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Review

THE USE OF NATURAL PRODUCTS IN 3D PRINTING OF PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Background

Three-dimensional printing (3DP) has been investigated widely for applications in pharmaceutical sciences. Different 3DP techniques have been employed such as fused deposition modelling (FDM 3DP), powder bed 3DP, stereolithography 3DP (SLA 3DP), selective laser sintering (SLS 3DP), pates-extrusion 3DP and inkjet 3DP.

Aim

This article aims to explore the use of natural products as active ingredient or excipient.

Methods

Literature search was conduced for latest applications of 3DP for pharmaceutical dosage forms, and typical employed materials were identified.

Results

Polymeric materials form the main bulk of 3DP excipients such as polyvinyl alcohol or ploy lactic acid. Chemical stabilisers may be added to these polymers to increase their stability at high temperatures during hot melt extrusion for making filaments or printing. In addition, photoinitiators have been added such as diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide in SLA 3DP, or candurin gold sheen in SLS 3DP. Presence of lead has been detected in FDM £DP, which originated from the nozzle. Currently, natural products have been employed only in paste extrusion 3DP of pharmaceutical dosage forms. We have identified a protentional natural thermoplastic polymer that may be used in 3DP FDM.

Conclusion

Natural products may be employed in 3DP of pharmaceutical dosage forms to improve the safety profile of printed objects.

Keywords: Three-dimensional printing; polymers; thermoplastics; photoinitiators, natural polymers.

INTRODUCTION

3D printing (3DP) of pharmaceutical dosage forms is expanding fast.(Melocchi et al, 2020; Prasad & Smyth, 2016) This technique provides a variety of dosage forms that cannot be prepared by conventional methods, as well as the opportunity for preparing personalised medicine. Spritam is a 3D printed tablet that has acquired the FDA approval, setting the grounds for the utilization of 3D printing for the preparation of drug delivery systems, but in particular for oral dosage forms. Spritam tablets contain 250, 500, 750, or 1000 mg of levetiracetam for oral suspension. It is reported that each Spritam tablet contains the following inactive ingredients: colloidal silicon dioxide, glycerin, mannitol, microcrystalline cellulose, polysorbate 20, povidone, sucralose, butylated hydroxyanisole, both natural and artificial spearmint flavour (https://www.spritam.com/pdfs/spritam-full-prescribing-information.pdf). While in this formulation major polymers such as poly lactic-acid (PLA) was not employed, polymers play a major role in the formulation of 3DP pharmaceuticals. There is a high demand for PLA, as it is a biobased polymer derived from biomass, that degrades in the environment or biological systems rapidly into non-toxic compounds. Lactic acid can be produced by a synthetic method or microbial fermentation.(Jem & Tan, 2020) However, polymers are not pure materials. They contain residues of stabilisers, catalyst, and initiators.(Ball et al, 2012) Depending on the route of administration, these impurities could have health issues and be harmful.(Stults et al, 2015) For example, polynuclear aromatics (found in sulfur-cured elastomers) are carcinogenic.(Norwood et al, 2008) Irgafos 168 is an antioxidant which is added to polymers,(Hermabessiere et al, 2020) and this compound can be degraded to bis(2,4-di-tert-butylphenyl) phosphate,(Dorival-García et al, 2018) which has cell toxicity.(Hammond et al, 2013) PLA is usually processed by melting and this affects significantly on the stability and mechanical properties of PLA. A process that is performed regularly in 3DP. It has been suggested to add Ifragos 168 (in combination with other antioxidant Irgnox 1076) to improve the stability of PLA during the production process involving melting of the polymer.(Oliveira et al, 2016)

