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**Review**

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Review

# Recent progress in three-dimensionally-printed dosage forms from a pharmacist perspective

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## Abstract

**Objective** Additive manufacturing (AM), commonly known as 3D printing (3DP), has opened new frontiers in pharmaceutical applications. This review is aimed to summarise the recent development of 3D-printed dosage forms, from a pharmacists' perspective.

**Methods** Keywords including additive manufacturing, 3D printing and drug delivery were used for literature search in PubMed, Excerpta Medica Database (EMBASE) and Web of Science, to identify articles published in the year 2020.

**Results** For each 3DP study, the active pharmaceutical ingredients, 3D printers and materials used for the printing were tabulated and discussed. 3DP has found its applications in various dosage forms for oral delivery, transdermal delivery, rectal delivery, vaginal delivery, implant and bone scaffolding. Several topics were discussed in detail, namely patient-specific dosing, customisable drug administration, multidrug approach, varying drug release, compounding pharmacy, regulatory progress and future perspectives. AM is expected to become a common tool in compounding pharmacies to make polypills and personalised medications.

**Conclusion** 3DP is an enabling tool to fabricate dosage forms with intricate structure designs, tailored dosing, drug combinations and controlled release, all of which lend it to be highly conducive to personalisation, thereby revolutionising the future of pharmacy practice.

**Keywords:** 3D printing; dosage form; oral drug delivery; transdermal; implant; pharmacist

## Introduction

The growing and evident application of additive manufacturing (AM), also known as 3D printing (3DP), can be observed in its advancement into wide-ranging industrial sectors such as architecture,[1, 2] aviation,[3] culinary[4] and even in challenges posed by the current pandemic time of coronavirus disease 2019 (COVID-19).[5, 6] The historical breakthrough of 3DP was started by Charles Hull on the developing novel 3DP process, stereolithography. The University of Texas, Massachusetts Institute of Technology, Stratasys Ltd and other companies worked collaboratively to develop other 3DP techniques at around the same time. Scott Crump patented fused deposition modelling (FDM) printing process in 1989, which involves the heating and deposition of printing ink to form a desired structure. Fast forward to the present, there has been a rapid development of AM technology, such as powder bed fusion, material jetting and direct energy deposition.[7] Each of the printing processes has its own advantages and disadvantages as summarised in Table 1.

In pharmaceutical manufacturing, the current biggest roadblock is the limited ability to fabricate products with complex geometry and design for specific uses such as controlling drug release kinetics and site-specific drug release. Compared with the traditional manufacturing process, AM can overcome these problems and offers unique advantages. In addition, the traditional manufacturing process is inflexible in providing personalised customisation, as it offers mass-produced products for the public. Interpatient variability in therapeutic responses and toxicities is well documented, which is considered suboptimal patient care. AM allows the manufacturer to fabricate specific dosage forms to cater to the special needs of paediatric, geriatric or dysphagic patients.[8]

In the past, 3DP was popular among architects and designers to fabricate models and used for fast prototyping, due to the ease and cost of manufacturing. Currently, AM is becoming more accessible with the expiry of earlier patents and the availability of a variety of 3D printers, thereby allowing researchers and manufacturers to utilise this technology. The accessibility of 3DP in hospital and community pharmacy settings is further broadened with the rising affordability of 3D printers.[9]

To show the growing interest in 3DP in the pharmaceutical world, we charted the breakdown of the papers published for 3DP applications in the development of dosage forms (Figure 1). As observed from the bar chart above, there is a steady increase in the papers published in drug delivery and 3DP from

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**Table 1** The seven categories of AM defined by the American Society for Testing and Materials

| Type | Materials | Advantages | Disadvantages |
|---|---|---|---|
| Binder jetting (BJ): a liquid bonding agent is selectively deposited to join powder materials (e.g. 3D inkjet technology) | Polymers<br>Ceramics<br>Composites<br>Metals<br>Hybrid | Free of support<br>Design freedom<br>Large build volume<br>High print speed<br>Relatively low cost | Fragile parts with limited mechanical properties<br>May require postprocessing |
| Directed energy deposition (DED): focussed thermal energy is used to fuse materials by melting as they are being deposited (e.g. laser deposition, electron beam, plasma arc melting) | Metals<br>Hybrid | High degree control of grain structure<br>High-quality parts<br>Excellent for repair applications | Conflicts in surface quality and printing speed |
| Materials extrusion (ME): material is selectively dispensed through a nozzle or orifice (e.g. FDM) | Polymers<br>Hybrid<br>Metals<br>Composites | Widespread use<br>Inexpensive<br>Scalable<br>Large range of materials | Vertical anisotropy<br>Step-structured surface |
| Materials jetting (MJ): droplets of build material are selectively deposited (e.g. 3D inkjet technology, direct ink writing) | Polymers<br>Ceramics<br>Hybrid<br>Biologicals | High accuracy<br>Low waste<br>High compatibility | Support material is often needed<br>Conflicts in speed and resolution |
| Powder bed fusion (PBF): thermal energy selectively fuses regions of a powder bed [e.g. electron beam melting (EBM), select laser sintering (SLS)] | Metals<br>Ceramics<br>Polymers<br>Composites | Relatively inexpensive<br>Small footprint<br>Large range of material options | Conflicts in speed and quality<br>High power needed<br>Powder residue |
| Sheet lamination (SL): sheets of material are bonded to form a part [e.g. laminated object manufacturing, ultrasound consolidation (UC)] | Polymers<br>Metals<br>Ceramics<br>Hybrids | High speed<br>Low cost | Vertical quality depends on adhesive used<br>Limited materials |
| Vat polymerisation (VP): liquid photopolymer in a vat is selectively cured by light-activated polymerisation [e.g. stereolithography (SLA) and digital light processing (DLP)] | Polymers<br>Ceramics<br>Biologicals | Excellent resolution and surface quality | Limited materials<br>Relatively expensive |

2015 onwards, and we are projecting a higher increase in the number of published papers from 2021 onwards.

This work is aimed to provide a timely update of the recent applications of 3DP in the year 2020 specifically, which has observed a rapid increase with ~100 publications (**Figure 1**). Several reviews on this topic had been published previously but might be challenging for healthcare professionals to read, as the reviews were more focussed on technical aspects, such as machinery and materials.[7, 10] This may pose a barrier for the implementation of this technology as there is a gap between the researcher and end-user. Thus, our objective is to introduce and educate them about the applications of 3DP from the perspective of a pharmacist, providing a simple and methodical examination in a variety of printed dosage forms. We hope to empower healthcare professionals to utilise this disruptive technology in their practice, optimise the current technology and even cultivate new research directions.

In this review, we identified relevant articles by searching through the databases, including PubMed, Excerpta Medica Database (EMBASE) and Web of Science. The keywords that we have identified to gather the relevant articles are 3DP, additive manufacturing and drug delivery. The articles included in this review must be in English and published from January 2020 to December 2020. The reasoning behind such a time frame was that our group had published extensive reviews on drug delivery and drug testing applications of 3DP in 2018 and 2020.[11, 12] Both reviews covered the major aspects of various 3DP dosage forms before 2020, although not specifically from the pharmacist perspective. Interested readers are referred to these references for details. Based on these inclusion and exclusion criteria, we identified the articles that fit in this review and removed duplicates. The articles were analysed and tabulated to show the type of printer, the drug and materials used to fabricate each type of dosage form (Tables 1–17). The tables are arranged separately to help the readers to review the contents easily depending on the type of dosage forms and its subsections that they are interested in.

## Oral Drug Delivery

### Gastroretentive

Targeted drug delivery to a specific organ is desirable in many disease states, such as Crohn's disease and ulcerative colitis.[13] Gastroretentive dosage forms have a prolonged retention time in the stomach. The increased gastric residence time allows drugs to be better absorbed the stomach, therefore increasing the drug bioavailability. To this end, several studies have been conducted to fabricate tablets with complex structures, which increased the retention time of the tablets. In this section, we examined the development of the gastroretentive tablet for targeted drug delivery using AM (Table 2).

Chen *et al.* fabricated an ellipsoidal tablet with gastrofloating ability by controlling its infill density.[19] Infill density is a parameter that can be defined as the amount of printed region within the object as shown in Figure 2A.[15, 18] With complex design and low infill percentage, which reduced the overall density of the tablet, the tablet can float in the stomach for

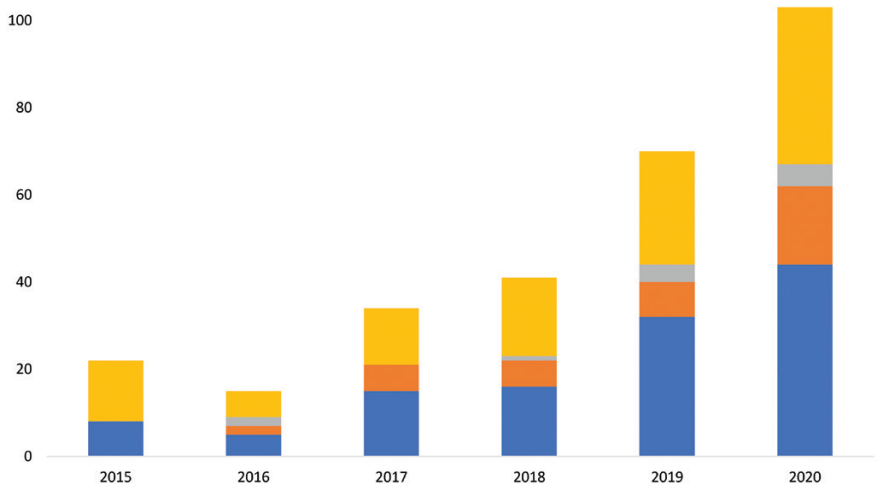


**Figure 1** The bar chart represents the publication trends of 3DP research on various dosage forms including tablet, capsule, film, transdermal patch, suppository, pessary and implants. The data were obtained by searching major databases [PubMed, Excerpta Medica Database (EMBASE) and Web of Science] from 2015 to 2020, using keywords such as 3D printing, additive manufacturing and drug delivery.

**Table 2** Type, drug and material of gastroretentive dosage forms

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| FDM (ANET-A8) | Theophylline | HPC, SA | [14] |
| FDM (Prusa i3) | Theophylline | HPC, EC | [15] |
| FDM (Raise 3D N2) | Baclofen | PLA | [16] |
| DLP (Envision Tec Micro Plus High-Res) | – | PVA | [17] |
| FDM (Ultimaker S3) | Ibuprofen | HPMC-AS polymers | [18] |
| FDM (FilaBot) | Propranolol | PVA | [19] |
| FDM (Prusa i3) | Cinnarizine | HPMC, Kollidon VA64 | [20] |

Abbreviations: DLP, digital light processing; EC, ethyl cellulose; HPC, hydroxypropyl cellulose; SA, stearic acid.

an extended period.[19] Instead of controlling the infill density, Vo *et al*. demonstrated the possibility of improving floating kinetics by manipulating the other printing parameters, such as shell-thickness. The combined methods of controlling infill percentage and shell thickness can also be used to fabricate gastroretentive tablets.[14, 15] Despite its effect on drug dissolution kinetics, controlling infill density must be taken into careful consideration as it can also affect the mechanical characteristics and printability of the tablet.[18–20] However, it was possible to optimise these parameters using a regression model to achieve the necessary qualities of an AM tablet.[20]

Furthermore, it was possible to produce a gastroretentive tablet by not controlling its inner content as demonstrated by Vaut *et al*. In their investigation, they developed controlled-release oral dosage forms with varying anchor-like surface for intestinal retention and controlled orientation (Figure 2B). It was shown that the increased tensile and flow retentive mucoadhesive characteristic with the unidirectional release of drugs improved the tablet performance in targeted release in the stomach.[17] In addition, a novel method of producing a gastroretentive tablet was through the development of an outer layer that encapsulates the tablet (Figure 2C). The method improved the tablet's buoyancy and the drug release kinetics. The floating ability and drug dissolution were independent of each other, which meant that they can be optimised separately to their specific requirements.[16]

