

# Next steps in 3D Printing of Fast Dissolving oral Films for Commercial Production

Touraj Ehtezazi<sup>1\*</sup>, Marwan Algellay<sup>1</sup>, Alison Hardy<sup>2</sup>

<sup>1</sup>School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK

<sup>2</sup>Knowledge Exchange and Commercialisation, Liverpool John Moores University, Liverpool, UK

Corresponding author

[t.ehtezazi@ljmu.ac.uk](mailto:t.ehtezazi@ljmu.ac.uk)

## **Abstract**

3D printing technique has been utilised to develop novel and complex drug delivery systems that are almost impossible to produce by employing conventional formulation techniques. For example, this technique may be employed to produce tablets or fast dissolving oral films (FDFs) with multilayers of active ingredients, which are personalised to patient's needs. In this article, we compared the production of FDFs by 3D printing to conventional methods such as solvent casting. Then, we evaluated the need for novel methods of producing fast dissolving oral films; and why 3D printing may be able to meet the short falls of FDF production. The challenges of producing 3D printed FDFs are identified at commercial scale by referring to the identification of suitable materials, hardware, quality control tests and Process Analytical Technology. In this paper we discuss that the FDF market will grow to more than \$1.3 billion per annum in next few years and 3D printing of FDFs may share part of this market. Although, companies are continuing to invest in technologies which provide alternatives to standard drug delivery systems, the market for thin film products is already well established. Market entry for a new technology such as 3D printing of FDFs will, therefore, be hard, unless, this technology proves to be a game changer. A few approaches are suggested in this paper.

Key words: 3D printing, Fused deposition modelling, extrusion, fast dissolving oral films, personalised medicine

## 1. Introduction

Three dimensional printing (3DP) has been employed for the development of novel pharmaceutical dosage forms. These include tablets,[1, 2] capsules,[3] nose patches,[4] filaments,[5] core-shell tablets,[6] gastro-floating tablets,[7] hollow cylinders,[8] dual compartmental dosage units,[9] multi-compartment capsular devices,[10] orodispersible films,[11] fast dissolving oral films,[12] and liquid capsules.[13] 3DP contributes to more end-stage personalisation of solid dosage forms.[14-18] One aspect of personalised medicine is the move away from the concept of ‘one-size fits-all’ to treatment of patients meeting their particular needs. This provides better management of patients’ health and achieving desired therapies with the best therapeutic outcomes. In particular, 3DP allows the adjustment of a drug dose based on patient’s health state. Additionally, 3DP permits the combination of more than one active pharmaceutical ingredient (API) in tablets to produce polypills and reduce the number of administered tablets, which would improve patient compliance.[19, 20]

Although 3DP appears to produce one dosage form at-a-time for each individual, this technique has been applied at industrial scale. The Food and Drug Administration (FDA) approved Spritam® (brand name of Levetiracetam) as a 3D-printed tablet for the treatment of epilepsy. The main advantage of Spritam is instantaneous disintegration over few seconds, which cannot be achieved by conventional tablet formulations.

Fast dissolving oral films (FDFs) are commonly used in the administration of drugs to paediatric and geriatric patient populations, where the difficulty for swallowing solid oral dosage forms is eliminated. This approach can also be useful for patients who have swallowing difficulties (dysphagia). It is estimated that approximately one in 25 adults has swallowing problems. [21] In addition, elderly and children are more prone to swallowing difficulties. Some patients with

dysphagia have problems swallowing certain foods or liquids, while others can't swallow at all.

There are two classifications of dysphagia:

- A. Oropharyngeal dysphagia refers to difficulty in the passage of liquids or food from the mouth to the oesophagus.
- B. Oesophageal dysphagia refers to difficulty with the passage of food through the oesophagus.

FDFs can be used for both standard oral drug delivery where the active ingredient is swallowed by the patient and absorbed in the gut, or for buccal drug delivery where the active ingredient is absorbed within the mouth. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules.[22]

The market for FDFs has been under development for at least two decades, and it is well established in certain indications, in particular, over-the-counter. FDFs are manufactured by hot-melt extrusion or solvent-casting methods.[23-26] Although the solvent-casting process is popular, the application of hot-melt extrusion process is growing, this is due to its solvent-free, continuous production, and resulting in less chance of drug instability. Fused-deposition modelling 3D printing (FDM-3DP)-described in the following-is closer to hot-melt extrusion method. Previous works have shown the feasibility of producing FDF by 3DP.[11, 12, 27] The aim of this article is to explore production of FDF at the industrial scale by 3DP and identify challenges to achieve this goal. This is important, as companies are continuing to invest in technologies which provide alternatives to standard drug delivery systems. While, the market for thin film products is already well established, market entry for a new technology such as 3D printing of FDFs will have to

overcome barriers to entry, unless, this technology proves to be a game changer, and in this paper a few approaches are suggested.

## 2. Principles of 3DP

In 1971, Wyn Kelly Swainson filed a patent for producing three-dimensional figure product,[28] followed by Charles W. Hull, who filed a patent for 3D printing by stereolithography in 1984.[29] Generally 3DP processes start with a computer-aided design (CAD) model or a digital scan. The CAD models are produced by computer software such as SolidWorks (Dassault Systèmes) as shown in Figure 1A. Then this is converted into the Standard Tessellation Language (STL) format, which is modified into thin cross sections by a slicing software (Figure 1B). This software also allows to adjust other 3DP parameters such as type and colour of 3DP material (Figure 1C), infill percentage and thickness of each layer (Figure 1D), 3DP printing extruder temperature and build-plate temperature (Figure 1E), and the speed of printing (Figure 1F). The thickness of each layer ranges from 500 nm [30] to 2500  $\mu\text{m}$ . [31] This allows the creation of highly personalised and detailed 3D physical objects from digital designs. Then, a 3D printer conducts the printing process, which usually prints or forms (laser curing) a 2D pattern on a printer build-plate or in a liquid [32]. Following completion of this layer, the printer makes another layer (usually on top of that). This iteration process is continued until the object is materialised in full-size.

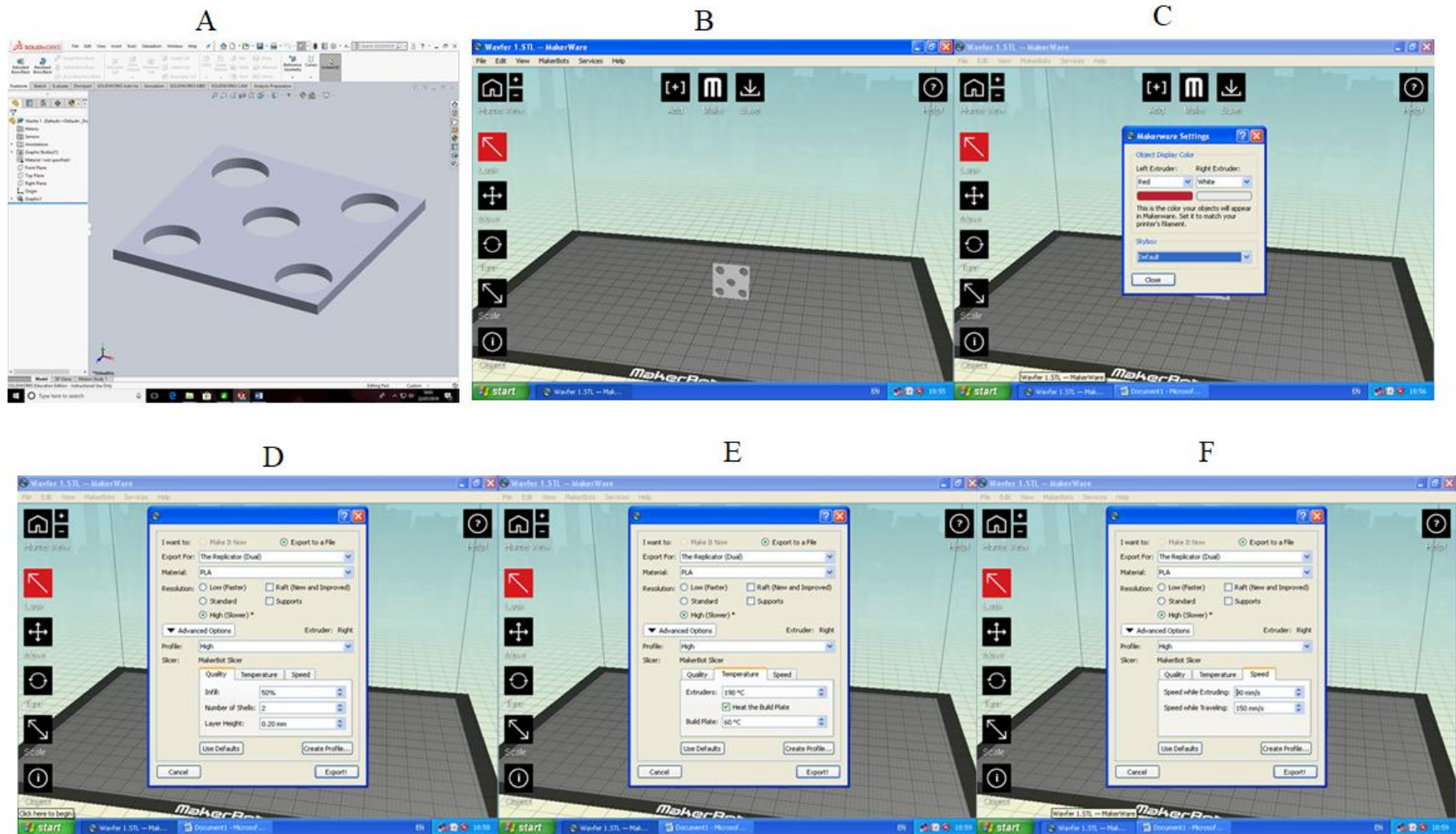


Figure 1: Digital steps in 3DP: A) CAD model is produced by software, B) Software to slice the CAD model to thin sections, C) Adjusting type and colour of filament in FDM 3DP, D) Adjusting infill percentage and layer height, E) Adjusting temperature of extruder in FDM printing and the temperature of build-plate, F) Adjusting the speed of printing.

### 3. Types of 3DP

There are three types of 3DP that widely used for the manufacture of solid dosage forms. These are explained in the following.

#### 3.1 Inkjet 3DP

Inkjet method produces uniform droplets from an inkjet device. [33] The first application of inkjet 3DP was published by Katstra *et al.* 2000 to produce tablets.[34] In this method the 3DP was composed of spreading a thin layer of powder over a piston plate. Then a liquid binder solution was passed through a nozzle, which was rastered back and forth over the powder bed, which allowed printing droplets on the powder and binding powder particles. This generated a 2D pattern. Then the piston was lowered by a fixed distance and another powder layer was spread over the previous layer and the process was repeated. It appears that a continuous inkjet printing mode was utilised in the work, as the droplets were estimated to be 80-90  $\mu\text{m}$  from a 45  $\mu\text{m}$  nozzle. [33] Clearly this method would require drying manufactured tablets, which could delay production process and increase costs. This inkjet method is the basis of producing Spirtam tablets (the Aprecia's patented ZipDose ®Technology). In a similar approach, Shi *et al.* 2019 reported the application of Z Corp 3D printer in the manufacture of tablets with 10-15 mm diameter.[35] In this technique, an inkjet printing head moved across a bed of powder containing mainly  $\text{CaSO}_4$ , which precisely deposited a liquid binding material containing 5-fluorouracil, PEG and Soluplus in the shape of tablet. A fresh layer of powder was spread across the top of the model, and the process was repeated. When the tablet was complete, unbound powder was removed.[35] Increasing the tablet diameter increased the dissolution rate of the API.