These compounds are additives to polymers. The majority of such impurities are common chemical additives used to improve the physicochemical properties of a wide range of plastic materials and these appear as extractables or leachables in pharmaceutical products.(Li et al, 2015) The term extractables refers to a profile of extracted compounds found in studies under harsh conditions, but the term leachables refers to those impurities that leach from the materials under real-use conditions and may be present in final drug products. In the development of a drug product, careful consideration should be given to impurities that may originate from manufacturing equipment, process components, and packaging materials. Normally, plastics are not consumed in the drug delivery systems, however, in 3D printing these plastics may contain active ingredients and taken orally. Therefore, suppliers and drug manufacturers for 3DP should conduct studies to identify chemical additives from the plastic materials in order to screen and predict potential health issues in particular if taken on a regular basis. Clearly, biomaterials play an increasing role in contemporary intelligent drug delivery technologies as well as modern health care systems. Identifying biocompatible material poses a significant challenge for both researchers and manufacturers of modern drug delivery systems from material development to market approval.

In the following sections different 3DP techniques are introduced that have been employed for pharmaceutical dosage forms. In addition, typical materials are provided with potential health/toxicity issue. Then potential natural products are explained that can be substituted.

DIFFERENT 3DP METHODS

Fused Deposition Modelling

Fused deposition modelling (FDM) is commonly used 3DP in preparation of solid dosage forms.(Ehtezazi et al, 2018; Gorkem Buyukgoz et al, 2020; Gültekin et al, 2019; Ibrahim et al, 2019; Kempin et al, 2018; Kempin et al, 2017; Okwuosa et al, 2018; Reddy Dumpa et al, 2020; Solanki et al, 2018; Tagami et al, 2019; Wei et al, 2020) In this technique, normally a filament is inserted into the printer which melts and extrudes the filament through a narrow nozzle, typically 0.4 mm diameter, although nozzles are available with diameters as large as 1 mm for printing highly viscous compounds. The molten filament is deposited on a platform, like glass, according to the design created using the slicer software. The rastered back and forth movement of the printer head leaves the molten material side-by-side, or more interestingly the printhead is fixed but the build-plate moves in different directions (x, y, z). When one layer is complete, then the z-axis movement of the platform deposits the molten filament in the layer above. This process is

repeated until the object is fully materialised, and the molten state of the filament attaches the layers. FDM 3D printers can produce objects with uniform drug distribution,(Trenfield et al, 2018) and reproducible dimensions, in particular when filaments are used with uniform diameters (low diameter tolerance).(Goyanes et al, 2015) The drug is usually loaded during the preparation of the filament,(Ehtezazi et al, 2018) however, soaking a blank filament into the drug solution may be used.(Tagami et al, 2019) Typical materials and temperatures used in FDM 3DP are: hydroxy propyl cellulose (140-145°C),(Gorkem Buyukgoz et al, 2020) polyvinyl alcohol (180-200°C),(Ehtezazi et al, 2018; Wei et al, 2020) ethyl cellulose (165°C), (Reddy Dumpa et al, 2020) polyvinyl pyrrolidone (100°C),(Kempin et al, 2018) polyethylene glycol 20,000 (100°C),(Kempin et al, 2018) hydroxypropyl methylcellulose acetate succinate (150-170°C),(Solanki et al, 2018) polycaprolactone (47-140°C),(Kempin et al, 2017)and poly(ethylene) oxide (120-130°C).(Gültekin et al, 2019) Rindelaub et al 2019 identified extractable profiles from different grades of PLA. Surprisingly lead (Pb) was found in the printlets in the range of 0.11-1.46 ng/g, which was originated from the printing nozzle.(Rindelaub et al, 2019) In addition, Irganox 1010 (an antioxidant) was found in FDA approved PLA at the level of 1232 µg/g.(Rindelaub et al, 2019)

Filaments are produced in the temperature range of 47-200°C.(Gorkem Buyukgoz et al, 2020; Gültekin et al, 2019; Kempin et al, 2018; Kempin et al, 2017; Reddy Dumpa et al, 2020; Solanki et al, 2018; Wei et al, 2020) The temperature of the 3DP normally is higher than the filament extrusion temperature.(Kempin et al, 2017) This is because the 3DP nozzle diameter is smaller than extrusion nozzle (die) diameter; and for viscose molten polymers larger nozzle diameters are needed to allow flow of molten polymer from the nozzle, otherwise the nozzle will become blocked.