## Buccal adhesive

Instead of targeting the stomach, many studies had been carried out to exploit the buccal mucosa as a targeted site for drug delivery, for example, nicotine replacement therapy, and fungal and periodontal diseases.[21] This method of administration is advantageous either as localised treatment or as systemic treatment because the drugs would bypass the first-pass metabolism in the liver. In addition, mucoadhesive buccal films have a longer residence time in the mouth and are not easily washed down by saliva when compared with oral gel and ointment.[22] Regarding the oromucosal films, Tian *et al*. had published an extensive review that covered patient centricity to the production process. The authors highlighted the novel production techniques of pharmaceutical inkjet printing and 3DP, FDM and semi-solid extrusion approaches.[23]

Eleftheriadis *et al*. fabricated mucoadhesive buccal films containing medications such as ibuprofen, ketoprofen and lidocaine hydrochloride with a unique approach. The production process consisted of a two-step process, where the backing layer of buccal films was printed using an FDM printer to allow the unidirectional release of medications to the buccal mucosa.[24, 25] This approach streamlined the manufacturing process of mucoadhesive buccal films as they do not require multistep printing processes and are suitable in printing thermolabile active pharmaceutical ingredients (APIs), unlike the conventional methods.[26] The group bypassed the temperature

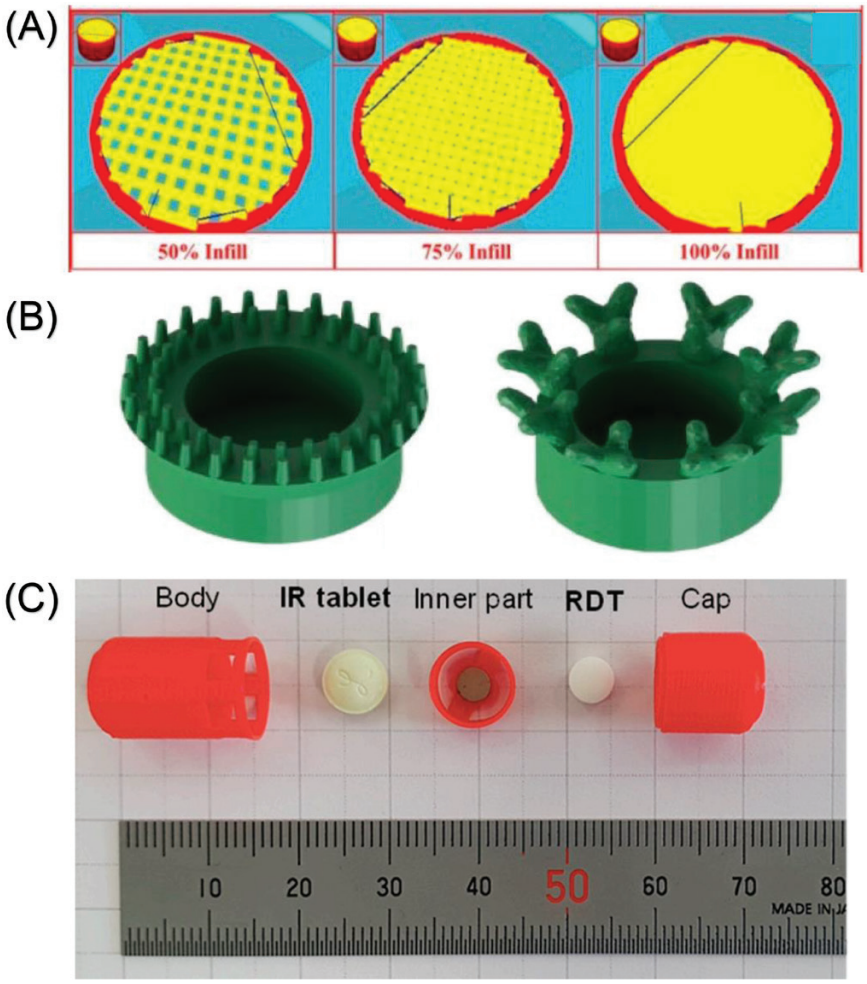


**Figure 2** (A) Circular-shaped gastroretentive tablets with varying infill percentages from 50 to 100%.[15] (B) Anchor-like surface designs of drug reservoir.[17] (C) Capsular device to encapsulate commercially available tablet for gastroretentive and sustained drug release.[16]

limitation of the FDM approach using inkjet printing to successfully load the medication onto the FDM-printed films while minimising API degradations. The mucoadhesive films exhibited satisfactory mucoadhesion, residence time and release characteristics[24, 25] (Table 3).

## Immediate release

Various drug release rates such as constant, linear, increasing, decreasing and pulsatile are important as they have wide-ranging uses in drug delivery.[30] In an emergency setting, a fast-dissolving formulation is favoured because it allows a swift onset of action compared with sustained drug release. Hussain *et al.* prepared fast-dissolving tablets containing captopril to be used for hypertensive crisis. The incorporation of sodium starch glycolate and croscarmellose sodium as disintegrant improved the tablet dissolution significantly. The tablets containing both excipients showed almost complete drug release in 20 min when compared with tablets without those excipients.[31] There are other studies that utilised formulation methods to improve tablets disintegration leading to rapid release.[32, 33]

Instead of incorporating different excipients, it is possible to affect the tablet dissolution by exploiting the tablet geometry and structure. Cui *et al.* utilised semi-solid extrusion to fabricate tablets with high levetiracetam loading, up to 96% (w/w) without manipulating the tablet formulation. In this study, the authors accelerated the drug unloading rate by fine-tuning the lattice cell size, which affected the tablet's infill percentage. The most significant drug dissolution was achieved by having a 50% infill percentage; the torus-shaped tablets exhibited almost 100% drug release in less than 2 min.[34] Furthermore, immediate-release tablets can be produced by manipulating the crystal polymorphism with different printing materials.[35]

The development of the 3D-printed (3DP) orodispersible film has increased rapidly since our last reviews.[11, 12] Yan *et al.* developed customisable orodispersible film based on hydroxypropyl cellulose. The printed films exhibited favourable wetting property, which is beneficial in achieving swift disintegration.[36] Cho *et al.* developed a single-step printing process for manufacturing orodispersible film loaded with olanzapine in polyethylene oxide (PEO), using the same semi-solid extrusion approach as the previous group. In this study, the authors investigated a wide range of plasticisers such as Kollidon VA64, Kolliphor P407 and Kolliphor P188 to determine the suitability of printing performance and dissolution characteristics. Among all the plasticisers, the formulation containing Kolliphor P188 was deemed the best as it had the fastest dissolution with slightly better mechanical strength, which are desired qualities for drug handling and transportation[27] (Table 4).

**Table 3** Type, drug and material of buccal adhesive dosage forms

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| PE (ROKIT INVIVO) | Olanzapine | PEO | [27] |
| SE (Biobot 1, Bocusinin and Zmorph) | Prednisolone | PEO, HPC | [28] |
| SE | Ibuprofen, paracetamol | PCL | [29] |
| FDM (MakerBot Replicator 2X) and inkjet printer (Canon) | Ibuprofen | HPMC | [25] |
| FDM (MakerBot Replicator 2X) and inkjet printing (Canon MG2950) | Ketoprofen, lidocaine | HPMC | [24] |

Abbreviations: HPC, hydroxypropyl cellulose; PE, pneumatic extrusion; PEO, polyethylene oxide; SE, syringe extrusion.

**Table 4** Type, drug and material of rapid release dosage forms

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| FDM (ZMorph 2.0) | Itraconazole | PVA, Kollidon VA64, CL-M | [35] |
| FDM (MakerBot Replicator 2X) | Paracetamol | PVA | [31] |
| FDM (MakerBot Replicator 2X) | Paracetamol | PVA | [33] |
| FDM (MakerBot Replicator 2X) | Carvedilol, haloperidol | PVA | [37] |
| SE (BioScaffolder) | Levocetirizine HCL | HPMC | [36] |
| Binder-jet printing (660 CJP Pro) | Indomethacin | CSH, LM | [32] |
| SE (MAM II) | Levetiracetam | HPMC | [34] |

Abbreviations: CSH, calcium sulfate hemihydrates; LM, lactose monohydrate; SE, syringe extrusion

## Controlled release

Controlled release of medications refers to the approach to release small amounts of the drug after being administered to humans, over a prolonged period. It is also known as sustained release, prolonged release or extended release. The aim of achieving controlled release is to maintain a steadier drug concentration in blood and reduce the frequency of administration, which, consequently, lead to reduced dosing frequency and improvement in the therapeutic effectiveness of the medication.[14]

One way to attain sustained delivery is to adjust the formulation of the tablet.[38–40] Nevertheless, formulation changes do affect the tablet's printability. It was found that a higher concentration of methylcellulose increased the hardness and reduced the adhesiveness, springiness and cohesiveness of the feeding material, thus reflecting a low breaking force of the tablet and poor extrudability in the printing process.[38] Unlike methylcellulose, hydroxypropyl methylcellulose (HPMC) K4M and E4M had minimal effect on cohesiveness and springiness of the printing materials.[39] Tan *et al*. utilised the same approach in designing tablets with sustained release profiles. They found that the tablets with higher Eudragit composition had slower drug release. Moreover, incorporating Eudragit improved the plasticity and smoothness of printing filament, thus improving the dosage forms' printability.[41]

The effect of tablet design on drug-release behaviour has been identified and described in many previous papers.[42, 43] Clark *et al*. demonstrated tablet geometry on sustained drug delivery by constructing tablets with varying shapes such as cylinder, film, ring and mesh. The release for carvedilol ranged from 10 h to more than 20 h depending on the shape of the 3DP tablet. The difference in the release rate for a cylindrical-shaped tablet when compared with film- and ring-structured tablets can be explained through the changes in surface area to volume ratio.[43] In addition, Stanojević *et al*. demonstrated the effect of tailoring drug release by varying tablet thickness and drug loading using artificial intelligence. Similar results were obtained, where the tablet dissolution rate can be controlled by changing these parameters.[44] Similar to producing gastroretentive tablets, infill density manipulation was utilised as an effective method to prolong drug release. However, it is crucial to note that an increase in infill density with HPMC inversely affected the percentage of drug release as observed from the experiments and kinetics modelling.[18]

The development of a tablet with an insoluble shell that controls the drug release of the inner core removes the need to reformulate the composition of excipient as observed in the work done by Fina *et al*. (Figure 3). This insoluble shell acted as a rate-limiting step in the drug release process, where PEO formed a hydrogel upon absorbing water from the surrounding. This viscous environment allowed slow diffusion of the drug from the tablet into the dissolution medium ranging from 16 to 48 h *in vitro*.[45] Likewise, the insoluble shell can be further modified with cellulose acetate and d-mannitol as rate-controlling polymer and pore-forming agent, respectively, at a different ratio to control dissolution.[46]

A novel method of developing controlled release involves forming a separate outer layer that encapsulates a tablet, thus negating the time and cost for the formulation development.[16, 47] This method allowed a commercially available immediate-release tablet to be modified into a customisable release rate. This method would broaden the frontier of personalisation of medication in the compounding pharmacy setting. In addition, the ease of changing the printing parameters made this technique more practical for pharmacy applications (Table 5).