Inkjet printing has also been employed for the manufacturing of tablets with internal honeycomb structure to control drug release.[1] A molten (90°C) mixture of beeswax and drug was fed to a piezoelectric inkjet nozzle, which was operated under drop-on-demand mode. The nozzle diameter was 35 µm. These tablets did not need a drying process, which accelerates the production process. In addition, the operating temperature is relatively low (90°C) compared to fused deposition modelling (165-190°C [12]), which makes this approach more attractive. Finally, this method does not require high molecular-weight polymers, which would be useful for the 3DP of fast dissolving oral films.[12] Buanz *et al.* applied thermal inkjet printing to deposit droplets of salbutamol solution on oral films made of potato starch.[36] This method was useful for depositing a single layer of drug solution; as multiple layers damaged the films, which would be expected by considering hygroscopic nature of the starch films. The same approach was applied to deposit warfarin on hydroxypropyl methylcellulose (HPMC) films.[37] On the other hand, Eleftheriadis *et al.* 2018 applied thermal inkjet printing to deposit diclofenac sodium solution (containing water and ethanol) on Décor Paper Plus edible sugar sheets in multiple prints; and they found that the sugar sheets maintained their integrity up to 9 repeated prints.[38] Janßen *et al.* 2013 applied Flexographic printing to print on orodispersible films. Although this is not an inkjet printing, it is a common technique for industrial printing onto surfaces such as capsule shells.[39] Genina *et al.* 2012 combined inkjet printing and Flexographic printing to produce papers containing APIs (deposited by inkjet printing) and coated by polymers (using Flexographic printing).[40] In another approach, Kollamaram *et al.* 2018 utilized drop-on-demand inkjet printing to deposit paracetamol and indomethacin on hydroxypropyl methylcellulose films. The inkjet nozzles had diameters in the range of 150-300 µm due to high viscosity of the ink solutions. The films contained average amounts of 447 µg of paracetamol and 703.1µg of indomethacin.[41] The investigators avoided



using aqueous solutions in the inks to prevent disintegration of the films. This is important as, the surface roughness of the films may have a negative impact on patient experience. Planchette *et al* 2016 showed that deposition of drug solutions on orodispersible films by inkjet method could be optimised to avoid this drawback.[42] Interestingly, Buanz *et al* 2015 found that inkjet-printed films did not exhibit drug crystallisation in the films, while solvent-casting method encountered this problem.[43] To achieve product traceability and combat drug counterfeiting, Trenfield *et al.* 2019 combined inkjet printing and 3D printed tablets. The inkjet printing was utilized to deposit QR codes on 3D printed tablets. The ink was made of methylparaben (20% w/v), Eudragit RS100 (10% w/v) and sodium benzoate (2% w/v) in a mixture of ethylmethylketone, acetone and methanol (50:20:30).[44] In a recent work, Thabet *et al.* 2018 reported a continuous production of orodispersible films by inkjet method.[45] Initially a roll of orodispersible film was made as base-film by a solvent casting method; and then a dye solution was printed on the base-film. The printed layers were produced in the drop-on-demand mode utilising an inkjet head with 30  $\mu\text{m}$  nozzle diameter. This approach allowed producing multi-layered films. As it would be expected, a drying process was involved to convert the wet film into a dried film, for both the base-film and printed-film. The printed films disintegrated in 15 s.[45]

To increase the loading capacity of inkjet printed solid dosage forms, Iftimi *et al.* 2019 applied inkjet printing on pharmaceutical solid foams. They found that the plasticised HPMC foams had a superior absorption capacity and fast penetration speed for different solvents due to the open cell pore structure and higher porosity as compared to nonplasticised additive-free foams.[46] To achieve foams with different porosity, methods were applied such as freeze-drying, vacuum oven drying and drying at room temperature.[46] The surfaces of foams changed after inkjet printing of

the API-containing ink, due to a partial dissolution and/swelling by water-based ink during printing, however, the foams were able to maintain integrity up to 35 repeated prints.[46]

### 3.2. Fused Deposition Modelling

Fused deposition modelling has been applied widely in manufacturing of novel pharmaceutical dosage forms.[47-55] Filaments (typically 1.75-3 mm) are feedstock of conventional FDM 3D printers. In these printers, the filament passes through a tubing system and rotating pulleys/gears in the 3D printer head, which melts and extrudes the filament through a narrow nozzle (typically 0.4 mm diameter). The molten filament is deposited on a platform according to the design created using the slicer software. The rastered back and forth movement of the printer head deposits the molten material side-by-side, and the z-axis movement of the platform deposits the molten filament layer-by-layer. The molten-state of the filament fuses the layers. This process is repeated until the object is fully materialised. FDM 3D printers can produce objects with homogenous drug distribution,[56] and reproducible dimensions, in particular when filaments are used with uniform diameters (low diameter tolerance).[49] Polylactic acid (PLA), polyvinyl alcohol (PVA) and acrylonitrile butadiene styrene (ABS) are the main polymers used in FDM-3DP.[32] To ensure that each deposited layer can hold another layer on the top, the melting point of the filaments should be much higher than the printing environment temperature. The typical melting temperatures are above 100°C. Therefore, the filaments should be thermally stable, non-volatile and non-aerosolising.[57] The API usually is incorporated in the filament, hence, the stability of the API during 3DP is essential. The low cost of FDM printers has been the main reason for the wide application of FDM 3DP in pharmaceutical dosage forms.

In the FDM 3DP the drug is loaded into the filament either by extrusion method or absorption. Pietrzak *et al.* 2015 employed a twin-screw extruder operating at 130°C to produce a filament of

theophylline and Eudragit.[47] Similarly, Maroni *et al* 2017 used a twin-screw extruder (Haake™ MiniLab II, Thermo Scientific, US-WI) equipped with counter-rotating screws, to produce filaments made of HPMC, Kollicoat® IR (KIR), and hydroxypropyl methyl cellulose acetate succinate (HPMAS) at operating temperature of 165°C.[5, 10] This research group produced filaments of hydroxypropyl cellulose (HPC) at slightly less temperature 150°C.[3] Also, Gioumouxouzis *et al.* 2017 mixed hydrochlorothiazide, PVA and mannitol to create a homogenous mixture, which was fed to Filabot Original® single-screw hot-melt extruder operating at 170°C.[8] In a different approach, PVA and Aripiprazole was mixed in ethanol to ensure good drug content uniformity in the extruded filament. The mixture was dried at 70°C for six hours to prevent formation of air bubbles during extrusion. The filament was produced using Noztek® Pro filament extruder at 172°C.[11] To reduce the operating temperature of the hot melt extrusion, Okwuosa *et al.* 2016 incorporated polyvinylpyrrolidone (PVP) into the filament formulation, which reduced the operating temperature down to 90-100°C.[58] While, this research group also found that Eudragit EPO can be extruded at 90°C.[13] Similarly, Ehtezazi *et al.* 2018 employed polyethylene oxide to reduce the operating temperature down to 60°C.[12] On the other hand, Goyanes *et al.* 2015 immersed PVA filament in a beaker containing ethanol where the drug (5-ASA or 4-ASA) was dispersed.[49] This was to absorb drug into the filament. It should be noted that filaments should have suitable strengths to withstand the stresses during printing. To achieve this, high molecular weight polymers will be required, at least 40 kDa,[58], or preferably greater than 100 kDa.[12] A simplex centroid mixture design experiment may be applied to predict the best polymer combination for hot melt extrusion.[59]

### 3.3. 3D Based Extrusion Printing

This is an example of direct-writing 3DP and has been applied for the formulation of tablets.[2, 19, 60-62]. In this approach, a paste of drug and excipients is prepared and fed to cartridges such as syringes. Then the paste is extruded through tips with nozzle diameter of 500  $\mu\text{m}$ . [19] Similar to the FDM, the paste is deposited on a platform according to the design created using the slicer software. The back and forth movement of the printer head deposits a thin layer of the paste and the z-axis movement of the platform deposits the paste layer-by-layer. After completion of the printed dosage form, the object is dried at temperatures such as 40°C over 24 hrs, or lyophilised. It is evident that this technique of 3D printing does not require the formation of filament. However, a drying process is required to reduce the solvent residue, less than limits set by ICH guidelines.[19]

A powder based extrusion 3DP has been used for printing of tablets. [63] This is another example of direct-ink writing 3DP, where the powder mixture containing drug and excipients is feed to the nozzle. The nozzle temperature is high enough (170°C) to melt the powder mixture and leave a molten deposit on the printing platform. The advantage of this method is avoiding need for the formulation and preparation of filament. Zidan *et al* 2019 applied X-ray tomography to study 3D micro-extrusion printing technology; and they found presence of air pockets in the printing cartridges that were formed during packing the printing cartridges.[64] Although the produced tablets did not show any defects due to the air pockets, the risk of producing defective tablets was still there. As an advantage, 3D micro-extrusion printing method avoids exposing the drug and excipient molecules to high temperatures (FDM) or UV irradiation (UV-curing 3DP), but the paste formulation requires pressures between 0.5-4.5 bar to extrude from the nozzle. Hence, the paste

formulation should be optimised to allow consistent flow of the paste from the nozzle to achieve reproducible products.[64]

#### 4. Conventional Methods of Manufacturing Fast Dissolving Oral Films

Fast dissolving oral films (FDFs) are thin films with the area of 5-20 cm<sup>2</sup> containing an active ingredient. The fast dissolution/disintegration is achieved in water or saliva by water-soluble polymers. The fast dissolving feature would improve patient compliance.[65] Typically the loading dose of FDFs is less than 15 mg. The formulation contains a matrix polymer, plasticiser, taste masking agent, colour, and API. There are two methods that are widely used for the formulation of FDFs: solvent casting technique, and hot melt extrusion.[66] Other methods have been also reported in the literature such as semisolid casting, solid dispersion extrusion, rolling, [67] electrospinning, and electrospraying.[68]

##### 4.1. Solvent casting

The solvent casting method is the most popular method for the manufacture of FDFs.[69-81] In this method, all the formulation components are dissolved/dispersed in an aqueous media. Then, the homogenate is cast over a flat and wide surface (usually glass) for drying to form a thin film. This is followed by peeling-off the film and cutting to desired sizes. Recently, Visser *et al.* 2017 reported the formulation of bilayered FDFs. This was achieved by a double-casting method. Initially, the first layer of casting solution was cast using a casting height between 500 and 2000  $\mu\text{m}$ . The film layer was dried for 1.5–8 h at 30 °C and ambient relative humidity. After drying of the first layer, the second layer was cast and dried.[82]

There are challenges when the formulation is scaled up from the small laboratory scale to industrial scale. The casting and drying processes are the critical steps. Then, the optimization of casting

speed and drying time are important from the commercial point of view. As the thickness of wet strip cast, the rheological and physicochemical properties of the cast solution affect the drying speed.[83, 84] These limit the scale-up process, which could affect the final thickness of the dried strip. Furthermore, the selection of solvents depends on the solubility of the API, its stability in the solvents and its heat sensitivity during the drying process. The suitable solvent for the API may affect the solubility of plasticiser and taste masking agents. It should be added that solvent residues should be determined in the FDFs according to ICH Q3C.[85] This document recommends acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. Also, it recommends the use of less toxic solvents; and describes solvent levels, which are considered to be toxicologically acceptable for some residual solvents. This document recommends avoiding using toxic solvents such as 1,2-Dichloroethane (Class I solvents). Solvents such as chloroform and dichloromethane are recommended for limited use (Class II solvents). According to this document, the residues of dichloromethane should be less than 600 ppm, and the residues for chloroform should be less than 60 ppm. Ideally, less toxic solvents (Class 3) should be used, where this is practical.[86] These include solvents such as acetone, ethanol, and ethyl ether.