As FDM requires a filament and manufacturing of the filament may appear as a barrier, direct 3DP has been invented.(Goyanes et al, 2019a) The powder blend is added directly into the printer head. Hydroxypropyl cellulose (HPC) was employed with this printer with printing temperature of 170°C. Recently, direct 3DP was employed to produce tramadol printlets using HPC.(Ong et al, 2020) Fanous et al. 2020 employed direct 3DP to produce immediate release tablets at printing temperature of 155-180°C.(Fanous et al, 2020) PEG4000 and Kollidon VA64 were added to achieve rapid release.

Powder bed 3D printing

In powder bed 3D printing, a liquid (ink) is deposited on a flat layer of powder, and the ink causes adhesion of the solid particles together. A defined shape is formed by precise movements of the printer head. When one layer is formed, the platform is lowered for the thickness of one layer and then the old layer is covered with fresh powder, and the cycle starts again. Normally, the ink is a binder solution.(Katstra et al, 2000) Spritam is produced by this method, and Spritam is the only approved 3DP dosage form so far. However, clogging of the inkjet nozzle is the main challenge, when the ink contains a binder. Infanger et al. 2019 overcame this problem by using water and ethanol mixture as the ink, but including HPC as the solid binder.(Infanger et al, 2019) However, the 3D printed tablets disintegrated in the range of 131-1854 s depending on the type of HPC. While Spritam is known for disintegration in less than 5 s. Katstra et al. 2000 were applied powder 3D printing to formulated porous tablets; and a solution of Eudragit E100 in ethanol (20% w/w) was used as the binder solution. The powder bed was Avicel PH301.(Katstra et al, 2000) While Wu et al 1996, prepared a solution of poly-ε-caprolactone (PCL) in chloroform (5% w/w) to be deposited on polyethylene oxide (PEO) and PCL powder.(Wu et al, 1996) An inkjet nozzle with 45 µm was utilised. This interesting drug delivery design had walls of PCL (with different thicknesses) with internal compartments made of PEO. Yu etal 2009 employed powder bed 3DP to produce drug delivery devices that provided linear drug release profiles.(Yu et al, 2009) The binder solution contained ethyl cellulose in ethanol, or active ingredient (paracetamol) in ethanol.

The infiltration of the binder solution (ink) through the porous structure of powder bed is governed by capillary forces, and this infiltration determines the printing resolution. Barui et al. 2020 demonstrated that the ink (ethylene glycol) could penetrate within one second to the depth of a model powder (alumina).(Barui et al, 2020)

Stereolithography (SLA) 3D printing

In SLA 3D printing laser light is employed. In this method a resin such as polyethylene glycol diacrylate (PEGDA) is held inside a container with a photoinitiator (PI) such as diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (DPPO).(Wang et al, 2016) Then precise movement of laser light (such