## Multiple-drug formulation

The concept of incorporating multiple drugs in a single tablet has been an attractive idea for drug administration. Currently,

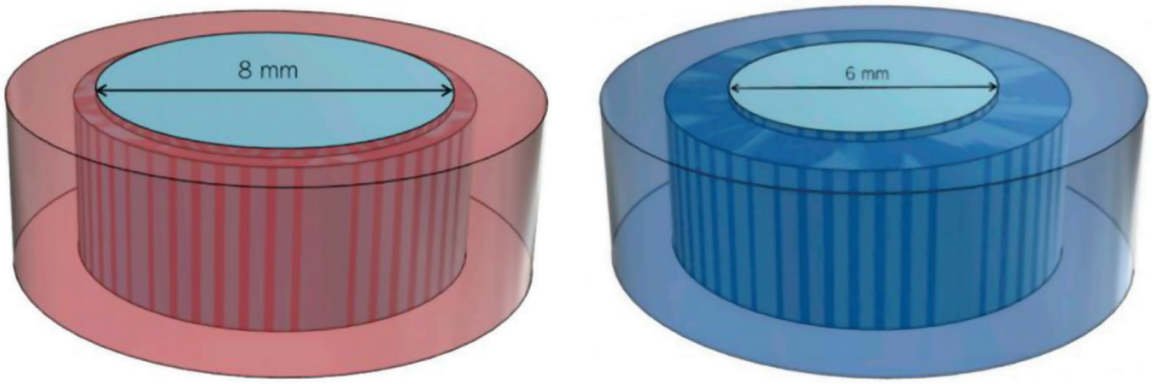


**Figure 3** The wide-ranging geometrically complex designs to achieve controlled-release profile oral drug dosage forms with different thicknesses of the insoluble shell.[45]

**Table 5** Type, drug and material of controlled-release dosage forms

| Type of printer | Drug | Materials | Reference |
|---|---|---|---|
| FDM (Flashforge Creator Pro) | Nifedipine | PVA, PLA | [48] |
| SE (Biobot 1) | Propranolol HCL | Cellulose acetate | [46] |
| DLP | Atomoxetine hydrochloride | PEGDA 700, PEG 400 | [40] |
| FDM (Prusa i3) | – | EC and HPMC | [49] |
| SE (VElleman K8200) | Theophylline | MC A4M | [38] |
| FDM (MakerBot Replicator 2X) | Theophylline | HPC, Eudragit, PEG | [41] |
| SLA (Anycubic Photon) | Ascorbic acid | PEGDMA | [42] |
| FDM (Prusa I3) | Sodium cromoglicate | PVA | [47] |
| FDM (MakerBot Replicator 2X) | Paracetamol | HPC | [45] |
| SE (Velleman K8200) | Theophylline | HPMC (K4M and E4M) | [39] |
| DLP (Wanhao Duplicator 8) | Atomoxetine | PEGDA, PEG 400 | [44] |

Abbreviations: DLP, digital light processing; EC, ethyl cellulose; HPC, hydroxypropyl cellulose; PEGDA, polyethylene glycol diacrylate; SE, syringe extrusion; SLA, stereolithography.

there are several such medications used in clinical practice (e.g. Starpill tablet, Polycap capsule and Trinomia capsule).[50, 51] This strategy has been proved successful in improving medication adherence and therapeutic outcome for cardiovascular health management, as demonstrated in multiple clinical trials.[52–54] Recently, the concept has been further developed by using various AM technologies.

Wei *et al.* printed tablets containing haloperidol and carvedilol using the FDM method. The tablets dissolved completely in 60 min, indicating that the polymer polyvinyl alcohol (PVA) was useful for fabricating immediate-release tablets containing multiple drugs.[37] The current development of AM even allows the development of customisable drug release for each active ingredient (Figure 4A). For example, the fabrication of regular- and inverted triangular-shaped sections in a tablet containing different medications possessed increasing and decreasing drug profile consecutively. Similarly, Tan *et al.* achieved the combination of constant release with a pulsative release through fabricating 'I'-shaped tablets. The experimental result was shown to be well correlated with the theoretical simulation.[30]

The AM technology has also been applied for fabricating a novel dosage form of a Traditional Chinese Medicine, by Wang *et al.* The herbal medicine is comprised of seven different types of plant extracts, namely *Aspongopus chinensis* Dallas, *Pericarpium citri reticulatae*, *Pseudostellaria heterophylla* (Miq.) Pax, *Dioscorea oppositifolia*, *Ziziphus*, barley and *Amomum villosum*. The conventional production method used to prepare this medicine faces challenges owing to the instability of the active ingredients. Using screw-driven extrusion to prevent the loss of some unstable active ingredients, they fabricated tablets with diverse shapes. In addition, the newly developed process complied with the regulatory guidelines of the Chinese Pharmacopoeia 2015 edition.[56]

Pereira *et al.* fabricated capsules to encapsulate multiple drugs to accommodate complex therapeutic regimens, thus overcoming poor adherence in patients with polypharmacy issues. The capsules had two different formats such as concentric and parallel, based on the required drug release patterns (Figure 4B). On the one hand, the parallel format allowed the immediate release of two drugs and the extended release of the other two drugs. On the other hand, the concentric format allowed the sequential release of two drugs, followed by the delayed release of two other drugs. In the capsule design, the drugs were separated in different compartments to minimise potential incompatibility of drugs and excipients, which is a known issue in drug formulations.[57] The capsules showed promising dissolution results for control drug release.[55] Similarly, Yu *et al.* developed an extrusion-based process to allow the rapid production of capsules containing

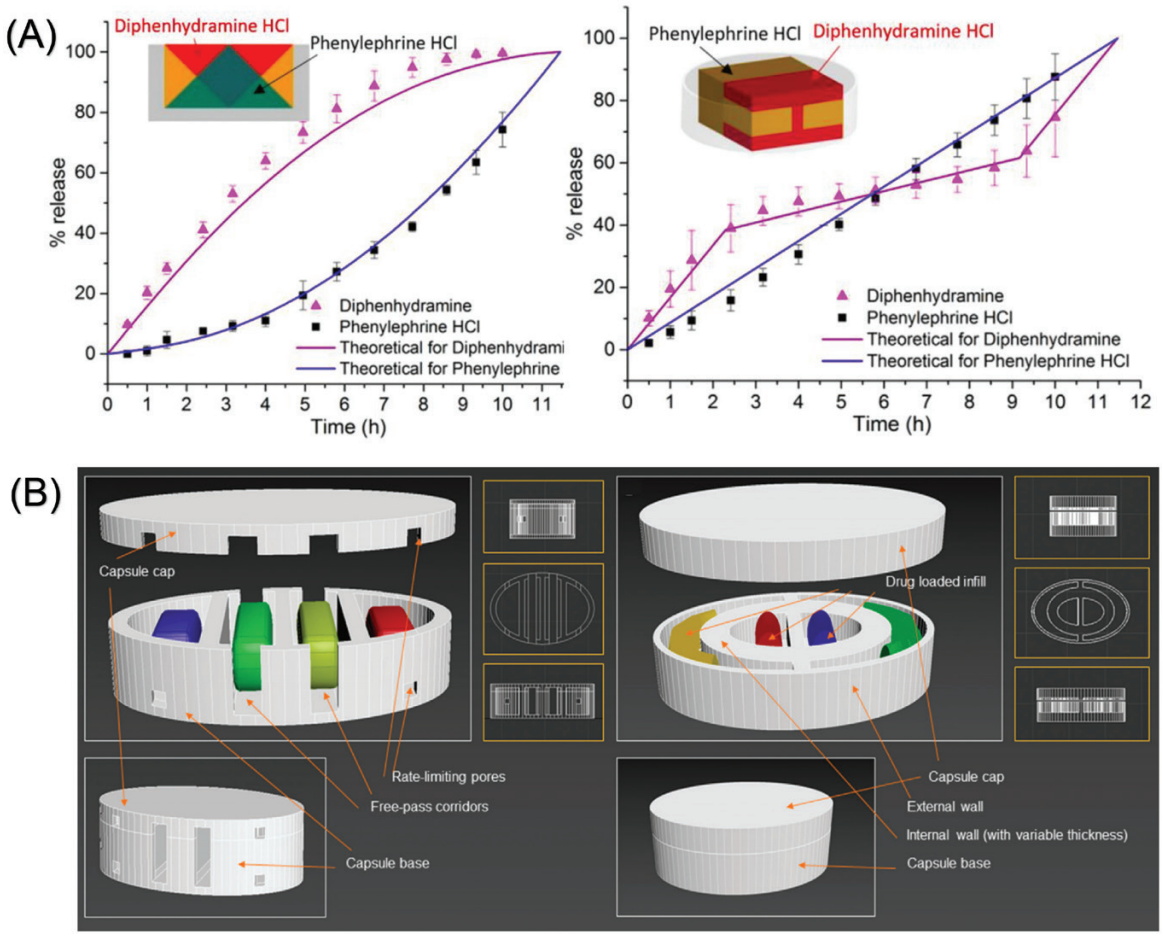


**Figure 4** (A) Fabrication of tablet with customisable and unique drug dissolution profile for diphenhydramine, paracetamol and phenylephrine.[30] (B) Schematic illustration of PLA capsule with parallel (left) and concentric (right) configurations.[55]

different drugs with varying release rates. Besides, the unique manufacturing process improved the cost-effectiveness of 3DP, which would help 3DP medications to become more applicable in clinical practice.[58]

In another study, Wu *et al*. fabricated composite drug films containing two drugs, namely paracetamol and ibuprofen, using an electrohydrodynamic printing approach (Figure 5). The composite membrane consists of two polymers, namely cellulose acetate and polycaprolactone (PCL). The dose of a drug in the composite films can be easily modified by changing the number of layers of membrane printed. Paracetamol showed a first-order release profile, whereas ibuprofen showed a Higuchi-type release curve. Due to the flexibility of the printed film, it can be folded and inserted into a capsule to ease swallowing, thereby making it a dysphagic-friendly dosage form.[29] The combination of two analgesic drugs is more effective for the treatment of acute pain than monotherapies (Table 6).

## Paediatric formulation and ease of swallowing

The commercially available pharmaceutical medications for paediatric patients are usually in liquid form. This method of administration using syringes, a calibrated spoon or a measuring cup is favoured among parents and carers due to ease of swallowing.[60] However, it has been reported that parents and carers were unable to administer volume accurately to their child, which can lead to underdosing or overdosing. In a 2012 study, it was shown that 1 in 10 research participants made significant dosing errors of more than 10%, even after using a dosing spoon and an etched dosing cup.[61] The dosing problem can be worse, given that some products require shaking or mixing before use, ensuring the homogeneity of suspension, which parents and carers often overlook.[62]

To overcome these challenges, 3DP may provide a useful solution. The ability to produce flexible and personalised dosage forms depending on the weight and age is feasible with the current 3DP technology (Figure 6). Karavasili *et al*. fabricated paediatric-friendly tablets containing ibuprofen and paracetamol using chocolate and corn syrup as the printing materials. The shape of the printed tablet can be customised according to patients' requests. On the basis of the printability and dissolution results, the study confirmed the possibility of fabricating personalised solid dosage forms for paediatric patients without the above-mentioned dosing issues.[59]

Apart from paediatric formulations, ease of swallowing can also be achieved by utilising food-grade 3D printable ink. Andriotis *et al*. developed a film-based dosage form loaded with cannabidiol–cyclodextrin complexes, using pectin and honey mixture as the printing ink. Pectin is, a soluble fibre in plants, widely used in the food industry as a gelling agent. Besides, honey can be used to facilitate the formation of a

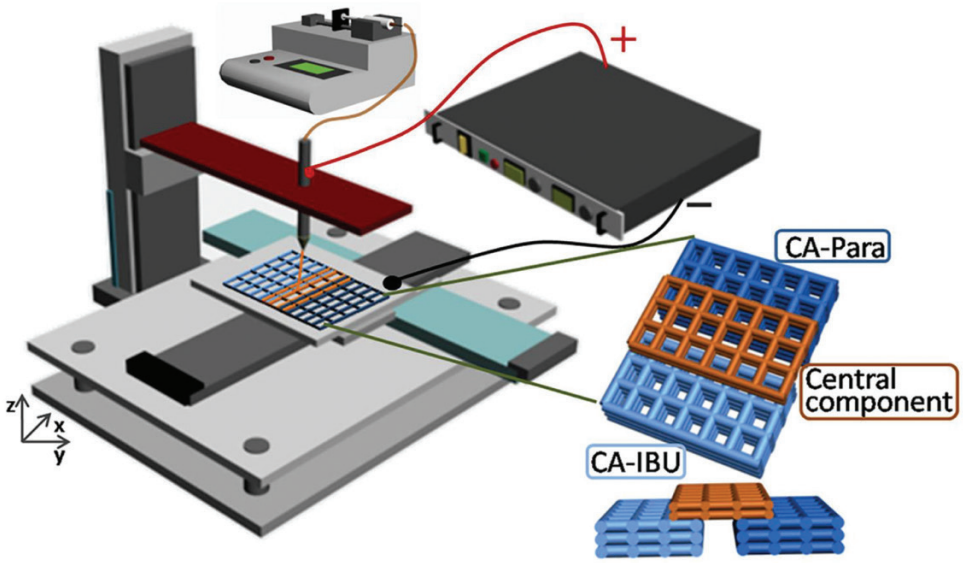


**Figure 5** The electrohydrodynamic printing set-up for the fabrication of flexible composite membranes consisting of multiple components.[29]