When FDFs are dried, they are cut into suitable shapes and sizes according to the required dosage. Sometimes, the companies roll and keep the uncut FDF batch, known as ‘rollstock’.[66] However, this should be avoided, as the properties of the product may change over the storage period, in particular it may absorb moisture from the environment.[83]

The structured orodispersible film templates (SOFTs) have been developed by the solvent casting method. The SOFTs were developed to achieve a highly porous, drug free template for the individualised loading of API suspensions from the top side.[87]

#### 4.2. Hot melt extrusion

The hot melt extrusion (HME) is becoming a popular method.[23] In this approach, all the components are mixed and fed into a screw extruder, which is most widely accepted for pharmaceutical industry. The extruder operates at temperatures in the range of 40-180 °C. [88-91] Then the molten mixture is introduced into a die system, which determines the shape of the film.[66] There are benefits to HME such as: lack of drying process, avoiding degradations in a solvent, and better product homogeneity.

### 5. The Application of 3DP for the Manufacture of FDFs

3DP or additive manufacturing has been applied in the formulation of FDFs or oral films. Jamróz *et al.* 2017 applied FDM 3DP to produce FDFs of aripiprazole.[11] As explained in the above, the API and PVA powder initially dispersed in ethanol to ensure a homogenous mixture, which was dried at 70°C. The dried powder was fed to an extruder to produce filament at 172°C. Although the manufactured filament was not smooth, it was possible to be used in FDM 3DP. The presence of air bubbles made the surface of the filament uneven. At this stage it is not clear the reason for the formation of air bubbles. As this has not been observed in other studies, then it is possible that residual ethanol was released at high temperature of extrusion. In addition, the filaments were brittle. On the other hand, PVA filaments had suitable mechanical properties in other studies. Therefore, it remains to be determined that whether aripiprazole itself or its fraction in the PVA caused undesired mechanical properties of the filaments. The dimensions of designed aripiprazole FDFs were 20×30×0.15 mm. During 3DP the adhesion of PVA film on the printer build-plate was an issue. The authors utilized BuildTak® adhesive and heated printer build-plate to overcome the problem. These adjustments are critical since the 3DP object had only one layer; and this must be defective-less. The authors compared 3DP FDFs with FDFs prepared by the solvent casting

method. As reported previously, crystals of aripiprazole was observed in the FDFs by the solvent casting method, while these were absent in 3DP FDFs. The FDFs disintegrated in the range of 27.5-43.0 seconds. Incorporation of the API increased the disintegration time. The thickness of films prepared by solvent casting method was approximately 2 times smaller than 3DP films, but the disintegration time was only 5 s faster.

Ehtezazi *et al.* 2018 applied FDM 3DP for the formulation of multi-layered FDFs[12]. In the formulation PVA (Mw= 89-98 kDa) was used as powder to be mixed with paracetamol (acetaminophen). The filaments were manufactured by employing Noztek Pro Filament Extruder, operating at 130°C. This was to ensure that a stiff paste would be extruded. This was reflected in the X-RD data that PVA crystals were present in the filament and to some degree in the film. The resulting filaments showed suitable strength for FDM 3DP. In this work another layer of taste masking agent was printed on the drug containing layer. A smooth filament was produced using strawberry powder and PEO (Mw=100 kDa). The printed films had thickness of greater than 197  $\mu\text{m}$ , which were thicker than FDFs reported by Jamróz *et al.* 2017,[11] however, the disintegration time was similar in some formulations and much longer for tripled layer FDFs. As for Jamróz *et al.* 2017 work [11], the adhesion of printed FDFs on the printer build-plate was a problem, which was rectified by using sticky masking blue tape (3M™). The FDFs were printed at 190°C for PVA drug containing layer (similar to previous work [11]) and 160°C for taste masking layer.

In another work reported in 2018 by Musazzi *et al.*, a hot melt ram extrusion 3D printer was employed to produce FDFs.[27] In this method ,maltodextrin, glycerol, glycine, titanium dioxide and paracetamol were mixed and introduced into the chamber of piston, which was thermostatically set in the range of 30-200°C. Using a ram, controlled amounts of the molten mixture were deposited on a mobile plate. The produced films had thickness in the range of 150-



250  $\mu\text{m}$ , with disintegration time in the range of 65-111 s, which was slightly longer than for previously reported FDM 3DP films. [11, 12] One of the main advantages of this approach is the elimination of the filament manufacturing process. Drug loading was 40%, which allowed to load up to  $73.56 \pm 3.90$  mg of paracetamol, which is comparable to the loading of FDM 3DP films reported previously ( $91.12 \pm 4.40$  mg).[11] The hot melt ram extrusion 3D printer produced films at  $85^\circ\text{C}$ , [27] which was much lower than the operating temperature of previous works ( $190^\circ\text{C}$ ) that used PVA as the polymer.[11, 12] This is another main advantage of the hot melt ram extrusion 3D printer, which would not compromise the stability of the active ingredient. About 80% of paracetamol was released within 6 minutes from FDFS produced by the hot melt ram extrusion 3D printer.[27] While for FDFs produced by the FDM, the drug release rate was similar only to single layered FDFs, adding taste masking layer reduced the drug dissolution rate.[12] Interestingly, the drug release was faster for aripiprazole FDM 3DP films, compared to films made by the solvent casting method. The FDM 3DP films released about 90% of aripiprazole within 5 minutes, while this was about 50% for FDFs made by the solvent casting method.[11] It should be noted that the principles of the hot melt ram extrusion 3D printer is similar to the regenHU 3D printer (regenHU, Fribourg, Switzerland, Figure 2), which was employed to produce paracetamol tablets by extrusion-based 3D printer.[60]. Table 2 presents a summary of recent research work on FDFs.

Table 2. Summary of some research work conducted on FDFs

Polymers	Manufacturing Method	Drug	Dose	Film Thickness	Reference
Maltodextrins	Solvent Casting	Piroxicam	<sup>a</sup> 28.2 mg	204 $\mu\text{m}$	[88]
Maltodextrins	Hot Melt Extrusion	Piroxicam	<sup>a</sup> 27	229 $\mu\text{m}$	[88]
PVA	3D FDM	Paracetamol	<sup>b</sup> 8.5 mg	298 $\mu\text{m}$	[12]
PEO 200 kDa	3D FDM	Ibuprofen	27.1 mg	245 $\mu\text{m}$	[12]
Maltodextrins	Hot melt ram extrusion 3D printing	Paracetamol	73.56 mg	150-250 $\mu\text{m}$	[27]
Hypromellose E15	Solvent Casting	Lercanidipine HCl	25 mg	57.5 $\mu\text{m}$	[92]
HPMC (15 cps)	Solvent Casting	Granisetron Hydrochloride	1 mg	67 $\mu\text{m}$	[74]
HPMC K4M	Solvent Casting	Piroxicam	10 mg	200 $\mu\text{m}$	[93]
PVA/PVP	Electrospinning	Piroxicam	1 mg	43 $\mu\text{m}$	[94]
Dextran and Maltodrextrin	Solvent Casting	Amphotericin B	<sup>d</sup> 0.3 mg	140 $\mu\text{M}$	[95]

HPC	Extrusion 3D printing	Warfarin	3.9-7.4 mg	100 µm	[96]
HPMC	Solvent Casting	Captopril	10 mg	400 µm	[97]
Maltodextrins	Solvent Casting	<sup>e</sup> Melatonin	<sup>f</sup> 3.4 mg	235 µm	[98]
Lycoat® RS 780	Hot-melt extrusion	Chlorpheniramine Maleate	4 mg	60-110 µm	[99]
HPMC	Solvent Casting	Diclofenac sodium	20 mg	576 µm	[100]
Trehalose/pullulan	Solvent Casting	<sup>g</sup> Therapeutic Proteins	0.8 mg	600 µm	[22]
PVA	Solvent Casting	<sup>h</sup> Prednisolone (poorly soluble drug)	0.003 mg	90 µm	[101]
HPMC	Solvent Casting	Warfarin	2.5 mg	72 µm	[37]
poly(sodium methacrylate, methyl methacrylate)	Solvent Casting	Paracetamol	<sup>i</sup> 123 mg	189 µm	[102]

<sup>a</sup>Based on a 2×3 cm film size

<sup>b</sup>Dual layer film with one taste masking layer

<sup>c</sup>Without taste masking layer

<sup>d</sup>Based on 1×1 cm film

<sup>e</sup>Melatonin as free drug + lipid microparticles loaded with melatonin

<sup>f</sup>Based on 30 mg FDF

<sup>g</sup>Lysozyme and  $\beta$ -galactosidase were considered in the study, but the application can be extended to insulin

<sup>h</sup>Drug was loaded into mesoporous silica nanoparticles

<sup>i</sup>Based on 2×3 cm film

### *5.1. Critical Comparison between Conventional and 3D Printed FDFs*

The machinery is well established for industrial scale and continuous production of films by the solvent casting method. There are several suppliers in the market that can provide industrial scale film making equipment such as Harro Höfliger, Umang Pharmatech Pvt. Ltd, and Aligned Machinery. The machine evenly coats a layer of liquid material on the surface of a reel base roll. The solvent is evaporated and dried through drying channels. The film is collected after cooling in a roll. In addition, packaging machines have been developed that cut the film rolls into desired sizes and packed in pouches or sachets.

On the other hand, 3D printers for mass production are about to enter to the market. A modular, automated FDM 3D printing system has been developed by the Stratasys Ltd with interconnected, high-throughput capabilities. This allows to achieve scalable volumes. Although currently machinery is not available commercially for the mass production of 3D printed FDFs, the technology is improving, and it appears in near future this aim will be achieved.

For 3D printing of FDFs by the FDM, this would require the manufacture of filaments, which would allow feeding the material to the 3D printer. The formulation of the filament would require optimisation based on the drug and dose. Perhaps this would be equivalent to the manufacture of

slurry/solution for the production of FDFs by the solvent casting method. The use of filaments provides the possibility of continuous production by 3D printing. Although direct ink writing 3D printing by screw-fed method [103] may eliminate the use of filament in 3D printing of FDFs in a continuous mode for mass production, this approach would require its own optimisations. This includes suitable mixing of the powder in the printer head, formation of suitable molten paste at the tip of the printer nozzle permitting manufacture of a 3D object.