as HeCd) in a 2D pattern, cures the resin, also known as photopolymerisation. When a layer is cured, then the platform with the cured structure attached is lowered in the bottom-up approach and therefore, another layer of uncured liquid resin spreads over the top. The SLA provides the opportunity of 3DP by bottom-to-top approach, where the laser light is emitted from the bottom of the resin pool. Usually, the drug molecule is dissolved in the resin solution. The resolution of SLA 3DP is much higher than FDM;(Kjar & Huang, 2019) and it is in the range of 30-140 µm, or as small as 16 µm.(Chia & Wu, 2015) In the SLA 3DP, the kinetics of the curing reaction are critical, which depend on energy imparted by the laser and the power of the light source, the scanning speed, the exposure time and the amount of polymer and photoinitiator.(Chia & Wu, 2015) Wang et al. 2016, applied SLA to produce oral dosage forms loaded with 4-aminosalicylic acid (4-ASA) and paracetamol. The release of active ingredients was modified by adjusting the amounts of PEGDA.(Wang et al, 2016) The active ingredients were released from the oral dosage forms due to the dissolution of the polymer in the testing media. In another study, Martinez et. al. 2017 applied SLA 3D to produce hydrogels of ibuprofen.(Martinez et al, 2017) PEGDA was used as the photopolymerisable monomer with PEG300 and water to adjust the crosslinking density of the hydrogel. This study used two different PIs: DPPO and riboflavin (with triethanolamine as a co-initiator). The objects were printed at the resolution of 300 µm. Dissolution data showed that increasing water content increased drug release rate.(Martinez et al, 2017) Xu et al. 2020 employed SLA 3DP to produce polyprintlets (a multilayer polypill).(Xu et al, 2020) To achieve this, the printer software was modified, which allowed changing the resin solution containing different active ingredients. Undesirable reactions between API and photoreactive monomers should be investigated or eliminated when SLA 3DP is employed.

In Process Drying 3DP

In process drying 3DP is a semisolid extrusion 3DP. In this method, an aqueous based semisolid formulation was prepared that contained hydroxyethylcelulose, drug, and sorbitol as plasticizer. The 3D printer was a modified FDM that the printhead was connected to a syringe pump and a 2 mm glass sheet was used as the print surface.(Elbl et al, 2020) The printer platform was heated to 75°C to dry the printed objects. After printing, films were kept on heated bed for 10 min to ensure desired drying degree of all films. Apply in-process drying 3D printer allowed to manufacture FDFs with thickness from 45-205µm with disintegration time of less than 40 s (for 100 µm thickness films).(Elbl et al, 2020) Films with the thickness of 40 µm disintegrated within 10 s. Printing multilayer objects seems challenging with the in drying process, as initial layers dry and subsequent layers may not deposit suitably. In another approach, Sjöholm and Sandler 2019 employed semi-solid extrusion 3DP to manufacture warfarin FDFs. The films were printed on the platform of a Biobot 3DP and were left to dry over 24 hr. Interestingly, blank films (drug unloaded) disintegrated within 3 s, while drug loaded films disintegrated at much longer time.(Sjöholm & Sandler, 2019) It should be noted that the disintegration time was measured by a drop method, which is putting one film in a texture analyser film support rig and one drop of 0.2 mL purified water is placed in the hole on top of film. The time is recorded when the film breaks (the drop falls-through).(Sjöholm & Sandler, 2019)

Direct 3DP

As mentioned in the previous section, conventional FDMs require a filament to produce the 3D objects and manufacturing a suitable filament can be challenging that can withstand the mechanical stresses of printer head.(Ilyés et al, 2019) Therefore, avoiding preparation of filaments could help the development 3D printed pharmaceutical dosage forms. To achieve this, a direct powder 3DP was developed, which was based on mounting a single-screw HME on the top of the printer head. Then, the rotation speed and the extrusion were controlled by the 3DP software. The HME extruder and printer head assembly (including a nozzle with 0.8 mm diameter) moved in 3 dimensions to make the objects in a layer-by-layer style.(Goyanes et al, 2019a) Use of direct powder/pellet FDM 3DP now is becoming wider.(Liu et al, 2019) It was found that the stepper motor's speed had the most significant effect on the diameter of the printed fibres.(Liu et al, 2019) In another approach, a pneumatic direct FDM 3DP was developed, in which powder is fed into a cylinder and the content is melted using an heating element and extruded through a nozzle with 0.4 mm aperture with the help of air pressure.(Cho et al, 2020) Using this printer allowed to prepare orodispersible films that disintegrated in the range of 17-21 s. PEO and PVPVA (Kollidon® VA64) and poloxamer 188 were used in the orodispersible formulation with disintegration time of 17 s.(Cho et al, 2020)