**Table 6** Type, drug and material of multidrug dosage forms

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| SE | Aspirin | PEG, HPMC2910, HPMC2208, PAA | [58] |
| FDM (Up! Plus 2) | Paracetamol, phenylephrine HCL, diphenhydramine | Carnauba wax, sodium alginate, croscarmellose sodium, HEC | [30] |
| MJ (Dimatix DMP) | Carvedilol | NVP and PEG diacrylate | [43] |
| SE (Shiyin CO) | TCM | Ethanol and HPMC | [56] |
| FDM (MakerBot Replicator 2X) | Lisinopril, amlodipine, indapamide, rosuvastatin | PLA | [55] |
| SE | Ibuprofen, paracetamol | PCL | [29] |

Abbreviations: HEC, hydroxyethyl cellulose; MJ, material jetting; PAA, poly acrylic acid; SE, syringe extrusion.

viscous gel, thereby rendering it suitable for 3DP. Both, pectin and honey, have made easy the ingestion of the oral dosage form. The semi-solid mixture was utilised to print the drug-laden films. The printing process can be operated at room temperature when compared with FDM printing, which is operated at elevated temperatures. This would be beneficial for temperature-sensitive APIs and excipients to minimise their degradation during the printing process.[63]

Similarly, in an investigation carried out by Elbl *et al.*, they developed orodispersible films from two commonly used pharmaceutical excipients, namely maltodextrin and sorbitol, to mask the bitter taste of benzydamine hydrochloride, a locally acting non-steroidal anti-inflammatory drug. Maltodextrin is a polysaccharide, an easily digestible food additive. Sorbitol is a sugar substitute. The 3DP films had favourable characteristics in terms of mechanical properties and drug release profile, but the authors emphasised the need for further study in short- and long-term stability before they can be employed for pharmacy use[64] (Table 7).

### Alcoholic-deterrent formulation

Currently, several strategies have been implemented to combat the increase in controlled substance abuse, one of which is the abuse-deterrent tablet formulation. The aim of the abuse-deterrent tablet is to prevent the abuser from tampering with the medication or even making them less attractive to be abused, which ranges from incorporating agonist/antagonist, physical and chemical barriers.[65]

Nukala *et al.* were among the pioneers who explored the possibility of utilising AM to print abuse-deterrent formulations.[66] Recently, Ong *et al.* developed a single-step process to print tablet containing tramadol with abuse-deterrent and alcohol-resistant properties. The tablet passed the assessment for abuse potential via the intravenous route, due to the poor solubility and formation of viscous gel, which made it harder to inject. In addition, the formation of gel in the nasal cavity upon nasal inhalation can result in some distress to deter the abuser from utilising this method of administration. In drug dissolution assay, the tablet showed a lower dissolution rate in the presence of alcohol to minimise it being abused with alcohol as well[67] (Table 8).

## Transdermal Delivery

### Vaccine

The current research focus for targeted vaccine delivery is performed using either microscale or nanoscale carriers to carry the antigens or carrier-free antigens. The former approach

**Figure 6** Flexibility in the shape of 3D printed oral dosage forms such as bat, bone, star and mickey mouse to improve the dosage form's appearance.[59]

**Table 7** Type, drug and material of dosage forms for paediatric formulation and ease of swallowing

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| SE (XYZ 3C10A) | Ibuprofen, paracetamol | Corn syrup, chocolate | [59] |
| SE (Cellink Inkredible) | Cannabidiol | Pectin, honey | [63] |
| FDM | Benzydamine HCL | Maltodextrin, sorbitol | [64] |

Abbreviations: HCL, hydrochloride; SE, syringe extrusion.

**Table 8** Type, drug and material of alcohol-deterrent dosage forms

| Type of printer | Drug | Material | Ref |
|---|---|---|---|
| SE (M3DIMAKER) | Tramadol HCL | HPC | [67] |

Abbreviations: HCL, hydrochloride; HPC, hydroxypropyl cellulose; SE, syringe extrusion.

has disadvantages, such as poor cytocompatibility, antigen-loading efficiency and lack of morphological design.[68] The latter approach presents with limited stability, polydispersity, versatility and biocompatibility of the antigens.

Nishiguchi *et al.* investigated the novel targeted vaccine delivery using a carrier-free approach and 3DP antigen nanoparticles to overcome these limitations. The printing precision of antigens of up to nanoscale was possible by using the multiphoton lithography-based printing method. The surface morphology of the antigen nanoparticles was controlled meticulously to induce specific immune response as observed in other studies.[69, 70] The antigen nanoparticles showed acceptable cytocompatibility, which was demonstrated in the lactate dehydrogenase experiment.[68] The fabrication method would be potentially useful for developing future vaccine delivery systems (Table 9).

**Table 9** Type, drug and material of vaccine dosage forms

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| 2PP (Nanoscribe) | Antigen | Bovine serum albumin, ovalbumin, and gelatine | [68] |

Abbreviation: 2-photon polymerisation.

## Microneedle array

There is a growing interest in the use of microneedle as an alternative to injectables and conventional transdermal patches. Microneedle array, consisting of multiple needles of a few hundred microns, can pierce through the skin to create microscale passages to allow the permeation of drug molecules, nucleic acids[71] and proteins.[72] As the topmost layer of skin, the stratum corneum acts as a primary barrier to drug transdermal absorption, microneedle delivers the drug directly into the skin with minimal pain.[73, 74]

For example, cellulite management involves either suctioning of the excess fat from the body or using oral slimming

medications that present with many inconveniences ranging from minimal efficacy, patient discomfort, side effects and high cost of the procedure. Alternatively, most topical creams that are available commercially are not scientifically tested for their efficacy and toxicity. To this end, Amer *et al.* developed a new approach for delivery of anti-cellulite herbal extracts, such as *Vitex agnus-castus* and *Tamarindus indica*, using a microneedle for the effective treatment of cellulites. The microneedle loaded with the plant extracts showed significant changes in terms of inflammatory biomarkers, structure and morphology of the tissue, commonly observed in the pathogenesis of cellulite. Nonetheless, these results did not translate to a reduction in body weight and improvement in the skin condition as expected.[75]

Minoxidil is generally considered an effective treatment option in promoting hair regrowth and minimising hair loss. To improve the effectiveness of the therapeutic effect, Fang *et al.* utilised magneto-responsive transdermal composite microneedle to encapsulate minoxidil to treat androgenic alopecia (Figure 7A). Instead of relying on passive subcutaneous absorption into the skin, the microneedle allowed quicker transdermal delivery of minoxidil. Furthermore, the microneedles generated heat upon external magnetic trigger causing vasodilation, thus promoting regrowth of hair. The improvement in hair growth up to 8-fold with minimal side effects was observed in the animal model, which confirmed the effectiveness of the microneedles and their potential for application in treating androgenic alopecia.[76]

In addition to small drug molecules, it is also possible to deliver vaccines via microneedle administration. The method of administration for vaccines is usually subcutaneous or intramuscular and sometimes requires multiple-dose administration at different times. Tran *et al.* reported the development of microneedle delivery with programmable burst release to deliver vaccine via the skin. With only a one-time skin application, the microneedle array could release its payloads in a few days to months as programmed. In addition, the authors reported the superiority of the microneedle patch when compared with the commercial vaccine product, namely Prevnar-13, in terms of better survival percentage, when tested in rats.[78] In another study involving microneedle for vaccine delivery, Balmert *et al.* fabricated dissolving microneedle arrays that were tip-loaded with model antigens with/without adjuvant, by using the moulding method. Based on the results, these microneedle arrays stimulated better antigen-specific cellular and humoral immune responses than the regular intramuscular administration.[79]

Further advancement in the microneedle technology can be found in the work performed by the following authors. Lopez-Ramirez *et al.* developed an autonomous and degradable microneedle for enhanced drug delivery. The improvement in the drug release efficiency was possible as the microneedles contained magnesium particles that reacted with interstitial fluid to produce hydrogen bubbles, leading to deeper and faster deposition of drugs.[80] El-Sayed *et al.* fabricated microneedles using soft lithography to reduce the manual insertion force and, consequently, improve patient compliance. Moreover, the quick separation of microneedles from the patch was advantageous, as it allowed further drug release

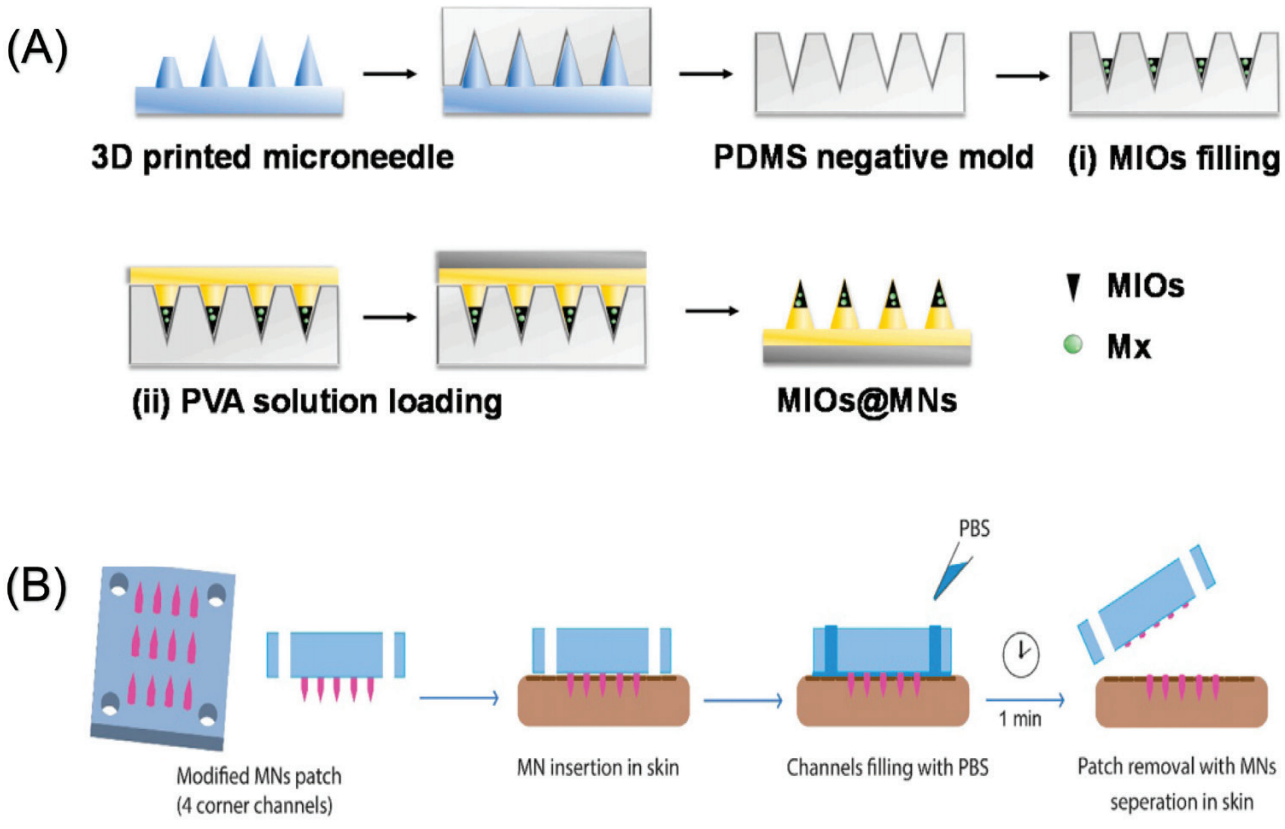


**Figure 7** (A) The basic schematic process to demonstrate the production process of 3D printed microneedle.[76] (B) Stepwise process for the early separation of microneedle from the patch via the introduction of phosphate buffered saline (PBS) solutions at the corner channels.[77]

under the skin while minimising the administration time and sharp biohazard wastes (Figure 7B).[77] Contrastingly, Han *et al*. fabricated microneedle with backward-facing barbs for extended drug release. The improvement in the microneedle barb thickness and bending curvature showed promising results with significant tissue adhesion as much as 18 times when compared with microneedles without barbs. Other than drug delivery, this bioinspired microneedle array can also be applied in interstitial fluid collection for bioassay and biosensing applications[81] (Table 10).