Recrystallisation may occur by using the solvent casting method, [104, 105] which inadvertently can affect active ingredient homogeneity. While this is less likely to occur by employing 3D FDM, due to uniform distribution of drug molecules/particles within a polymer matrix.[12, 106] Using the solvent casting technique, the incorporation of a particulate API may alter mechanical strength of the FDF, [88] whereas 3D printing provides the opportunity to print the drug/taste masking layer as a separate layer on a support/drug load base.[19, 39, 107, 108]

Both 3D FDM and solvent casting methods may require a new development of an FDF formulation for each API. However, these may be avoided by applying flexographic printing technology, as drug is printed on a base, [39] although a high drug dose may not be loaded on the film.

Furthermore, 3D FDM provides easily both scale-up and scale-down of the process, than solvent casting method.[109] This is because 3D FDM allows to print FDFs in single units, the number of printed films can be adjusted according to the needs. While for the solvent casting method, scale-up of the process requires suitable adjustments to ensure achieving homogenous mixtures with suitable viscosity to form a film.[105] Also, less cleaning may be required for the manufacture of FDFs by both 3D FDM and flexographic printing technology[39] than solvent casting method, as it may require cleaning homogeniser and tanks for manufacturing the casting mixture. It should be noted that cleaning of extruder will be required for 3D FDM, while cleaning the printer can be

achieved relatively easily. There is a potential risk of leachables and extractables from the plastic liner in the solvent casting method, [110] however, this may be minimised by the 3D FDM, when a metal printer bed is utilised. Finally, a range of doses can be realised by 3D FDM,[47, 106] by printing different layers, but this could be challenging by using a solvent casting method.[111]

## 5.2. Characterization of 3D Printed FDFs

There are several methods to characterize FDFDs,[112] which are also applicable for 3DP FDFs. These are explained in the following.

### 5.2.1. Tensile properties

Tensile properties may be considered as tensile strength, elongation (strain), and Young's modulus (elastic modulus). Tensile strength is defined as maximum stress applied at which the film or filament (if this is applicable) breaks. This test should be performed for both 3DP FDF and the filament. Tensile strength test is performed to measure the mechanical strength of films and filaments. A suitable mechanical strength of filament is required, to ensure withstanding the mechanical stress during printing. It can be calculated from applied load at the rupture point divided by the strip/filament cross-sectional area given in the equation below[113]:

$$\text{Tensile Strength} = \frac{\text{Load at Breaking Point}}{\text{Film Width} \times \text{Film Length}} \quad [1]$$

As well as tensile strength, film/filament elongation is calculated from Equation 2.

$$\%E = \frac{L-L_0}{L_0} \times 100 \quad [2]$$

Where  $L_0$  denotes initial length of the film and  $L$  depicts final length of the film after applying force. Typically, the tensile properties of FDFs are measured by employing a texture analyser [12, 47, 88, 114, 115]. Tensile properties provide information about the integrity of the product while handled by the user or during packaging procedure. Tensile properties also reveal the interaction between plasticizer and polymer in the FDF, whether the polymer and plasticizer mix freely.[88] It has been suggested to calculate tear resistance of FDFS too.[112]

The film stiffness is measured by Young's modulus ( $Y$ ) as the following.

$$\sigma = \frac{F}{A} \quad [3]$$

$$Y = \frac{\sigma}{E} \quad [4]$$

Where  $\sigma$  denotes the stress on the film and  $E$  is defined as strain.

Maltodextrin FDFs (prepared by hot melt extrusion) showed tensile strength in the range of 1-7 MPa, with % $E$  of 92-559%, and Young's modulus of 0.26-1.93 MPa, [88] while tensile strength of  $10.7 \pm 0.5$  MPa has been reported for films prepared by solvent casting method.[116] The inclusion of nanoparticles increased tensile strength of FDFs prepared by the solvent casting method, but reduced film elongation when the film breaks.[117]

### 5.2.2. Film flexibility

The film flexibility is determined by bending the film over a shaft/mandrel and the film is examined for cracks over the area of the bend. The film is assumed flexible if no cracks are visible at a 5 times magnification.[88]

### 5.2.3. Folding endurance

A film/strip is repeatedly folded until it breaks. It is stated as the number of folds at the breaking point. A film is considered structurally durable (having a good folding endurance number) if the folding endurance is in the range of 200-300; and the film is considered structurally acceptable (having an average film endurance number) if the folding endurance is less than 200 but the film withstands few folds. If the film is brittle, then it has poor folding endurance.[92]

#### 5.2.4. Morphology study

The morphology of films or filaments are evaluated by Scanning Electron Microscopy (SEM) [11, 12, 45, 118-120] and optical microscopy.[11, 120, 121] These evaluations allow to determine the smoothness of filament or film surfaces or small air bubbles intrusions into filaments or films. The SEM studies of film cross sections showed the formation of a network between the polymer and drug.[119]. The rough surface of films would affect acceptance of the film by the patient.[120]

#### 5.2.5. Swelling property

Although measuring the swelling properties of FDFs has been suggested,[112] this would be more suitable for buccal films that are designed to adhere to the surface of mucosa in the oral cavity.[122] This is because FDFs are designed to disintegrate in the range of 5-60 seconds, and this would be relatively a short time to make accurate measurements. The degree of swelling may be calculated from the following Equation

$$\text{Degree of Swelling} = \frac{W_t - W_0}{W_t} \quad [5]$$

Where  $W_t$  denotes the final weight,  $W_0$  depicts the initial weight.

#### 5.2.6. *In vitro* disintegration time



The disintegration test is one of the important characteristics of FDFs. However, there is no official apparatus to determine the disintegration of films accurately. The disintegration time may be estimated by two methods: a) the Disintegration Test Apparatus b) petri dish. For the Disintegration Test Apparatus, the film is placed in a basket over 2-mm-size mesh with disintegration disk on it. The basket is raised and lowered in a solution (typically distilled water) at 37°C. The time is recorded for each film to disintegrate and pass the residue completely through the wire mesh. The estimated disintegration time may become longer than it is, if film residues adhere to the mesh, or the immersion liquid gets cloudy. For the petri dish method, the film strip (about 4 cm<sup>2</sup>) is placed in a petri dish (internal diameter of 5 cm), which contains 10 ml of simulated saliva. The disintegration time is considered as a time when film starts to disintegrate.[92]

#### 5.2.7. *In vitro* dissolution studies

Dissolution testing is carried out for FDFs according to compendial methods.[123] A phosphate buffer is utilised with pH of 6.8 [123] or 5.7 (to simulate saliva).[102] The solution temperature is maintained at  $37 \pm 1^\circ\text{C}$ , however, the compendial apparatus usually is not suitable for measuring the dissolution rate of drug from FDFs. Therefore, Adrover *et al.* 2015 developed a microfluidic device for dissolution studies of FDF.[124] In another approach, Krampe *et al.* 2016 modified the compendial paddle apparatus and developed a novel device to simulate the conditions in the mouth by adapting the composition of the saliva, the mechanical force of the tongue, the saliva volume and saliva flow.[125]

#### 5.2.8. Fourier infrared transform spectroscopy

Fourier Transform Infrared Spectroscopy (FTIR) is conducted on FDFs to allow identifying the interaction between drug, plasticizer molecules with the polymer.[12, 126] Hence, an efficient plasticizer would show modifications of the polymer peaks.[88]

#### 5.2.9. Differential scanning calorimetry

Thermodynamic properties of pure API, polymer, mixtures, filaments and 3D printed films are examined using a differential scanning calorimeter (DSC).[11, 12] The DSC analysis helps to identify recrystallisation of API or its amorphous state in the film or filament.[12] Furthermore, DSC data shows if water is present in the film, which may be identified by the evaporation of water from the film. In addition, DSC data provides information whether the API is dispersed at the molecular level in the polymer. This is found by alterations in the melting temperature of the polymer.[12]

#### 5.2.10 Palatability

Palatability is defined as the property of being acceptable to the mouth. This is important for the patient compliance. Palatability test is conducted by obtaining suitable ethical approval. Then subjects (volunteers) are asked to provide an evaluation of the FDFs by answering questions related to taste, comfort and sensation after administration. [88, 114],] The evaluation is done by using a scale system, such as score: 0 (very satisfied), 1 (quite satisfied), 2 (not satisfied) and 3 (not at all satisfied). [114] The parameters for comfort included convenience of administration, speed of disintegration and suitability of pharmaceutical form for taking without water.[88] Sensation was evaluated by considering residues left in the mouth after administration. E-tongue assessment is also performed to evaluate the taste masking effects.[113]

#### 5.2.11. X-Ray diffraction

The crystalline structure of the samples are analyzed typically at ambient temperature using X-ray diffractometer, 3° to 70° with 5°/min step.[11] The XRD data would indicate whether the drug is dispersed in the film as particles (usually XRD data present crystalline structures), or dissolved in the polymer (this is identified by the absence of drug crystalline signals).[126]

#### 5.2.12. Uniformity of Dosage Units

The uniformity of dosage units can be demonstrated by the *Content Uniformity* or *Weight Variation* tests. The *Content Uniformity* test can be conducted on all dosage form units, but the *Weight Variation* test is conducted on certain dosage units, which the API content is greater than 25 mg. Therefore, part of FDF formulations that contain more than 25 mg of API would be eligible for both tests. The aim of *Content Uniformity* test is to determine that drug dose from one FDF to another is consistent. The test is conducted on 10 samples (BP-2019 Appendix XIIC and USP42 <905>), when active ingredient is less than 25 mg. The amounts of drug in each FDF unit is measured by applying a suitable analytical technique such as high performance liquid chromatography. According to the BP and USP, if each individual drug content is between 85 per cent and 115 per cent of the average content and standard deviation is less than or equal 6%, then the preparation complies with the test.

#### 5.2.13. Uniformity of drug content in each sample

Fourier transform infrared (FTIR) imaging have been employed to determine the content uniformity in each sample of FDF.[92] In this approach, FTIR spectroscopic imaging with Focal plane array Detector is used to analyse the spatial distribution of the drug in the FDF. Following acquiring chemical images of films by using a microscope with FTIR system (e.g. Bruker, Germany); the images are obtained in transmittance mode by placing the film over a white ceramic

disk. Images of an area of approximately  $300\text{ }\mu\text{m} \times 300\text{ }\mu\text{m}$  are obtained. The uniformity of drug content in each sample is analysed at different locations. The spectra is obtained with a scan in the spectral range of  $4000\text{--}900\text{ cm}^{-1}$ . Then data is analysed using a suitable software such as integrated OPUS operation and evaluation software.[92]

#### 5.2.14 *In vivo* Evaluation

FDFs have been evaluated in animal models.[126, 127] In one approach, rats were fasted overnight before administration of film. Then,  $50\text{ }\mu\text{L}$  aliquot of distilled water was dropped into the rat oral cavity under light ether anesthesia and then film preparation (animal dose =  $0.087\text{ mg/kg}$ ) was placed on the tongue. After ensuring disintegration of the film, anesthesia was discontinued. This was followed by measuring drug concentration in the animal plasma to determine drug pharmacokinetic parameters.[126]

#### 5.2.15. Film thickness

The thickness of each film may be determined by using a digital vernier caliper,[12, 102] with an accuracy of  $2.5 \pm 0.5\text{ }\mu\text{m}$ . [102]

### 6. Formulations in various stages of the clinical process

The current clinical trials are shown in Table 1 in relation to FDFs and few oral strips. The information was obtained from <https://www.clinicaltrials.gov>.