The direct powder 3DP was employed to produce itraconazole printlets using four different grades of HPC.(Goyanes et al, 2019a) In addition, direct 3DP was employed to fabricate rapid release dosage forms

by incorporating a honeycomb structure into the printlets.(Fanous et al, 2020) Furthermore, direct powder 3DP was used to prepare nifedipine minitablets containing 20 mg of API with 15% PEG 4000 Da, 40% HPC, 19% hydroxy propyl methyl cellulose acetate succinate, and 1% magnesium stearate.(Sánchez-Guirales et al, 2021) An Engine SR Hyrel FDM 3DP was used to print the minitablets, but a modular head TAM-15® extruder was used to extrude the powder through a 1 mm aperture nozzle. M3DIMAKER™ pharmaceutical direct powder 3D printer was employed to produce paediatric praziquantel printlets.(Boniatti et al, 2021) As praziquantel has an unpleasant taste, then splitting conventional tablets exposes the taste to paediatric patients and compromising their compliances. Therefore, 3DP allowed to produce personalised tablets without the need for adjusting the dose by splitting a larger dose tablet.

Direct 3DP has its own challenges. Usually, direct 3DP nozzles are greater than conventional 3DP FDM, therefore, fine resolutions may not be achievable. Furthermore, the viscosity of molten powder could be high and therefore, stronger electromotors are needed. However, these are bulky, and their torque may damage the printhead (authors experience with initial Noztek extruder that with certain powders the viscosity was so high that the electromotor of the extruder twisted the chassis of the extruder and the whole frame got damaged. As a result, new Noztek extruders have a sensor that above a certain force the extruder shuts off). Therefore, these could be the reasons why direct 3DP has not been used extensively in the formulation of pharmaceutical dosage forms.(Fina et al, 2020) Furthermore, the cleaning of the head can be difficult due to small spaces and using brushes. Therefore, direct 3DP can be useful only for a small range of material. Advanced extruders have three different temperature regions with twin screws, while achieving these arrangements in a 3D printhead may be challenging.

Two-Photon Polymerisation 3DP

In two-photon lithography (TPL) 3DP, a liquid material is converted into solid by light.(Harinarayana & Shin, 2021) The liquid contains monomer and by absorption of two photons (two laser beams) in the infrared range polymerisation is initiated and small voxel of the liquid is solidified. The laser emitting duration is short in the range of 100 femtosecond. This leads to a short photopolymerisation, therefore basically, it is pin-pointing polymerisation. This techniques allows to fabricate at sub-micro resolution (0.5 µm, i.e. a castle model can be built on the tip of a pencil).(Maibohm et al, 2020) A suitable material for TPL-3DP has two components: 1) a monomer or mixture of monomers, 2) photoinitiator.(Selimis et al, 2015) SU8 is one of the widely used material in TPL.(Selimis et al, 2015) Both monomer and photoinitiator must be transparent at the laser wavelength, so the laser beam can penetrate inside the liquid, and not being absorbed at the surface.(Selimis et al, 2015) Preloading of drug molecules have been suggested into fine structures that are prepared by TPL-3DP.(Limongi et al, 2020) In another approach, TPL-3DP was employed to manufacture templates of microneedle arrays for transdermal drug delivery.(Cordeiro et al, 2020) The ultra-low resolution of the TPL-3DP allowed to produce templates with needle length in the range of 900-1300 µm with different shapes (pyramidal, conical). These templates permitted to produce dissolving microneedle arrays made from PVP and PVA.(Cordeiro et al, 2020) Do et al 2018 applied TLP-3DP to produce drug delivery devices made of PEG dimethacrylate (PEGDMA). Irgacure 369 was employed as the photoinitiator. The model drug was dissolved in the PEGDMA and photoinitiator aqueous solution.(Do et al, 2018) Devices were manufactured with pore sizes in the range of 5-15 µm, which allowed to control drug release from the devices. The devices were found biocompatible by presenting no cell viability issues. In fact, the toxicological aspects of fabrication process would be the point of concern due to presence of free radicals following polymerisation.