## Skin patch

The use of well-known diterpene quinone extract of *Salvia miltiorrhiza*, namely cryptotanshinone, as a treatment for acne can be observed in the work done by Yu *et al*.[83, 84] The group loaded the cryptotanshinone inside the patch for skin application due to the advantages of ethosomes as drug carrier. The ethosomes containing cryptotanshinone reduced the inflammation of the skin, when compared with conventional skin, showing its anti-acne efficacy.[84]

Further improvement in anti-acne management was possible as Wang *et al*., developed niosomal hydrogel formulations to encapsulate the cryptotanshinone. The enhanced anti-acne effect could be explained by increasing the skin hydration, changing the intercellular lipid re-arrangement and widening inter-corneocyte gaps in the stratum corneum. Given the promising results, the researchers aimed to realise the potential application of AM in fabricating personalised acne treatments by adapting the printed patches to the patient facial contour, size and acne severity in future studies.[85] In the fabrication process, the niosomes were first encapsulated in the hydrogel, which was then printed into a patch with a specific drug dose, shape and size, using a semi-solid extrusion method. Currently, most of the commercial products, such as facemasks, cannot provide a perfect fit to represent human facial contour and hence not optimal for drug delivery. To this end, the 3DP skin patches may provide an individualised solution (Table 11).

**Table 10** Type, drug and material of microneedle dosage forms

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| SLA | Anti-CTLA-4 | PVP | [80] |
| SLA | *Vitex agnus-castus*, *Tamarindus indica* | Chitosan | [75] |
| DLP | Minoxidil | PVA | [76] |
| 2PP (Nanoscribe) | Cabotegravir, ibuprofen | PVP, PVA | [82] |
| DLP (Perfactory Micro Plus) | – | PVA, sucrose | [77] |
| 2PP (Nanoscribe) | Ovalbumin | Sodium CMC, d-trehalose | [79] |
| 2PP (Nanoscribe) | Prevenar | PLGA | [78] |
| DLP | Rhodamine B | PEGDA | [74] |
| SLA | Rhodamine B | PEG diacrylate | [81] |

Abbreviations: 2PP, 2-photon polymerisation; DLP, digital light processing; PEGDA, polyethylene glycol diacrylate; PLGA, poly-lactic co-glycolic acid; PVP, polyvinylpyrrolidone; SLA, stereolithography.

**Table 11** Type, drug and material of patches

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| SE (ZBOT) | Cryptotanshinone | Sodium polyacrylate, glycerol | [85] |

Abbreviation: SE, syringe extrusion.

## Wound dressing

Wound dressing has been investigated extensively with the advancement in AM, as we have seen in recent years. Muwaffak *et al*. produced antimicrobial wound dressing made from PCL functionalised with metals such as zinc, copper and silver.[86] The following groups carried out similar works in designing 3DP wound dressing. Aranci *et al*. fabricated wound dressing patches using sodium alginate scaffold loaded with propolis using the casting method in combination with 3DP. Propolis possesses wide-ranging properties such as antiseptic, antibacterial, antioxidant and immunomodulatory effects that can be useful for the healing process.[87] The alginate scaffold can be further modified to include starch as an ingredient. The reorganisation of alginate polymer with the addition of starch affected drug diffusion. Based on the result, it was possible to modulate drug release by fine-tuning the amount of starch incorporated, but it affected other properties as well, especially the printability of the hydrogel ink.[88] The presence of methylglyoxal in honey-enhanced propolis's antibacterial properties and formed an optimal condition for wound healing due to its high osmolarity of honey and conducive pH environment.[89]

The popularity of natural polysaccharides such as collagen, gelatine and polysaccharide as the building materials for wound dressing can be attributed to their many favourable characteristics such as water-retaining capacity and biocompatibility.[90] However, synthetic hydrogels are gaining more attention as they have better water-retaining capacity, gel strength and stability against chemical and varying temperatures.[91] Qiao *et al*. utilised the double-network hydrogels formed mainly from acrylamide-modified hyaluronic acid and polyacrylamide for their wound regeneration studies. The cross-linking from hyaluronic acid and polyacrylamide worked synergistically in supporting the hydrogel structure. The incorporated folic acid in the hydrogel is important for the synthesis of DNA for new cells. In this study, the authors demonstrated the pH-responsive drug release, where aspirin had a faster release rate in an acidic environment, which suits the acidic environment of wounds.[90]

Furthermore, Zhang *et al*. investigated the fabrication of self-adhesive dressing to promote nerve regeneration in peripheral nerve injury using synthetic hydrogel composed of N3-GelMA and DBCO-GelMA. The accuracy and flexibility in the digital light processing method were utilised in printing around the nerve to cushion the injured nerve and simultaneously allowed unidirectional drug release of XMU-MP-1, which can promote proliferation and migration of Schwann cell, thus promoting remyelination of the nerve cell.[92]

Ko *et al*. developed a self-healing hydrogel composed of glycol chitosan, hyaluronic acid and superparamagnetic iron oxide nanoparticles (SPIONs; Figure 8A). The 3DP hydrogel could transform its shape in the presence of a magnetic field and return to its original shape even after gel breakage (Figure 8B). The characteristic of this hydrogel can be controlled by

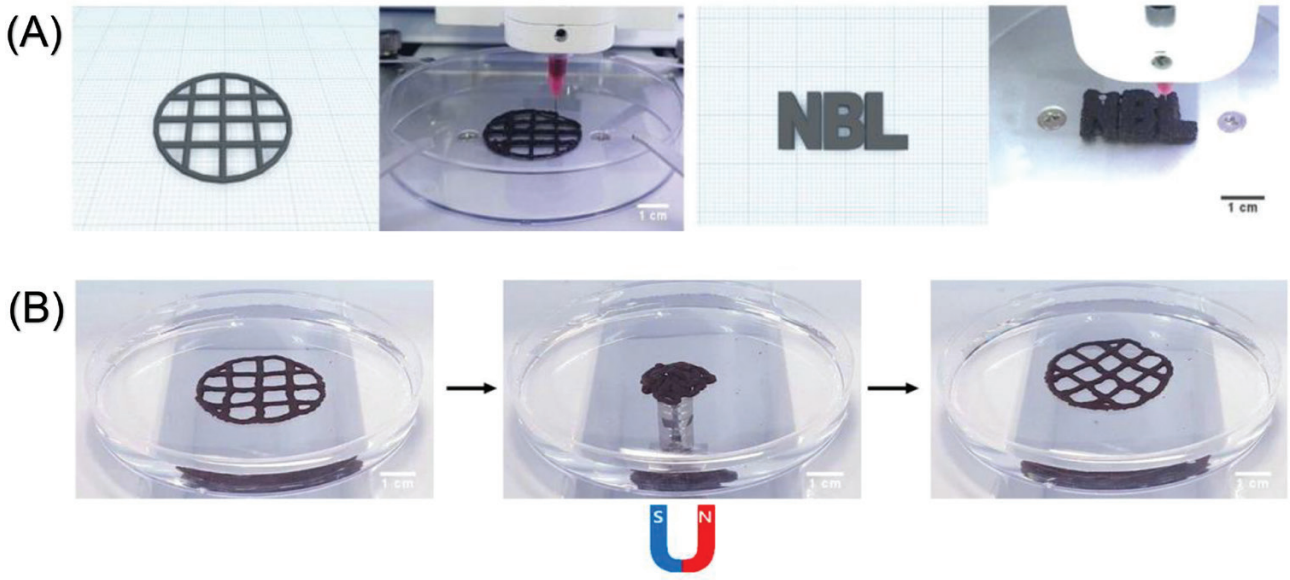


**Figure 8** (A) The hydrogel printed in different shapes. (B) The 3D printed ferrogel returned to its original shape upon the removal of the magnetic field.[93]

glycol chitosan/hyaluronic ratio, the concentration of SPIONs and total concentration of polymer, which can be utilised for specific needs, especially in drug delivery and wound dressing applications[40] (Table 12).

## Rectal Delivery

The use of suppository can be traced back to ancient Egyptian and Greek practices.[96] This route of administration allows the delivery of medication locally with minimal first-pass effect and adverse effect.[97] In the production process of suppository with intricate design, AM has been applied in fabricating suppository with matryoshka type as observed in recent years.[98, 99] The suppositories were fabricated using the moulding technique similar to the conventional manufacturing process. Many challenges are involved in the moulding technique, as it required multiple steps for mixing, filling and hardening.[100] In recent years, researchers explored new methods of fabricating suppositories without using any moulds. The absence of mould in the manufacturing process would expedite the process and reduce material and equipment costs.[97]

Calcineurin inhibitor such as tacrolimus is routinely used for the treatment of ulcerative colitis.[101] This medication shows an excellent prognosis in inducing remission in patients with ulcerative colitis who are corticosteroid resistant but has systemic side effects, namely increased risk of opportunistic infections, gastrointestinal disorders and kidney issues.[101] One solution to minimise the systemic side effects is to deliver the medication locally to the affected gastrointestinal tract, colon and rectum using suppositories.

Using the syringe extrusion printing method, Seoane-Viaño *et al.* printed suppositories loaded with tacrolimus. Gelucire 44 and 48 as excipients were advantageous due to low melting point, which allows the printing process to be performed at low temperature and rapid solidification post-printing.[100] To evaluate the therapeutic effect of the suppositories, the group tested them in an animal model using rats that were induced to develop colitis with trinitrobenzene sulfonic acid. The in-vivo assessment of the therapeutic effect of tacrolimus suppositories using positron emission tomography/computed tomography (PET/CT) imaging and histopathological analysis showed a significant difference in inducing remission of inflammation, compared with the non-treated groups. The authors also concluded no significant difference in the 3DP tacrolimus suppositories as opposed to the other proposed treatments such as methylprednisolone, resveratrol and melatonin[97] (Table 13).

**Table 12** Type, drug and material of wound dressings

| Type of printer | Drug | Materials | Reference |
|---|---|---|---|
| SE (CELLINK Inkredible) | Propolis extract | Pectin | [89] |
| SE (Invivo) | – | Glycol chitosan, hyaluronate | [93] |
| PAM (3D Focus) | Rhodamine | Alginate, starch, calcium chloride | [88] |
| DLP | XMU-MP-1 | $N_3$-GelM, DBCO-GelMA | [92] |
| DLP | GF | HA, HA-GM, HEP-SH | [94] |
| FDM (Ultimaker$^{2+}$) | Propolis | Sodium alginate | [87] |
| SLA | Acetylsalicylic acid, folic acid | Acrylamide-modified hyaluronic acid | [90] |
| DLP (EnvisionTEC) | Halofuginone | Keratin | [95] |

Abbreviations: DBCO-GelMA, dibenzyl cyclooctyne modified gelatin methacrylate; DLP, digital light processing; GF, growth factors; HA, hyaluronic acid; HA-GM, hyaluronic acid glycidyl methacrylate; HEP-SH, thiolated heparin; PAM, pressure-assisted micro syringes; SE, syringe extrusion; SLA, stereolithography.

## Vaginal Delivery

The conventional vaginal meshes that are usually made of polypropylene for hernia repair have been reported to cause

**Table 13** Type, drug and material of rectal dosage forms

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| FDM (Monoprice MP Select Mini Pro) | Artesunate | PEG, PVA | [102] |
| SE (M3DIMAKER) | Tacrolimus | Gelucire 44/14, Gelucire 48/16, coconut oil | [97] |
| SE (M3DIMAKER) | Tacrolimus | Gelucire 44/14, coconut oil | [100] |

Abbreviations: SE, syringe extrusion.