*Table 1: FDFs and some oral films at different stages of clinical trials.*

Company	Active Ingredient/ Formulation	Condition/Disease	Dosage/Form	Phase

Indivior Inc.	Buprenorphine/ Naloxone	Opioid-Related Disorders	Buprenorphine/ naloxone dosed between 4/1 mg to 32/8 mg once a day for 12 weeks by buccal route	2
Armata Pharmaceuticals, Inc.	C16G2	Dental Caries	C16G2 Strip Antimicrobial Peptide	2
Procter and Gamble	Crest® Sensi- Stop™ Strips	Dentin Sensitivity	Self Applied Strips	N/A
Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey	sniffin sticks and taste strips	Fibromyalgia	Taste strips are applied by putting them on the tongue and closing the mouth.	N/A
University of Strathclyde	(Potassium acid phosphate oral thin films	Hypophosphataemia	Potassium acid phosphate oral thin films 0.2, 0.3 and 0.4 mM	2

Hadassah Medical Organization	Insulin loaded orally dissolved films	Diabetes	NPH-Insulin	1
Aquestive Therapeutics	Diazepam	Epilepsy	Diazepam Buccal Soluble Film	2
BioDelivery Sciences International	Buprenorphine	Pain	buprenorphine HCl buccal film (300 µg)	2
BioDelivery Sciences International	Oxycodone	Dental Pain	Oxycodone 2 mg buccal film	2
Janssen Research & Development, LLC	(S)-ketamine	Healthy	Oral thin film 7 mg	1
Milton S. Hershey Medical Centre	Nicotine	Smoking Cessation	Nicotine 4 mg oral film	1

## 7. The Barriers for 3DP of FDFs at Industrial Scale

FDF market will grow to more than \$1.3 billion per annum in next few years and 3D printing of FDFs may share part of this market. 3DP of FDFs generally has been a solvent-less process, which

can be considered as an important advantage. Amongst the methods published in literature, hot melt ram extrusion 3D printer and powder based extrusion 3DP appear to have several advantages over FDM 3DP. As explained previously, 3D printing technologies have the potential to allow patients to be given a personalised regime, which could include multiple active ingredients, either as a single blend or potentially as layers in a multi-layer printed tablet, based on their treatment needs. There is no unique regulatory

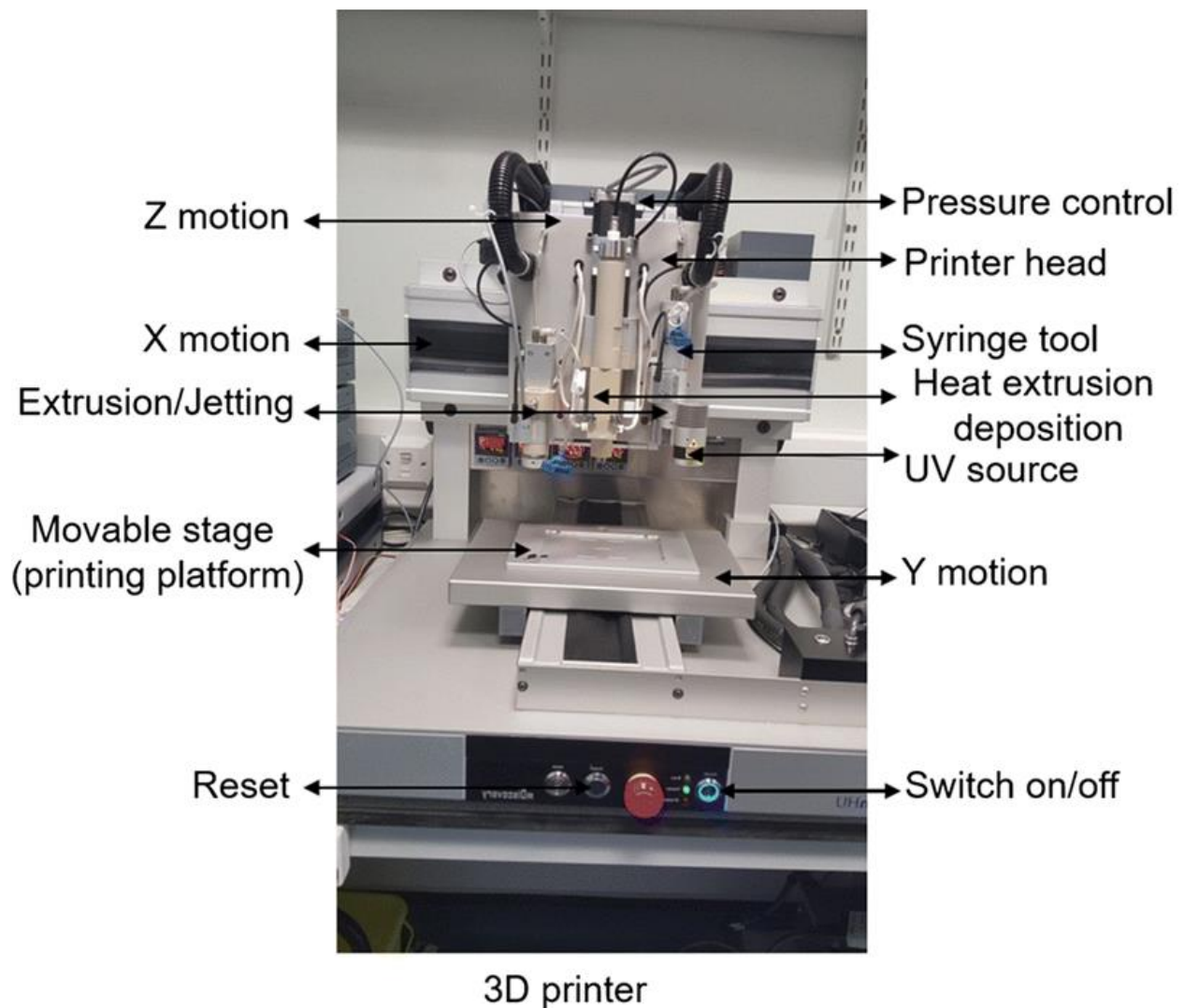


Figure 2: The regenHU 3D printer reproduced with permission from Reference [60].

pathway for the approval of 3DP drugs,[128] but there are existing approval pathways that are flexible enough to address new technologies, small batches, orphan drugs, expedited approval programs, and personalised medicines. Three major risk areas have been identified relating to 3D printing of pharmaceuticals.

- Product liability risk: if a pharmaceutical company licenses its blueprint to pharmacies or healthcare providers to print drugs locally, it still needs to consider the potential product liability implications and free from printing defects.[129]
- Counterfeit risk: the proliferation of counterfeit medicines is perhaps the industry's greatest concern with 3D printing. Printers are much more vulnerable to hackers than traditional manufacturing processes, and the incredibly short production time magnifies the risk of counterfeits.
- The safety and efficacy of 3D printers: traditional mass-manufacturing facilities are subject to oversight from regulatory bodies. However, the FDA/MHRA would be pushed to regulate every instance of 3D printing. Therefore determining the safety of products developed and responsibility for adverse events are difficult.

Development of thin films has been ongoing for many years and there are a number of companies who are focused exclusively on developments in this field. Companies are continuing to invest in technologies which provide alternatives to standard tablet based drug delivery systems. The market for thin film products is already well established with a number of products launched on the market, some of which have achieved block buster drug status. Market entry for a new technology will therefore be harder than it would, when it enters a rapidly growing market sector.

The current competitors have identified a number of clinical areas that benefit from rapid oral/buccal delivery, [130, 131] and Table 1 presents part of recent clinical trials. It may be difficult



to identify additional pharmaceutical agents that have not already been taken to market using existing FDF/ODT technologies. Alongside FDF technology there are a number of similar techniques for formulating drugs for rapid buccal drug delivery such as fast dissolving tablets. Some pharmaceutical agents have been formulated as both FDFs and oral dispersing tablets, which means clinicians already have a choice of products to use in the clinic.

Typically, partnerships with pharmaceutical companies are used as a route to market, with the two partner companies bringing different areas of expertise to product development. Commercialisation would also require a robust patent strategy to ensure that other operators in this sector would not find a way to circumvent the patent. As the concept of printing 3D pharmaceuticals is already well profiled and in the public domain, any patent in the area would need to be able to focus on unique characteristics of the organisational 3D printing process.

New market entrants will need to have clearly defined advantages over existing technologies to be able to attract funding for product development and finance clinical trials of this new technology.[132] The advantages of using 3D printing for the production of medicines primarily is focused on the ability to produce customised products for patients. This offers greater flexibility, but creates a number of regulatory and security hurdles to ensure that patient safety is not compromised. The role of personalised 3D printing within pharmaceutical industry remains unclear at the moment and its uptake will depend heavily on whether the regulatory and security hurdles can be overcome. Therefore, a recent work has started to address this issue.[44] Based on our experience, personalisation of 3DP FDFs would be challenging at pharmacies. This is due to the maintenance issues of 3D printers, which after a while would require spare parts; and whether these would be available by considering fast changing of 3DP market. While personalised 3D printing of dosage forms overcomes the regulatory and security hurdles, nothing is stopping to use

of 3D printing in pharmaceutical companies for mass production of FDFs. To achieve this target, 3DP of FDFs should clearly present advantages over well-established conventional methods of producing FDFs.

### 7.1. Process Analytical Technology

Process Analytical Technology (PAT) is considered a system for designing, analysing and controlling pharmaceutical manufacturing processes through measurements of critical quality and performance attributes. These are applied to both raw and processed materials to ensure final product quality. The aim is to build quality in to the product, rather than just testing the product at the final stage. Spectroscopic tools including near infrared (NIR) and Raman spectroscopy have been shown to be capable of monitoring tablet critical quality attributes (CQAs), namely drug content.[133, 134] Trenfield *et al* 2018 showed the application of portable near infrared spectroscopy and Raman confocal microscopy as PAT tools for 3D printed drug products.[56] Furthermore, Raman spectroscopy and Raman chemical imaging were applied to visualise drug distribution within a 2D inkjet printed formulations and quantify drug content.[135] Similarly, Vakili *et al.* 2017 applied a handheld NIR spectrometer to quantify the content of prednisolone and levothyroxine in orodispersible films.[136] These studies present methods that have been developed to implement PAT for the production 3DP FDFs. In addition, NIR has been applied to predict tablet hardness;[137] and an in-line pH monitoring system combined with in-line particle size monitoring was employed to predict disintegration of tablets, as part of PAT.[138] Further studies are required to identify suitable PAT technique to predict tensile strength and disintegration time of 3DP FDFs.

## 8. Conclusion

FDM 3DP and hot melt ram extrusion 3D printer have been applied to the formulation of FDFs. In addition, inkjet method has been employed to deposit APIs on edible films. Although the disintegration time of 3DP FDFs is less than 3 minutes, which complies with pharmacopeia specifications, the disintegration time of films made by solvent casting method is much shorter (usually within 20 seconds). FDFs usually contain taste masking agents, and FDM 3DP has made this feasible. Large-scale production of FDFs is still challenging by using additive manufacturing techniques, although recent progress shows promise. The commercial feasibility of the Spirtam 3DP tablet and FDA approval in August 2015 indicate the potential for commercial feasibility of FDFs by additive manufacturing. It should be noted that FDA encourages advanced manufacturing, as this can improve drug quality, address shortages of medicines, and increase speed of reaching marketable products. In this regard, FDA's Additive Manufacturing of Medical Products (AMMP) core research facility is a multi-centre collaboration. It expands Centre-specific resources and accommodates high-end, industry-grade 3D printing equipment, software, and expertise that can be used across the Agency to perform cutting-edge regulatory research with this advanced technology.

