing—original draft, Methodology, Investigation. **Edwin Tan:** Writing—review & editing, Supervision. **Lifeng Kang:** Writing—review & editing, Supervision, Conceptualisation.

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