**Table 14** Type, drug and material of vaginal dosage forms

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| FDM (Ultimaker 3) | Levofloxacin | Polyurethane | [104] |
| DLS (M1 DLS Printer) | – | Urethane-methacrylate resin | [106] |

Abbreviation: DLS, digital light synthesis.

chronic pain and infection even though the US FDA approves them.[103] Domínguez-Robles *et al*. fabricated novel vaginal mesh implants using a different polymer, namely polyurethane, as it has favourable properties to ameliorate the problem. The printed meshes were loaded with a macrolide antibiotic, namely levofloxacin, a commonly used medication for the treatment of urinary infections. The polyurethane-based vaginal meshes exhibited better elastic behaviour than polypropylene-based meshes, which suits the elastic tissue around the vagina. Based on the in-vitro studies, the 3DP meshes showed sustained release of levofloxacin for a minimum of 3 days depending on the total amount of drug loaded. The significant bacteriostatic effect against *Staphylococcus aureus* and *Escherichia coli* was deemed favourable, as they are the common causes for nosocomial bacterial infections.[104, 105]

As for the manufacturing process of intravaginal rings, the conventional methods are either hot-melt extrusion or injection moulding. These manufacturing techniques require high processing temperature and pressure, thus limiting the use of temperature and pressure-sensitive APIs. In addition, the manufacturers would overload the drugs into the ring as the drug release is dependent on the diffusion rate of the drug, consequently increasing the manufacturing cost. Janusziewicz *et al*. explored the possibility of improving the conventional process of fabricating vaginal rings using digital light synthesis to mitigate these problems.[106] The AM approach has allowed the manufacture of geometrically complex intravaginal rings, which was reported in a previous study by Fu *et al*.[107] The novelty in this study was that the mechanical and drug release kinetics could be tuned depending on the materials, shape and geometry of the intravaginal rings. In addition, Janusziewicz *et al*. developed a library of intravaginal designs based on the results collected for the systematic production of the next-generation personalised intravaginal ring[106] (Table 14).

## Drug Implant

The task of classifying implantable drug delivery systems is a complicated process. Thus, we utilised the general classification, based on passive and active implants, as described by Stewart *et al*.[108]

### Passive implant

#### *Non-biodegradable scaffold*

Hao *et al*. developed a novel approach to suppress tumour recurrence and metastasis by combining breast reconstruction therapy and chemotherapy. Paclitaxel and doxorubicin were added into microspheres for controlled drug release before being loaded into the non-biodegradable breast prosthesis, which is made of polydimethylsiloxane. The synergistic anticancer effect of paclitaxel and doxorubicin can be observed clearly as they showed significant inhibition on the local cancer recurrence and metastasis when tested in mice. The effectiveness in controlling the cancer cells was attributed to the synergistic effect and the continual release of both anticancer drugs for more than 3 weeks.[109]

For heat-sensitive drugs, the high processing temperature in some 3DP methods such as hot-melt extrusion can pose a major challenge. To address this challenge, Salimi *et al*. constructed drug-eluting implants using a novel non-biodegradable polymeric material. This polymer required low temperature for the extrusion process and cooled down rapidly to form a flexible and self-assembled structure due to the hydrogen bonding and other molecular interactions. The group verified the biocompatibility of polyurethane in mouse fibroblasts. The drug-eluting implant was predicted to release paracetamol for up to 8.5 months. Furthermore, the drug release profile can be modified by varying the percentage of polyethylene glycol (PEG) or its molecular composition. However, Salimi *et al*. also pointed out that further optimisation of drug-eluting implant was required as they observed some deformation during the dissolution testing.[110]

Steinbach *et al*. designed a subcutaneous drug-eluting implant using PEG dimethacrylate and poly-2-hydroxyethyl methacrylate. It was found that the polymer's long-chain molecules caused the model drug to diffuse quicker through its bigger mesh size. In addition, the drug release rate was increased with the increase of poly-2-hydroxyethyl methacrylate percentage in the scaffold, due to the swelling effect of this polymer. Steinbach *et al*. confirmed the possibility of controlling the drug release by fine-tuning the oligomer's chain length or increasing the percentage of swelling polymer in the scaffold.[111]

Another approach to control the delivery of a drug is through coating material of the drug-laden implants. The coating material can provide an additional barrier to control drug release from the implants. Stewart *et al*. developed a reservoir-type drug implant using polylactic acid (PLA) and PVA, coated with PCL to modify the release of a hydrophilic drug. The drug release rate from the implant ranged from 0.01 to 34.09 mg/day, with varying amounts of PCL in the formulation. Change in the formulation of PCL coating was achieved by either controlling the percentage of PCL or incorporating other excipients such as PEG. The PEG affected the hydrophilicity of the coating material. Based on promising results, the authors proposed to apply this approach in modulating drug release of a wider variety of drugs, not limiting to only hydrophilic drugs.[112]

#### Biodegradable scaffold

For the local and sustained delivery of chemotherapy for osteosarcoma, Wang *et al*. fabricated biodegradable drug

implant from PLA to deliver anticancer drugs, namely doxorubicin ifosfamide, methotrexate and cisplatin, based on the chemotherapy regimen for clinical post-operative osteosarcoma. The efficacy of the anticancer treatment and safety of the 3DP implant were compared with conventional chemotherapy. The drug concentration of four different drugs was consistently higher in the tissue surrounding the drug implants than adjacent tissues, thereby potentially minimising systemic side effects and off-target toxicities, unlike the traditional chemotherapy. In terms of overall toxicity, the group reported no abnormalities in the rats treated with the implants, while a reduction in spontaneous activity, hair loss and even death were observed in the conventional treatment.[113]

To achieve precise and localised drug delivery to cancer cells, Yang *et al*. fabricated injectable implants loaded with NVP-BEZ235, a reversible P13/mTOR inhibitor in combination with 5-fluorouracil (5-FU), a commonly used medication in the management of breast cancer (Figure 9). In this study, the group utilised electrohydrodynamic jet printing to form controlled release of the anticancer agents in poly-lactic-*co*-glycolic acid scaffolds. Yang *et al*. achieved the programmable release of those anticancer agents for the inhibition of breast cancer growth and metastasis. The dissolution studies indicated that the scaffold showed burst release during the first week, followed by slow release and, finally, a faster release of 5-FU and NVP-BEZ235 to the cancer cells. The localised implants resulted in significant improvement in anti-tumour efficacy than the intraperitoneal delivery of the same drugs. In addition, it was important to note that the intraperitoneal injections were given every 3 days, while the implantation of the drug implant was done only once, which was advantageous in reducing the frequency of drug administration.[114]

The current clinical management of retinal vascular diseases, which are the leading cause of vision impairment and blindness, involves multiple-dose administration because of the drug's poor chemical stability upon injection. Won *et al*. designed a polymeric shell containing hydrogel core loaded with bevacizumab and dexamethasone to ameliorate the need for multiple injections. Bevacizumab was used to minimise anomalous angiogenesis seen in the retinal vascular diseases, whereas the dexamethasone was essential in alleviating the inflammatory response associated with neovascularisation progress. The short- and long-term therapeutic efficacy of drug-laden rod was tested, to compare its efficacy against the current clinical management. The intravitreal drug implant showed marked improvement as the rod showed longer drug release for up to 60 days when compared with the conventional intravitreal injection, which lasted for up to 2 weeks only. In addition, a lower dose was required to produce the therapeutic effect using the rod loaded with drugs, which minimised the cost and side effects to the patients. Overall, the 3DP drug rod performed better than the conventional intravitreal bevacizumab injection.[115]

Owing to the limitation in finding a suitable formulation that suits specific drug loading and dissolution profile, He *et al*. utilised a reactive prodrug ink formulation approach not only in oral drug delivery but also in drug implants. The ability of the prodrug to hydrolyse and release the active drug can be controlled by many factors. For example, ibuprofen's release was modulated by modifying the geometry and composition of the implant. In addition, once the drug–polymer chain released the active drugs completely, it would dissolve into the surrounding aqueous environment, thus negating the need for another surgery to remove the implants in the future[116] (Table 15).

## Active implant

The conventional method for the treatment of postsurgery cancer tissues usually involves the use of systemic chemotherapy. This method brings forth many disadvantages such as being non-specific targeting, as it affects cancer and healthy cells equally. However, it is possible to overcome it by utilising localised and controlled drug delivery as observed in the work of Wei *et al*.. The group fabricated a hydrogel scaffold that can be manually controlled to locally deliver doxorubicin for treating residual and local recurrence in postsurgery of tumour cells. This was achieved through irradiating infrared laser to increase

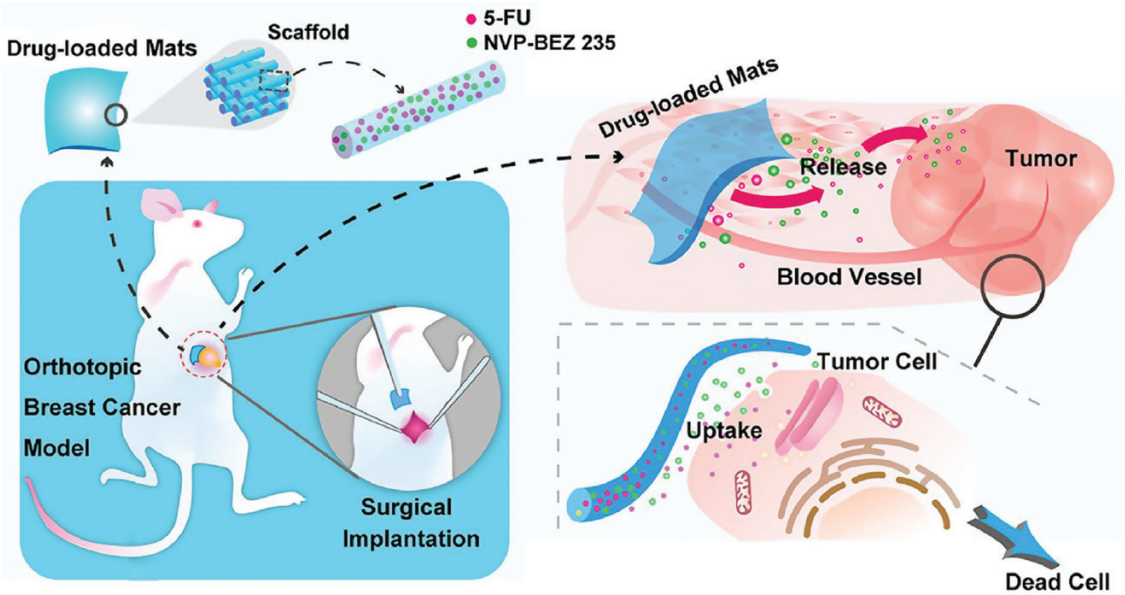


**Figure 9** Schematic illustration of implant for local delivery of 5-FU and NVP-BEZ235 to improve drug delivery precision, reduce the frequency of administration and minimise systemic toxicity.[114]

**Table 15** Type, drug and material of implants

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| SE | Cisplatin | PLGA | [117] |
| DLP (NOVA3D 101) | Ibuprofen | PEGDA, DPPO | [118] |
| SLA (Anycubic Photon-5.5) | Paclitaxel, doxorubicin | PDMS | [109] |
| FDM (Ultimaker) | Methylene blue, ibuprofen sodium, ibuprofen acid | PLA and PVA | [119] |
| FDM (Ultimaker 3) | Methylene blue, ibuprofen sodium | PLA and PVA | [112] |
| DLP (RAM500) | Chlorhexidine | PDMS | [120] |
| FDM | Doxorubicin | PCL | [121] |
| FDM (Ultimaker S5) | 5-FU | Polyurethane | [122] |
| MJ (Dimatix 10) | Ibuprofen | IBHEA-HEA | [116] |
| FDM (Prusa i3 MK2) | Diclofenac | PLA, PETG, PMMA | [123] |
| SE (Bioscaffolder) | Gentamicin sulfate | PCL | [124] |
| FDM | Dexamethasone | PCL | [125] |
| SE (Cellink INKREDIBLE) | PEGylated liposomal doxorubicin | Gelatine methacryloyl, CMC | [126] |
| SE (Cellink INKREDIBLE) | Paracetamol | PEG, polyurethane | [110] |
| SLA (ZcorpZprinter) | Doxorubicin, ifosfamide, methotrexate, cisplatin | PLA | [113] |
| SE (Inkredible) | – | Laponite, PDMS | [127] |
| SE | Bevacizumab, dexamethasone | Alginate, PCL | [115] |
| SLA | Methylene blue (model drug) | PEGDMA, pHEMA | [111] |
| MJ | 5-FU and NVP-BEZ235 | PLGA | [114] |
| FDM (Ultimaker 2+) | Fluorouracil | Calcium carbonate, nanocellulose | [128] |
| SE (Hyrel 30M) | Paclitaxel, rapamycin, lidocaine | PLGA | [129] |
| MJ (Dimatix 10) | Ibuprofen | IBHEA-HEA | [116] |
| Filament-free printing (PC Printer) | Propranolol | Collagen, PVA, hydroxyapatite | [130] |
| FDM (Prusa i3) | Cinnarizine | HPMC, Kollidon VA64 | [20] |