Applying additive manufacturing could be cost effective in the production of FDFs, in particular compared to manufacturing of FDFs by solvent casting method. This is because FDM 3DP and hot melt ram extrusion 3D printer do not require using solvents in the manufacture of FDFs. This also could improve the safety profile of FDFs by reducing the solvent residues. The production time could be faster by using the additive manufacturing compared to the preparation of FDFs by the solvent casting method, as there is no need for delays due to evaporation of solvents. It remains

to be determined whether 3DP of FDFs can be beneficial from early stages of FDF formulation development.

## 9. Future Directions

Simplifying the manufacturing process of 3DP FDFs will be an important future direction. As current FDM techniques require the usage of filaments; producing filaments with the desired smoothness and mechanical strength brings extra challenge for 3DP of FDFs. Inkjet technique utilising molten wax and hot melt ram extrusion 3D printer are additive manufacturing processes that do not require the use of filaments. Therefore, further developments of these techniques appear desirable. Also, taste-masking agents should be included in future formulations developed by novel additive manufacturing techniques. Hot melt ram extrusion 3D printing is an example of direct ink writing printing methods,[103] however, pneumatic or screw-fed direct methods [63] could be investigated to produce formulations that contain suspensions or to eliminate the piston in the printing instrument. The screw-fed direct ink writing method provides the opportunity of continuous FDF production. Reducing the printing temperature in 3D FDM would be another target to be achieved to ensure stability of the active ingredient or taste masking agents during the production process. Developing multi-nozzle 3D printers, where all nozzles print at the same time, would help mass production 3DP FDFs. In addition, 3DP of FDF rollstock may help integration of 3DP of FDF into current manufacturing process. This means the production of FDF roll by 3DP, and then cutting the roll by packaging machines into desired sizes and packing in pouches or sachets.

## References

1. Kyobula M, Adedeji A, Alexander MR, Saleh E, Wildman R, Ashcroft I, Gellert PR, Roberts CJ. 3D inkjet printing of tablets exploiting bespoke complex geometries for controlled and tuneable drug release. *J Controlled Release*. 2017;261:207-215.
2. Khaled SA, Burley JC, Alexander MR, Roberts CJ. Desktop 3D printing of controlled release pharmaceutical bilayer tablets. *Int J Pharm*. 2014;461(1):105-111.
3. Melocchi A, Parietti F, Loreti G, Maroni A, Gazzaniga A, Zema L. 3D printing by fused deposition modeling (FDM) of a swellable/erodible capsular device for oral pulsatile release of drugs. *Journal of Drug Delivery Science and Technology*. 2015;30:360-367.
4. Goyanes A, Det-Amornrat U, Wang J, Basit AW, Gaisford S. 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems. *J Controlled Release*. 2016;234:41-48.
5. Melocchi A, Parietti F, Maroni A, Foppoli A, Gazzaniga A, Zema L. Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling. *Int J Pharm*. 2016;509(1):255-263.
6. Okwuosa TC, Pereira BC, Arafat B, Cieszynska M, Isreb A, Alhnan MA. Fabricating a Shell-Core Delayed Release Tablet Using Dual FDM 3D Printing for Patient-Centred Therapy. *Pharmaceutical research*. 2017;34(2):427-437.
7. Li Q, Guan X, Cui M, Zhu Z, Chen K, Wen H, Jia D, Hou J, Xu W, Yang X, Pan W. Preparation and investigation of novel gastro-floating tablets with 3D extrusion-based printing. *Int J Pharm*. 2018;535(1):325-332.
8. Gioumouxouzis CI, Katsamenis OL, Bouropoulos N, Fatouros DG. 3D printed oral solid dosage forms containing hydrochlorothiazide for controlled drug delivery. *Journal of Drug Delivery Science and Technology*. 2017;40:164-171.
9. Genina N, Boetker JP, Colombo S, Harmankaya N, Rantanen J, Bohr A. Anti-tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage forms: From drug product design to in vivo testing. *J Controlled Release*. 2017;268:40-48.
10. Maroni A, Melocchi A, Parietti F, Foppoli A, Zema L, Gazzaniga A. 3D printed multi-compartment capsular devices for two-pulse oral drug delivery. *J Controlled Release*. 2017;268:10-18.
11. Jamróz W, Kurek M, Łyszczarz E, Szafraniec J, Knapik-Kowalczyk J, Syrek K, Paluch M, Jachowicz R. 3D printed orodispersible films with Aripiprazole. *Int J Pharm*. 2017;533(2):413-420.
12. Ehtezazi T, Algellay M, Islam Y, Roberts M, Dempster NM, Sarker SD. The Application of 3D Printing in the Formulation of Multilayered Fast Dissolving Oral Films. *J Pharm Sci*. 2018;107(4):1076-1085.
13. Okwuosa TC, Soares C, Gollwitzer V, Habashy R, Timmins P, Alhnan MA. On demand manufacturing of patient-specific liquid capsules via co-ordinated 3D printing and liquid dispensing. *European Journal of Pharmaceutical Sciences*. 2018;118:134-143.
14. Afsana, Jain V, Haider N, Jain K. 3D Printing in Personalized Drug Delivery. *Curr Pharm Des*. 2018;24(42):5062-5071.
15. Awad A, Trenfield SJ, Gaisford S, Basit AW. 3D printed medicines: A new branch of digital healthcare. *Int J Pharm*. 2018;548(1):586-596.

16. Khan FA, Narasimhan K, Swathi CSV, Mustak S, Mustafa G, Ahmad MZ, Akhter S. 3D Printing Technology in Customized Drug Delivery System: Current State of the Art, Prospective and the Challenges. *Curr Pharm Des.* 2018;24(42):5049-5061.
17. Edinger M, Jacobsen J, Bar-Shalom D, Rantanen J, Genina N. Analytical aspects of printed oral dosage forms. *Int J Pharm.* 2018;553(1):97-108.
18. El Aita I, Ponsar H, Quodbach J. A critical review on 3D-printed dosage forms. *Current pharmaceutical design.* 2018;24(42):4957-4978.
19. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. *Journal of controlled release : official journal of the Controlled Release Society.* 2015;217:308-314.
20. Haring AP, Tong Y, Halper J, Johnson BN. Programming of Multicomponent Temporal Release Profiles in 3D Printed Polypills via Core–Shell, Multilayer, and Gradient Concentration Profiles. *Advanced Healthcare Materials.* 2018;7(16):1800213.
21. Bhattacharyya N. The prevalence of dysphagia among adults in the United States. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2014;151(5):765-769.
22. Tian Y, Visser JC, Klever JS, Woerdenbag HJ, Frijlink HW, Hinrichs WLJ. Orodispersible films based on blends of trehalose and pullulan for protein delivery. *European Journal of Pharmaceutics and Biopharmaceutics.* 2018;133:104-111.
23. Jani R, Patel D. Hot melt extrusion: An industrially feasible approach for casting orodispersible film. *Asian Journal of Pharmaceutical Sciences.* 2015;10(4):292-305.
24. Cilurzo F, Cupone IE, Minghetti P, Buratti S, Selmin F, Gennari CGM, Montanari L. Nicotine fast dissolving films made of maltodextrins: a feasibility study. *AAPS PharmSciTech.* 2010;11(4):1511-1517.
25. Repka MA, Gutta K, Prodduturi S, Munjal M, Stodghill SP. Characterization of cellulosic hot-melt extruded films containing lidocaine. *European Journal of Pharmaceutics and Biopharmaceutics.* 2005;59(1):189-196.
26. Murata Y, Isobe T, Kofuji K, Nishida N, Kamaguchi R. Preparation of Fast Dissolving Films for Oral Dosage from Natural Polysaccharides. *Materials (Basel).* 2010;3(8):4291-4299.
27. Musazzi UM, Selmin F, Ortenzi MA, Mohammed GK, Franzé S, Minghetti P, Cilurzo F. Personalized orodispersible films by hot melt ram extrusion 3D printing. *Int J Pharm.* 2018;551(1):52-59.
28. Swainson WK. Method, medium and apparatus for producing three-dimensional figure product. In: 1971.
29. Hull CW. Apparatus for production of three-dimensional objects by stereolithography. In: 1984.
30. Xiong W, Zhou YS, He XN, Gao Y, Mahjouri-Samani M, Jiang L, Baldacchini T, Lu YF. Simultaneous additive and subtractive three-dimensional nanofabrication using integrated two-photon polymerization and multiphoton ablation. *Light: Science & Applications.* 2012;1:e6.
31. Attaran M. The rise of 3-D printing: The advantages of additive manufacturing over traditional manufacturing. *Business Horizons.* 2017;60(5):677-688.

32. Lamichhane S, Bashyal S, Keum T, Noh G, Seo JE, Bastola R, Choi J, Sohn DH, Lee S. Complex formulations, simple techniques: Can 3D printing technology be the Midas touch in pharmaceutical industry? *Asian Journal of Pharmaceutical Sciences*. 2019.
33. Martin GD, Hoath SD, Hutchings IM. Inkjet printing - the physics of manipulating liquid jets and drops. *Journal of Physics: Conference Series*. 2008;105(1):012001.
34. Katstra WE, Palazzolo RD, Rowe CW, Giritlioglu B, Teung P, Cima MJ. Oral dosage forms fabricated by Three Dimensional Printing™. *J Controlled Release*. 2000;66(1):1-9.
35. Shi K, Tan DK, Nokhodchi A, Maniruzzaman M. Drop-On-Powder 3D Printing of Tablets with an Anti-Cancer Drug, 5-Fluorouracil. *Pharmaceutics*. 2019;11(4).
36. Buanz ABM, Saunders MH, Basit AW, Gaisford S. Preparation of Personalized-dose Salbutamol Sulphate Oral Films with Thermal Ink-Jet Printing. *Pharm Res*. 2011;28(10):2386.
37. Vuddanda PR, Alomari M, Dodoo CC, Trenfield SJ, Velaga S, Basit AW, Gaisford S. Personalisation of warfarin therapy using thermal ink-jet printing. *European Journal of Pharmaceutical Sciences*. 2018;117:80-87.
38. Eleftheriadis GK, Monou PK, Bouropoulos N, Fatouros DG. In Vitro Evaluation of 2D-Printed Edible Films for the Buccal Delivery of Diclofenac Sodium. *Materials (Basel)*. 2018;11(5).
39. Janßen EM, Schliephacke R, Breitenbach A, Breitzkreutz J. Drug-printing by flexographic printing technology—A new manufacturing process for orodispersible films. *Int J Pharm*. 2013;441(1):818-825.
40. Genina N, Fors D, Vakili H, Ihalainen P, Pohjala L, Ehlers H, Kassamakov I, Haeggström E, Vuorela P, Peltonen J, Sandler N. Tailoring controlled-release oral dosage forms by combining inkjet and flexographic printing techniques. *European Journal of Pharmaceutical Sciences*. 2012;47(3):615-623.
41. Kollamaram G, Hopkins SC, Glowacki BA, Croker DM, Walker GM. Inkjet printing of paracetamol and indomethacin using electromagnetic technology: Rheological compatibility and polymorphic selectivity. *European Journal of Pharmaceutical Sciences*. 2018;115:248-257.
42. Planchette C, Pichler H, Wimmer-Teubenbacher M, Gruber M, Gruber-Woelfler H, Mohr S, Tetyczka C, Hsiao WK, Paudel A, Roblegg E, Khinast J. Printing medicines as orodispersible dosage forms: Effect of substrate on the printed micro-structure. *Int J Pharm*. 2016;509(1):518-527.
43. Buanz ABM, Belaunde CC, Soutari N, Tuleu C, Gul MO, Gaisford S. Ink-jet printing versus solvent casting to prepare oral films: Effect on mechanical properties and physical stability. *Int J Pharm*. 2015;494(2):611-618.
44. Trenfield SJ, Xian Tan H, Awad A, Buanz A, Gaisford S, Basit AW, Goyanes A. Track-and-trace: Novel anti-counterfeit measures for 3D printed personalized drug products using smart material inks. *Int J Pharm*. 2019;567:118443.
45. Thabet Y, Lunter D, Breitzkreutz J. Continuous inkjet printing of enalapril maleate onto orodispersible film formulations. *Int J Pharm*. 2018;546(1):180-187.
46. Iftimi L-D, Edinger M, Bar-Shalom D, Rantanen J, Genina N. Edible solid foams as porous substrates for inkjet-printable pharmaceuticals. *European Journal of Pharmaceutics and Biopharmaceutics*. 2019;136:38-47.

47. Pietrzak K, Isreb A, Alhnan MA. A flexible-dose dispenser for immediate and extended release 3D printed tablets. *European Journal of Pharmaceutics and Biopharmaceutics*. 2015;96:380-387.
48. Goyanes A, Buanz AB, Basit AW, Gaisford S. Fused-filament 3D printing (3DP) for fabrication of tablets. *International journal of pharmaceutics*. 2014;476(1-2):88-92.
49. Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. *European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV*. 2015;89:157-162.
50. Solanki NG, Tahsin M, Shah AV, Serajuddin ATM. Formulation of 3D Printed Tablet for Rapid Drug Release by Fused Deposition Modeling: Screening Polymers for Drug Release, Drug-Polymer Miscibility and Printability. *Journal of pharmaceutical sciences*. 2018;107(1):390-401.
51. Verstraete G, Samaro A, Grymonpré W, Vanhoorne V, Van Snick B, Boone MN, Hellemans T, Van Hoorebeke L, Remon JP, Vervaet C. 3D printing of high drug loaded dosage forms using thermoplastic polyurethanes. *Int J Pharm*. 2018;536(1):318-325.
52. Gioumouxouzis CI, Karavasili C, Fatouros DG. Recent advances in pharmaceutical dosage forms and devices using additive manufacturing technologies. *Drug Discovery Today*. 2019;24(2):636-643.
53. Isreb A, Baj K, Wojsz M, Isreb M, Peak M, Alhnan MA. 3D printed oral theophylline doses with innovative 'radiator-like' design: Impact of polyethylene oxide (PEO) molecular weight. *Int J Pharm*. 2019;564:98-105.
54. Gioumouxouzis CI, Eleftheriadis GK, Fatouros DG. Emerging 3D Printing Technologies to Develop Novel Pharmaceutical Formulations. *3D and 4D Printing in Biomedical Applications: Process Engineering and Additive Manufacturing*. 2019:153-184.
55. Krause J, Bogdahn M, Schneider F, Koziolk M, Weitschies W. Design and characterization of a novel 3D printed pressure-controlled drug delivery system. *European Journal of Pharmaceutical Sciences*. 2019;140:105060.
56. Trenfield SJ, Goyanes A, Telford R, Wilsdon D, Rowland M, Gaisford S, Basit AW. 3D printed drug products: Non-destructive dose verification using a rapid point-and-shoot approach. *Int J Pharm*. 2018;549(1):283-292.
57. Norman J, Madurawe RD, Moore CMV, Khan MA, Khairuzzaman A. A new chapter in pharmaceutical manufacturing: 3D-printed drug products. *Adv Drug Del Rev*. 2017;108:39-50.
58. Okwuosa TC, Stefaniak D, Arafat B, Isreb A, Wan KW, Alhnan MA. A Lower Temperature FDM 3D Printing for the Manufacture of Patient-Specific Immediate Release Tablets. *Pharmaceutical research*. 2016;33(11):2704-2712.
59. Malaquias LFB, Schulte HL, Chaker JA, Karan K, Durig T, Marreto RN, Gratieri T, Gelfuso GM, Cunha-Filho M. Hot Melt Extrudates Formulated Using Design Space: One Simple Process for Both Palatability and Dissolution Rate Improvement. *J Pharm Sci*. 2018;107(1):286-296.
60. Khaled SA, Alexander MR, Irvine DJ, Wildman RD, Wallace MJ, Sharpe S, Yoo J, Roberts CJ. Extrusion 3D Printing of Paracetamol Tablets from a Single Formulation with Tunable Release Profiles Through Control of Tablet Geometry. *AAPS PharmSciTech*. 2018;19(8):3403-3413.



61. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3D printing of tablets containing multiple drugs with defined release profiles. *Int J Pharm.* 2015;494(2):643-650.
62. Long J, Etxeberria AE, Nand AV, Bunt CR, Ray S, Seyfoddin A. A 3D printed chitosan-pectin hydrogel wound dressing for lidocaine hydrochloride delivery. *Materials Science and Engineering: C.* 2019;104:109873.
63. Goyanes A, Allahham N, Trenfield SJ, Stoyanov E, Gaisford S, Basit AW. Direct powder extrusion 3D printing: Fabrication of drug products using a novel single-step process. *Int J Pharm.* 2019;567:118471.
64. Zidan A, Alayoubi A, Asfari S, Coburn J, Ghammraoui B, Aqueel S, Cruz CN, Ashraf M. Development of mechanistic models to identify critical formulation and process variables of pastes for 3D printing of modified release tablets. *Int J Pharm.* 2019;555:109-123.
65. Jain A, Ahirwar HC, Tayal S, Mohanty PK. FAST DISSOLVING ORAL FILMS: A TABULAR UPDATE. *Journal of Drug Delivery and Therapeutics.* 2018;8(4):10-19.
66. Dixit RP, Puthli SP. Oral strip technology: Overview and future potential. *J Controlled Release.* 2009;139(2):94-107.
67. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: an innovative drug delivery system and dosage form. *Int J ChemTech Res.* 2010;2(1):576-583.
68. Shirvan AR, Bashari A, Hemmatinejad N. New Insight into the Fabrication of Smart Mucoadhesive Buccal Patches as a Novel Controlled-Drug Delivery System. *European Polymer Journal.* 2019.
69. Grammen C, Van den Mooter G, Appeltans B, Michiels J, Crucitti T, Ariën KK, Augustyns K, Augustijns P, Brouwers J. Development and characterization of a solid dispersion film for the vaginal application of the anti-HIV microbicide UAMC01398. *Int J Pharm.* 2014;475(1):238-244.
70. Shen B-d, Shen C-y, Yuan X-d, Bai J-x, Lv Q-y, Xu H, Dai L, Yu C, Han J, Yuan H-l. Development and characterization of an orodispersible film containing drug nanoparticles. *European Journal of Pharmaceutics and Biopharmaceutics.* 2013;85(3, Part B):1348-1356.
71. Choudhary DR, Patel VA, Chhalotiya UK, Patel HV, Kundawala AJ. Development and characterization of pharmacokinetic parameters of fast-dissolving films containing levocetirizine. *Sci Pharm.* 2012;80(3):779-787.
72. Ghorwade VM. Formulation and Evaluation of Montelukast Sodium Fast Dissolving Films. In.: RGUHS; 2011.
73. Nalluri BN, Sravani B, Anusha VS, Sribramhini R, Maheswari K. Development and evaluation of mouth dissolving films of sumatriptan succinate for better therapeutic efficacy. *Journal of applied pharmaceutical science.* 2013;3(8):161.
74. Chaudhary H, Gauri S, Rathee P, Kumar V. Development and optimization of fast dissolving oro-dispersible films of granisetron HCl using Box–Behnken statistical design. *Bulletin of Faculty of Pharmacy, Cairo University.* 2013;51(2):193-201.
75. Alayoubi A, Haynes L, Patil H, Daihom B, Helms R, Almoazen H. Development of a fast dissolving film of epinephrine hydrochloride as a potential anaphylactic treatment for pediatrics. *Pharmaceutical development and technology.* 2017;22(8):1012-1016.

76. Cilurzo F, Cupone IE, Minghetti P, Buratti S, Gennari CG, Montanari L. Diclofenac fast-dissolving film: suppression of bitterness by a taste-sensing system. *Drug development and industrial pharmacy*. 2011;37(3):252-259.
77. Yeola GS, Darandale S, Khire A, Vavia PR. Fabrication and statistical optimization of a polysaccharide-based sublingual film of buprenorphine hydrochloride for breakthrough pain management: in vitro and in vivo performance. *Drug delivery and translational research*. 2014;4(2):116-125.
78. Koland M, Sandeep VP, Charyulu NR. Fast Dissolving Sublingual Films of Ondansetron Hydrochloride: Effect of Additives on in vitro Drug Release and Mucosal Permeation. *Journal of Young Pharmacists : JYP*. 2010;2(3):216-222.
79. Tiwari A, Gangwar NK, Pathak K. Fast-dissolving ocular films of riboflavin acetate conjugate for treatment of keratoconus in UVA-CXL procedure: ex vivo permeation, hemolytic toxicity and apoptosis detection. *Expert opinion on drug delivery*. 2014;11(3):325-343.
80. Sayed S, Ibrahim HK, Mohamed MI, El-Milligi MF. Fast-Dissolving Sublingual Films of Terbutaline Sulfate: Formulation and In Vitro/In Vivo Evaluation. *Mol Pharm*. 2013;10(8):2942-2947.
81. Krull SM, Ma Z, Li M, Davé RN, Bilgili E. Preparation and characterization of fast dissolving pullulan films containing BCS class II drug nanoparticles for bioavailability enhancement. *Drug Dev Ind Pharm*. 2016;42(7):1073-1085.
82. Carolina Visser J, Weggemans OAF, Boosman RJ, Loos KU, Frijlink HW, Woerdenbag HJ. Increased drug load and polymer compatibility of bilayered orodispersible films. *European Journal of Pharmaceutical Sciences*. 2017;107:183-190.
83. Pechová V, Gajdziok J, Muselík J, Vetchý D. Development of Orodispersible Films Containing Benzydamine Hydrochloride Using a Modified Solvent Casting Method. *AAPS PharmSciTech*. 2018;19(6):2509-2518.
84. Velaga SP, Nikjoo D, Vuddanda PR. Experimental Studies and Modeling of the Drying Kinetics of Multicomponent Polymer Films. *AAPS PharmSciTech*. 2018;19(1):425-435.
85. ICH-Q3C(R7). [https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use\\_en-14.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-14.pdf).
86. Agency' EM. ICH guideline Q3C (R7) on impurities: guideline for residual solvents. In: *Harmonisation TICO*, editor.; 2018.
87. Steiner D, Finke JH, Kwade A. SOFTs – Structured orodispersible film templates. *European Journal of Pharmaceutics and Biopharmaceutics*. 2019;137:209-217.
88. Cilurzo F, Cupone IE, Minghetti P, Selmin F, Montanari L. Fast dissolving films made of maltodextrins. *European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV*. 2008;70(3):895-900.
89. Manning CB. Melt extruded nicotine thin strips. In: WO2011081628A1, 2009.
90. Robinson JWMR. Effervescence polymeric film drug delivery system. In: US20010006677A1, 2001.
91. Fuisz RC. Smokeless tobacco product. In: US20100242978A1, 2010.
92. Chonkar AD, Rao JV, Managuli RS, Mutalik S, Dengale S, Jain P, Udupa N. Development of fast dissolving oral films containing lercanidipine HCl nanoparticles in semicrystalline polymeric matrix for enhanced dissolution and ex vivo permeation. *European Journal of Pharmaceutics and Biopharmaceutics*. 2016;103:179-191.