Abbreviations: CMC, carboxymethyl cellulose sodium; DLP, digital light processing; DPPO, diphenyl-2,4,6-trimethylbenzoyl phosphine oxide; IBHEA, ibuprofen-hydroxyethylaryclate; MJ, material jetting; PDMS, polydimethyl siloxane; PDMS, polydimethyl siloxane; PEGDA, polyethylene glycol diacrylate; PEGDMA, polyethylene glycol dimethacrylate; PETG, polyethylene terephthalate glycol; pHEMA, poly-2-hydroxyethyl methacrylate; PLGA, poly-lactic co-glycolic acid; PMMA, polymethyl methacrylate; SE, syringe extrusion; SLA, stereolithography.

the temperature of polydopamine/alginate scaffold to promote the diffusion of the drug diffusion into surrounding tissues. The on-demand manner of drug release meant that the release of drug would be halted once the infrared irradiation stops. The authors concluded that the total effectiveness for eliminating cancer cells was attributed to the heat from the photothermal conversion of sol–gel transition of polydopamine/alginate scaffold and the release of doxorubicin.[131]

Forouzandeh *et al.* utilised drug reservoir technology to achieve effective and localised drug delivery by manufacturing dome-shaped microscale reservoirs using parylene-C. This microreservoir can be used either as an implant or as transdermal delivery patch. The manufacturing process depended on the accuracy of stereolithography to produce a microreservoir with varying drug loading capacity from 1 to 100 µl while maintaining its overall thickness. The highlight of this microreservoir was the absence of a pumping mechanism to control the drug release as it relied on the diffusion of drugs through the microneedle or microtubing into the body. Moreover, the 3DP microreservoir was able to withstand high amounts of leakage-free injections during the refilling process, thus negating the need for removal and reinsertion of drug implants[132] (Table 16).

**Table 16** Type, drug and material of vaccine dosage forms

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| SLA (Form 2) | – | Parylene-C layer | [132] |
| FDM (Robo R2) | 5-FU | PDMS | [133] |
| SE (Bioscaffolder 3.1) | Doxorubicin hydrochloride | PDA and Alginate | [131] |

Abbreviations: PDA, polydopamine; PDMS, polydimethyl siloxane; SE, syringe extrusion; SLA, stereolithography.

## Bone Scaffold

Recent development in 3DP technology can also be observed in the fabrication of scaffolds for bone regeneration and related infections. The process of incorporating APIs into the scaffold is usually done either by mixing directly into the polymer[134–137] or by impregnation in a solution.[136–142] For example, Lee *et al.* developed 3DP PCL-based scaffold loaded with rifampicin. The manufacturing process of the scaffold involved the mixing of PCL and rifampicin, and then it was printed at a low temperature to minimise the potential degradation of rifampicin. The antimicrobial activity of rifampicin was verified as the scaffold has shown better antimicrobial activity against *E. coli* and *S. aureus* than the conventional polymethyl methacrylate-based scaffold for preventing osteomyelitis. However, there is a concern regarding the direct mixing method whereby extreme heat and pressure may degrade the active ingredients. Ranganathan *et*

*al.* set out to assess the effect of drug's exposure to ultraviolet and high temperature in the 3DP and sterilisation process. The antimicrobial properties of doxycycline, vancomycin and cefazolin did not change significantly after exposure to ultraviolet and high temperature as observed in the in-vitro studies.[143]

The impregnation methods involve soaking either the filament produced from hot-melt extrusion or scaffold into a solution with the active ingredients. Li *et al.* incorporated aspirin-loaded liposomes and bone-forming peptide-1 using the impregnation method onto a 3DP PCL scaffold. Through impregnating in the final step, it was possible to load a temperature-sensitive drug onto the scaffold. The synergistic effect of aspirin and bone-forming peptide-1 was significant when tested in an animal model as they were shown to promote the formation of new bone and bone repair processes.[138] In another study, Sarkar and Bose impregnated three types of primary soy isoflavones, such as genistein, daidzein and glycitein, into 3DP scaffolds. Using the interconnected porosity and biodegradability of tricalcium phosphate scaffold, they were able to control the drug release for an extended period. The outcome was promising as the 3DP scaffold loaded with soy isoflavones showed an improvement in osteogenesis, anti-inflammatory and cancer cell suppression.[139] Nevertheless, the impregnation method relies on passive diffusion, which is a time-consuming process and high concentration of a drug is required for the drug. Similar to the limitation of direct mixing, filament loaded with drugs needs to withstand extreme temperature during the printing process in the FDM approach.[144]

One of the ways to overcome the limitation from direct mixing and impregnation methods is by manipulating the surface of 3DP scaffolds or implants.[145–147] Poudel *et al.* fabricated stainless-steel implants coated with a natural polymer, namely gelatine and chondroitin sulfate. Subsequently, the implant was loaded with dexamethasone using a high-precision air brush. The release kinetics of the dexamethasone was tuned through surface modification and gelatine concentration, whereby the groups managed to fabricate a biphasic release pattern that promoted bone regeneration and reduced joint inflammation. In-vitro study showed that the implants had rapid release initially in the first day and then slow release in the subsequent 3 days.[147]

A similar study was performed by Robertson and Bose in increasing the bioactivity of the bone implant through incorporating polydopamine and *Cissus quadrangularis* extract coating on a β-tricalcium phosphate scaffold. It was noted that the scaffold showed significant bone regeneration by promoting osteoblast proliferation and production of alkaline phosphatase in a rat model. In addition, the authors also highlighted the increase in drug release in an acidic environment, commonly found in early bone healing stages. In terms of mechanical strength, there was no significant difference between the scaffold with or without coating.[146]

The supercritical fluid technology is a promising alternative strategy for incorporating APIs into implants. Ngo *et al.* had chosen the supercritical fluid technology for drug deposition onto the scaffold to overcome the challenges associated with the direct mixing and impregnation method (Figure 10). This method is advantageous as the drug loading process occurs at low temperature and pressure, making it suitable for temperature-sensitive drugs. In addition, this drug loading process leaves no residual compound post-printing that may impair the patient health and safety. In the study, Ngo *et al.* printed polymethylmethacrylate loaded with flurbiprofen via supercritical carbon dioxide. The drug loading and surface roughness can be adjusted by changing the printing parameters, such as drug loading temperature and carbon dioxide density, to achieve specific needs.[144]

As bone possesses an intricate and geometrically complex porous network, it is vital to understand the effect of pore formation on drug release. Vu and Bose compared the formation of pores on the release kinetics of vitamin D. The authors found that 3DP scaffold had better open-pore interconnectivity, thus providing higher total surface area for the release of vitamin D for osteoblast proliferation. The effect on osteoblast was significant noticeably at Day 1, where osteoblast proliferation improved by 64% compared with the control. However, it was noted that the 3DP scaffold had lower compressive strength, affecting the load-bearing application for bone implant[148] (Table 17).

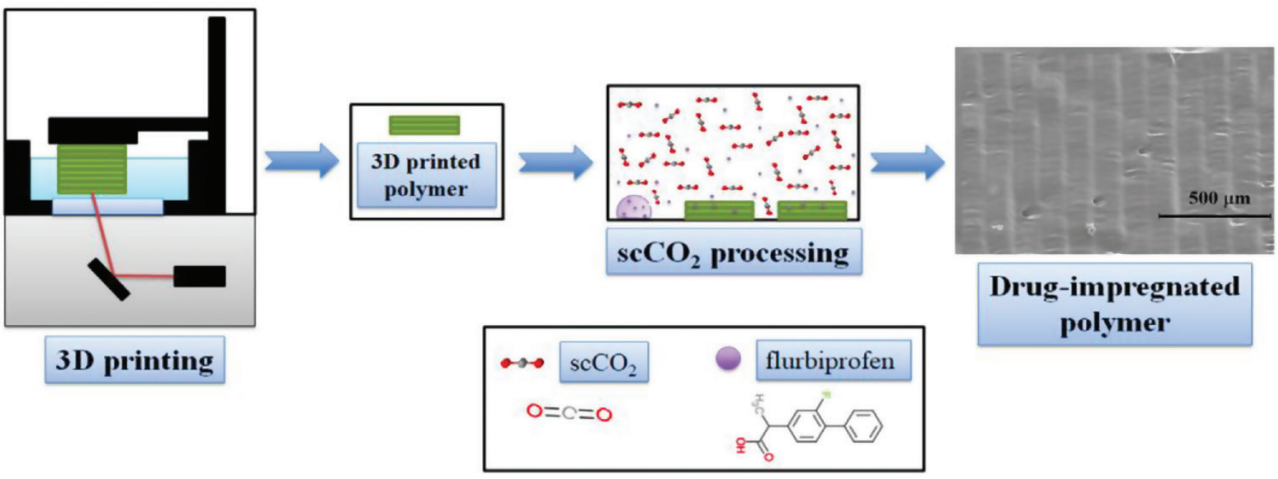


**Figure 10** Schematic illustration of the drug implantation process using supercritical carbon dioxide technology in conjunction with additive manufacturing to minimise drug exposure to heat.[144]

**Table 17** Type, drug and material of bone implants

| Type of printer | Drug | Material | Reference |
|---|---|---|---|
| SE | Vancomycin, ceftazidime, BMP-2 | PCL | [149] |
| (3D-Bioplotter) | Dexamethasone, BMP-2 | Bioactive glass, ethyl cellulose | [140] |
| FDM | Rifampicin | PCL | [135] |
| SLM (ProX DMP 320) | Vancomycin, rifampicin | Titanium, PCL, PLGA | [145] |
| (3D-Bioplotter) | Levofloxacin | PDA, PLA | [136] |
| DLP and FDM | Interleukin-4 | GelMA, PCL-HA | [137] |
| FDM (Ultimaker) | Polydatin, resveratrol | PC | [141] |
| SE | 5-FU | Calcium phosphate | [142] |
| MJ (ExONE) | Vitamin D | Tricalcium phosphate | [148] |
| SLS | Dexamethasone | PLA | [150] |
| SE (BioScaffolder) | Fibroblast Growth Factor-2 | PCL, calcium silicate | [151] |
| DLP/SLA | Acetylsalicylic | PEGDA | [134] |
| FDM | Aspirin and BFP-1 | PCL | [138] |
| FDM (Ultimaker 2+) and SLA (Kudo 3D) | Doxycline, vancomycin, cefazolin | PCL (FDM), PEGDA & PEG (SLA) | [143] |
| BJ (ExOne ProMetal) | Genistein, daidzein, glycitein | Tricalcium phosphate | [139] |
| BJ (ExOne Innovent) | *Cissus quadrangularis* | B-tricalcium phosphate, PDA | [146] |
| FDM | Ciprofloxacin, gentamicin | PEOT/PBT, magnesium aluminium or a-zirconium phosphate | [152] |
| SLS (Renishaw AM250) | Dexamethasone | Titanium | [147] |
| SLA (FormLabs Form 2) | Flurbiprofen | PMMA | [144] |

Abbreviations: BJ, binder jetting; DLP, digital light processing; MJ, material jetting; PBT, polybutylene terephthalate; PC, polycarbonate; PCL-HA, polycaprolactone-hyaluronic acid; PDA, polydopamine; PDA, polydopamine; PEGDA, polyethylene glycol diacrylate; PEOT, ethylene oxide terephthalate; PLGA, poly-lactic co-glycolic acid; PMMA, polymethyl methacrylate; SE, syringe extrusion; SLA, stereolithography; SLM, selective laser melting; SLS, selective laser sintering.