93. El-Bary AA, Al Sharabi I, Haza'a BS. Effect of casting solvent, film-forming agent and solubilizer on orodispersible films of a polymorphic poorly soluble drug: an in vitro/in silico study. *Drug development and industrial pharmacy*. 2019;1-19.
94. Song Q, Guo X, Sun Y, Yang M. Anti-solvent Precipitation Method Coupled Electrospinning Process to Produce Poorly Water-Soluble Drug-Loaded Orodispersible Films. *AAPS PharmSciTech*. 2019;20(7):273.
95. Serrano DR, Fernandez-Garcia R, Mele M, Healy AM, Lalatsa A. Designing Fast-Dissolving Orodispersible Films of Amphotericin B for Oropharyngeal Candidiasis. *Pharmaceutics*. 2019;11(8).
96. Sjöholm E, Sandler N. Additive manufacturing of personalized orodispersible warfarin films. *Int J Pharm*. 2019;564:117-123.
97. Talekar SD, Haware RV, Dave RH. Evaluation of self-nanoemulsifying drug delivery systems using multivariate methods to optimize permeability of captopril oral films. *European Journal of Pharmaceutical Sciences*. 2019;130:215-224.
98. Musazzi UM, Dolci LS, Albertini B, Passerini N, Cilurzo F. A new melatonin oral delivery platform based on orodispersible films containing solid lipid microparticles. *Int J Pharm*. 2019;559:280-288.
99. Pimparade MB, Vo A, Maurya AS, Bae J, Morott JT, Feng X, Kim DW, Kulkarni VI, Tiwari R, Vanaja K, Murthy R, Shivakumar HN, Neupane D, Mishra SR, Murthy SN, Repka MA. Development and evaluation of an oral fast disintegrating anti-allergic film using hot-melt extrusion technology. *European Journal of Pharmaceutics and Biopharmaceutics*. 2017;119:81-90.
100. Speer I, Lenhart V, Preis M, Breitzkreutz J. Prolonged release from orodispersible films by incorporation of diclofenac-loaded micropellets. *Int J Pharm*. 2019;554:149-160.
101. Şen Karaman D, Patrignani G, Rosqvist E, Smått J-H, Orłowska A, Mustafa R, Preis M, Rosenholm JM. Mesoporous silica nanoparticles facilitating the dissolution of poorly soluble drugs in orodispersible films. *European Journal of Pharmaceutical Sciences*. 2018;122:152-159.
102. Musazzi UM, Selmin F, Franzé S, Gennari CGM, Rocco P, Minghetti P, Cilurzo F. Poly(methyl methacrylate) salt as film forming material to design orodispersible films. *European Journal of Pharmaceutical Sciences*. 2018;115:37-42.
103. Truby RL, Lewis JA. Printing soft matter in three dimensions. *Nature*. 2016;540(7633):371-378.
104. Gaisford S, Verma A, Saunders M, Royall PG. Monitoring crystallisation of drugs from fast-dissolving oral films with isothermal calorimetry. *Int J Pharm*. 2009;380(1):105-111.
105. Garsuch V, Breitzkreutz J. Comparative investigations on different polymers for the preparation of fast-dissolving oral films. *J Pharm Pharmacol*. 2010;62(4):539-545.
106. Skowrya J, Pietrzak K, Alhnan MA. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*. 2015;68:11-17.
107. Rowe CW, Katstra WE, Palazzolo RD, Giritlioglu B, Teung P, Cima MJ. Multimechanism oral dosage forms fabricated by three dimensional printing™. *J Controlled Release*. 2000;66(1):11-17.

108. Robles-Martinez P, Xu X, Trenfield SJ, Awad A, Goyanes A, Telford R, Basit AW, Gaisford S. 3D Printing of a Multi-Layered Polypill Containing Six Drugs Using a Novel Stereolithographic Method. *Pharmaceutics*. 2019;11(6):274.
109. Thabet Y, Breitzkreutz J. Orodispersible films: Product transfer from lab-scale to continuous manufacturing. *Int J Pharm*. 2018;535(1):285-292.
110. Jenke DR, Story J, Lalani R. Extractables/leachables from plastic tubing used in product manufacturing. *Int J Pharm*. 2006;315(1):75-92.
111. Thabet Y, Lunter D, Breitzkreutz J. Continuous manufacturing and analytical characterization of fixed-dose, multilayer orodispersible films. *European Journal of Pharmaceutical Sciences*. 2018;117:236-244.
112. Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F, Khan A. Orally disintegrating films: A modern expansion in drug delivery system. *Saudi Pharmaceutical Journal*. 2016;24(5):537-546.
113. Shang R, Liu C, Quan P, Zhao H, Fang L. Effect of drug-ion exchange resin complex in betahistine hydrochloride orodispersible film on sustained release, taste masking and hygroscopicity reduction. *Int J Pharm*. 2018;545(1):163-169.
114. Scarpa M, Paudel A, Klopogge F, Hsiao WK, Bresciani M, Gaisford S, Orlu M. Key acceptability attributes of orodispersible films. *European Journal of Pharmaceutics and Biopharmaceutics*. 2018;125:131-140.
115. Speer I, Preis M, Breitzkreutz J. Prolonged drug release properties for orodispersible films by combining hot-melt extrusion and solvent casting methods. *European Journal of Pharmaceutics and Biopharmaceutics*. 2018;129:66-73.
116. Steiner D, Finke JH, Kwade A. Instant ODFs – Development of an intermediate, nanoparticle-based product platform for individualized medication. *European Journal of Pharmaceutics and Biopharmaceutics*. 2018;126:149-158.
117. Steiner D, Finke JH, Kwade A. Efficient production of nanoparticle-loaded orodispersible films by process integration in a stirred media mill. *Int J Pharm*. 2016;511(2):804-813.
118. Speer I, Steiner D, Thabet Y, Breitzkreutz J, Kwade A. Comparative study on disintegration methods for oral film preparations. *European Journal of Pharmaceutics and Biopharmaceutics*. 2018;132:50-61.
119. Adeleke OA, Tsai PC, Karry KM, Monama NO, Michniak-Kohn BB. Isoniazid-loaded orodispersible strips: Methodical design, optimization and in vitro-in silico characterization. *International journal of pharmaceutics*. 2018;547(1-2):347-359.
120. Woertz C, Kleinebudde P. Development of orodispersible polymer films containing poorly water soluble active pharmaceutical ingredients with focus on different drug loadings and storage stability. *Int J Pharm*. 2015;493(1):134-145.
121. Foo WC, Khong YM, Gokhale R, Chan SY. A novel unit-dose approach for the pharmaceutical compounding of an orodispersible film. *Int J Pharm*. 2018;539(1):165-174.
122. Peh KK, Wong CF. Polymeric films as vehicle for buccal delivery: swelling, mechanical, and bioadhesive properties. *J Pharm Pharm Sci*. 1999;2(2):53-61.
123. Khadra I, Obeid MA, Dunn C, Watts S, Halbert G, Ford S, Mullen A. Characterisation and optimisation of diclofenac sodium orodispersible thin film formulation. *Int J Pharm*. 2019;561:43-46.

124. Adrover A, Pedacchia A, Petralito S, Spera R. In vitro dissolution testing of oral thin films: A comparison between USP 1, USP 2 apparatuses and a new millifluidic flow-through device. *Chem Eng Res Des*. 2015;95:173-178.
125. Krampe R, Sieber D, Pein-Hackelbusch M, Breitzkreutz J. A new biorelevant dissolution method for orodispersible films. *European Journal of Pharmaceutics and Biopharmaceutics*. 2016;98:20-25.
126. Satyanarayana DA, Keshavarao KP. Fast disintegrating films containing anastrozole as a dosage form for dysphagia patients. *Archives of pharmacal research*. 2012;35(12):2171-2182.
127. Huynh N, Arabian N, Lieu D, Asatryan L, Davies DL. Utilizing an Orally Dissolving Strip for Pharmacological and Toxicological Studies: A Simple and Humane Alternative to Oral Gavage for Animals. *J Vis Exp*. 2016(109):e53770-e53770.
128. Cilurzo F, Musazzi UM, Franzé S, Selmin F, Minghetti P. Orodispersible dosage forms: biopharmaceutical improvements and regulatory requirements. *Drug Discovery Today*. 2018;23(2):251-259.
129. Dumitrescu I-B, Lupuliasa D, Drăgoi CM, Nicolae AC, Pop A, ȘARAMET G, DRĂGĂNESCU D. The age of pharmaceutical 3d printing. technological and therapeutical implications of additive manufacturing. *Farmacia*. 2018;66(3):365-389.
130. Karki S, Kim H, Na S-J, Shin D, Jo K, Lee J. Thin films as an emerging platform for drug delivery. *Asian Journal of Pharmaceutical Sciences*. 2016;11(5):559-574.
131. Borges AF, Silva C, Coelho JFJ, Simões S. Oral films: Current status and future perspectives II — Intellectual property, technologies and market needs. *J Controlled Release*. 2015;206:108-121.
132. Targum SD, Milbauer AJ. The process of getting new drugs to market. *Psychiatry (Edgmont)*. 2008;5(8):57-60.
133. Wartewig S, Neubert RHH. Pharmaceutical applications of Mid-IR and Raman spectroscopy. *Adv Drug Del Rev*. 2005;57(8):1144-1170.
134. Blanco M, Alcalá M. Content uniformity and tablet hardness testing of intact pharmaceutical tablets by near infrared spectroscopy: A contribution to process analytical technologies. *Analytica Chimica Acta*. 2006;557(1):353-359.
135. Edinger M, Bar-Shalom D, Rantanen J, Genina N. Visualization and Non-Destructive Quantification of Inkjet-Printed Pharmaceuticals on Different Substrates Using Raman Spectroscopy and Raman Chemical Imaging. *Pharm Res*. 2017;34(5):1023-1036.
136. Vakili H, Wickström H, Desai D, Preis M, Sandler N. Application of a handheld NIR spectrometer in prediction of drug content in inkjet printed orodispersible formulations containing prednisolone and levothyroxine. *Int J Pharm*. 2017;524(1):414-423.
137. Donoso M, Kildsig DO, Ghaly ES. Prediction of Tablet Hardness and Porosity Using Near-Infrared Diffuse Reflectance Spectroscopy as a Nondestructive Method. *Pharm Dev Technol*. 2003;8(4):357-366.
138. Xu X, Gupta A, Sayeed VA, Khan MA. Process Analytical Technology to Understand the Disintegration Behavior of Alendronate Sodium Tablets. *J Pharm Sci*. 2013;102(5):1513-1523.