## Discussion

### Patient-specific dosing

The therapeutic's dose depends on a multitude of factors ranging from age, body weight, body surface area, indications, pharmacogenomics, severity of diseases and many more. However, commercially available dosage forms are not flexible in administrating doses specific for patients. Tablet splitting is a common practice to achieve the necessary dose, but it causes inaccuracy in dosing, changes in drug release and increased drugs instability when exposed to the surroundings. In addition, it is suboptimal as strength, dexterity, good eyesight and mental cognition are required to perform the splitting and dividing process of a tablet.[153] One of the ways to overcome is through liquid preparation. However, the inaccuracy in the liquid form is due to poor method of administration that is prevalent in the community as described in the previous section. In addition, the inability to control dose leads to medication wastage, which incurs a significant loss to the patient and government.[154, 155] AM allows rapid modification of dose for specific patients with ease through controlling the printing parameters. This is not only applicable for oral or implantable dosage forms but also with the transdermal delivery, as described earlier with the personalised acne treatment based on the patient facial contour and severity of the disease.

### Customisable drug administration

On the one hand, AM enabled the fabrication of objects with complex and intricate designs, unlike the conventional manufacturing process. As there is plenty of evidence that supports paediatrics' patient acceptability to specific taste and shape, AM can be used to develop drug dosage forms to cater to the needs of this group of patients. The improvement in taste can be achieved through utilising food-grade ink such as honey, chocolate and maltodextrin. As for the drug dosage form's shape, paediatric parents can request shapes according to their preferences.

On the other hand, AM is also useful to provide 3D information, which will benefit patients with visual impairment by aiding them to obtain dosing information independently. Wong *et al.* produced 3D medication labels for blind and visually impaired (BVI) patients to ease their drug administration.[156] Shapes and symbols were used as dosing instructions according to the patient's medical conditions. Alternatively, dosing information can also be printed directly onto the tablets, so that the BVI patients can identify the time of administration, tablet's name and indications.[157] The customisable drug administration tools will be helpful in reducing medication errors and improving BVI patient compliance.

### Multidrug approach

The use of multiple drugs, also known as polypharmacy, is becoming a common trend, given that there is an increase in the ageing population with multiple comorbidities. This problem exists in the hospital and local settings but it is the most prevalent problem in residential aged care facilities. Polypharmacy affects negatively in many areas, such as healthcare costs, adverse drug events, drug interactions and risk of falls.[158] Instead of relying on the pharmacist, physician or multidisciplinary team-led intervention, pharmaceutical companies

can work collaboratively to provide an effective solution to combat the growing problem of polypharmacy.[159] As demonstrated in the multidrug release section, the current technology of AM is capable of fabricating oral drug dosage forms containing many medications with individualised release profiles to achieve the optimal therapeutic outcome.

## Varying drug release

The ability to control drug release is invaluable in providing the optimal therapeutic effect for patients. 3DP technology has shown its ability to produce customisable drug release profiles for tablets, capsules, implants and transdermal patches. For example, a novel method has been developed to produce tablets with customisable doses and release profiles easily and efficiently, making this technology potentially accessible in the community and hospital settings.[30] Similarly, We *et al*. developed a simple method to prepare hydrogel scaffolds with controlled drug release to treat breast cancer. On-demand delivery of anticancer drugs can be achieved by using infrared radiation as the drug release trigger.[131]

## Integrating AM in compounding pharmacies

Compounding involves the pharmacist preparing extemporaneous products based on the doctor's prescription. Compounding pharmacies can provide compounding services for patients with prescriptions for medicinal products that are not commercially available.[160]

In Australia, for example, a pharmacy needs to apply for a manufacturing license from the Therapeutic Goods Administration (TGA) and follow the *Guide to Good Manufacturing Practice for Medicinal Products* to become a compounding pharmacy.[161] The compounding pharmacy can only manufacture products for which its laboratory was designed. Guidelines regarding preparation, documentation, storage and labelling of compounding products can be found in the *Australian Pharmaceutical Formulary Handbook* (APF) from Pharmaceutical Society of Australia[162] and the Guidelines on Compounding of Medicines from the Pharmacy Board of Australia.[163] Some of the common reasons why patients require compounded products are as follows. First, higher strength medicine for therapeutic use is needed, for example, 5 mg melatonin capsule for sleep which is not commercially available. Second, the medicine to treat a certain condition is not marketed in Australia, for example, tetracycline for resistant *Helicobacter pylori* infection. Third, preparations with varying active ingredients and strengths are needed, for example, 8% *liquor picis carbonis* (LPC) and 6% salicylic acid cream for psoriasis recommended by a doctor. Fourth, medicine in another dosage form is needed, for example, omeprazole suspension for paediatrics. Compounding products and equipment can be purchased from pharmaceutical companies, such as MEDISCA Australia. Other ways to get medicines that are not available in Australia include applying for the Special Access Scheme (SAS)[164] to import products from overseas for individual patients requiring the medicine.

Based on its capability to supply highly personalised medications, compounding pharmacy provided a unique venue for the application of 3DP. A digital pharmacy model of applying 3D printers for making extemporaneous formulations in compounding pharmacies has been proposed recently.[165] The proposed digital pharmacy model is based on the cooperation between pharmaceutical industries and compounding pharmacies. In the model, a compounding pharmacy will be equipped with FDM printers which have been widely studied to make customisable medications.[166] The drug-laden filaments, used in an FDM printer, can be mass manufactured by pharmaceutical manufacturers. With the filaments, compounding pharmacies can print customisable medications accordingly. On top of highlighting the versatility of FDM printing, this review article focussed on the potential modification of the commercially available FDM printer for printing drug dosage forms. In addition, the hypothetical workflow and pharmacy layout were systematically planned out to allow the transition of this technology into reality easily. Compared with conventional pharmacy dispensing, the advantage of such a digital pharmacy includes providing personalised medications efficiently and reducing human errors.

## The regulatory progress of AM in medicine

Implementation and regulation of AM are continuously evolving throughout the years. In the USA, FDA released extensive guidance governing AM-enabled medical devices in 2017.[167] The publication covers a comprehensive regulatory framework ranging from product design, manufacturing and testing requirements. Afterwards, there has been an ongoing educational webinar on AM since 2019 by the Centre for Drug Evaluation and Research (CDER), one of FDA's Division of Drug Information with the healthcare professional.[168] In 2021, another 3DP drug, namely T19 by Triastek, has received Investigational New Drug (IND) clearance by the FDA for the treatment of rheumatoid arthritis, charting the next progress in AM.[169]

China and the UK have also been developing their own regulatory framework in 3D-printed products due to their huge market potential and significance to the economy. In 2018, China Food and Drug Administration (CFDA) called for professional input before proposing their own regulatory standards for 3DP devices that cover implantable devices, biomaterials and pharmaceutical devices.[170] The key proposals issued by the CFDA cover major issues such as validation testing, printing parameters, device cleaning and sterilisation. In the UK, Medicine and Healthcare products Regulatory Agency (MHRA) published a guidance on 3DP medical devices or components parts to ensure sufficient supply of medical devices during the COVID-19 pandemic in June 2020.[171]

In Australia, there was a proposed regulatory change for personalised medical devices that covers 3DP devices for TGA.[172] The reasons behind such a change were due to the projected annual growth in the healthcare market for 3DP. In July 2020, TGA released minor updates for medical devices, detailing the risk management during designing and manufacturing, selection of appropriate excipients, cleaning and sterilisation of the medical devices. In August 2021, TGA released a newer regulatory change that encompasses personalised medical devices, which includes 3DP devices.[173]

## Challenges and perspectives

To implement this new technology in a pharmacy, pharmacy managers need to consider several factors, including the cost of a new printer, staff training, raw materials and pharmacy layout changes. In addition, it is also important to be aware of the recurring cost, such as ongoing staff training, and printer maintenance. The major improvement that can be derived

from AM would be the ability to provide personalised medication to the public, especially to the special populations. In addition, the use of an automated 3D printer instead of manual compounding would improve the manufacturing speed. This would allow the pharmacists to focus more on other important matters such as patient care.

Next, potential end-users may be concerned about the effect of the printing process on the active ingredients and excipients, for example, the use of heat during the extrusion process in FDM and drug impregnation using organic solvents. There are several methods to overcome such limitations. For example, Eleftheriadis *et al.* utilised inkjet printing to deposit the drug onto the FDM-printed substrates to minimise drug degradation.[25] Similarly, supercritical carbon dioxide can be used for drug loading instead of organic solvents as reported by Ngo *et al*.[144] Moreover, exposure to ultraviolet and high temperature has been shown to have a limited effect on the antimicrobial properties of antibiotics as reported by Ranganathan *et al*..[143]

Furthermore, drug–drug and drug–excipient incompatibility should be taken into consideration due to the intimate contact between each other in the dosage forms. Pharmacists should actively verify the necessary information such as stability, safety and chemical incompatibilities from major references, such as pharmacopoeia, Martindale and Monthly Index of Medical Specialities (MIMS), to avoid such incompatibilities from occurring. It should be noted that chemical and physical incompatibility can lead to the change in the API, which may affect the treatment outcome.

As mentioned earlier, the appearance and quality of the 3DP dosage forms depend on the printing method, printing resolution and materials. Thus, to ensure the quality, safety, efficacy and stability of the 3DP medication, there is a need for quality assurance and quality control mechanisms in place. In terms of quality assurance, the operator and pharmacist should possess the appropriate education and training before operating the 3D printer. However, this printing process can be made easier, faster and better with the incorporation of artificial intelligence as observed in the work of Stanojević *et al*.[44] As for quality control, analytical methods such as high-performance liquid chromatography and ultraviolet spectroscopy are common methods. However, the use of non-destructive analytical methods for 3D-printed drug dosage forms is advisable for rapid drug quantification and economical reason. For example, colour density-based analytical measurements have been demonstrated to be useful in pharmacies.[174]

From the patient's point of view, the added cost of medication can be a significant consideration. However, given the continuous development of the AM, the cost of the 3D printer is becoming more affordable. In addition, patients may feel that the cost is justified, especially if the 3D-printed dosage forms are tailored to their specifications. With the advent of electronic prescriptions, patients can order their medication by sending their prescription to their pharmacy of choice. When the electronic prescription is received, the pharmacist can print medications even without the patient being in the store.

## Conclusion

The AM technology opens new horizons in fabricating pharmaceutical dosage forms. With complex geometry and multiple materials, novel oral dosage forms can be prepared to achieve rapid release and sustained release profiles. In addition, 3DP is also applied in the development of next-generation wound dressing patches, microneedles and implants. The unique characteristic of AM is its ability to fabricate personalised dosage forms, which is complementary to mass-produced dosage forms. Since the first FDA-approved tablet, namely SPIRITAM, this technology is becoming more accessible to the public due to the expiring patents and decreasing cost of the 3D printers. The AM technology is expected to become a common tool in compounding pharmacies to make polypills and personalised medications.

On the one hand, as a mass manufacturing tool, 3DP has already been used to make novel dosage forms under the existing regulatory framework. However, personalised medication is not possible as the dosage forms are still mass manufactured. On the other hand, as a compounding tool to be used in a pharmacy to make extemporaneous formulations, personalisation is achievable with 3DP. The formulation can be printed by using drug-laden filaments and/or other types of printing inks. However, new regulations may be required to ensure the safety and efficacy of this proposed pharmacy practice.

## Author Contributions

Conceptualization, J.S.K., N.N.K. and L.K.; methodology, A.F.A.F. and L.K.; data curation, A.F.A.F.; Investigation, A.F.A.F. and L.K; writing—original draft preparation, A.F.A.F.; writing—review and editing, A.F.A.F., Y.Y., L.W., J.S.K., N.N.K. and L.K.; supervision, L.K. All authors have read and agreed to the published version of the manuscript.

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## Conflict of Interest

None declared.

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