Hot Melt Ram and Hot-Melt Pneumatic Extrusion 3DP

Other approaches to avoid filament manufacturing are hot-melt ram and hot-melt pneumatic extrusion 3DP. In hot-melt ram 3DP, maltodextrins, drug, and other excipients were mixed (in a mortar) and coated with a plasticizer (i.e. glycerine). Then, the mixture was fed in the cylinder (chamber) of the ram-extruder, which was connected to an 18G needle. The cylinder was heated to melt the mixture. It should be noted that the whole cylinder down to the needle was covered by a thermostated support. This is essential to ensure that mixture stays molten within the 3DP. The ram-extruder was mounted on a 3DP FDM, to achieve a raster fashion movement. This method was employed to manufacture orodispersible films, which disintegrated in less than 1 min (73 ± 15s).(Musazzi et al, 2018) The hot-melt pneumatic extrusion 3DP is similar to hot-melt ram extrusion 3DP, but instead of ram, the molten mixture was extruded with applying air pressure. Oh et. al. 2020 applied hot-melt pneumatic extrusion 3DP to produce orodispersible films by employing

PEO (100k Da), ploxamer 188 and citric acid. The films disintegrated in less than 25 s, (Oh et al, 2020) and the air pressure was in the range of 250-350 kPa. Furthermore, hot-melt pneumatic extrusion was employed to produce 3DP tablets of dutasteride.(Kim et al, 2021) Th excipients were: Soluplus®, Kollidon® VA 64, Eudragit® E PO, and HPC. The nozzle diameter was 0.4 mm, indicating of printlets with a high resolution. However, the tablets were printed at 160°C-190°C, which means that a large quantity of the formulation was kept at high temperatures, potentially causing drug stability issue. (Kim et al, 2021)

Paste-Extrusion 3DP

In paste-extrusion 3DP, a gel-based material (semisolid) is filled inside a syringe, which the feedstock is connected to a stepper motor, (Amza et al, 2017) or air pressure(Tagami et al, 2021) to pass the paste through an extrusion nozzle. Paste-extrusion 3DP has been employed to produce gummies that contain active ingredients.(Goyanes et al, 2019c; Herrada-Manchón et al, 2020; Rycerz et al, 2019; Tagami et al, 2021) Herrada-Manchón et al 2020 developed a paste formulation comprising gelatine, corn starch, carrageenan, and xanthan gum with ranitidine as the active ingredient.(Herrada-Manchón et al, 2020) The gel was heated up to 37°C and then was filled into 3 ml syringes followed by 3D printing. The printhead temperature was set to 37°C too, with printing bed at 15°C, which help rapid solidifying of the printed gummy. Printlets with suitable finish were obtained with 80% infill density. Solidification of the gel in the syringe is one of the drawbacks of this approach. Therefore, Tagami et al 2021 developed a gel formulation containing gelatine, HPMC, and reduced syrup with lamotrigine as the active ingredient.(Tagami et al, 2021) This formulation was not set at room temperature and extruded through a nozzle (27 G, 0.413 mm internal diameter). However, the printed objected were dried overnight at room temperature. This formulation led to printing main shapes such as star or disk, while it appears printing object with the shape of animals could be challenging. Meaning that if gels are solidified at higher temperatures, then there is a better chance of printing with fine details. It should be noted that we found the paste formulation with HPMC could solidify at temperatures less than 25°C (when the environment temperature is cold such autumn or winter). Therefore, we are developing a paste extruder with heating jacket and the results will be published shortly. The pate-extrusion 3DP has been tested in paediatric patients (3-16 year) for the delivery of isoleucine.(Goyanes et al, 2019b) The chewable printlets were only in the shape of cylinders, however, they were accepted by the patients. The above information indicates that the paste-extrusion 3DP may employ natural products to FDM 3DP or SLA 3DP. Table 1 presents the use/potential use of natural products in 3DP of pharmaceutical dosage forms.

Selective Laser Sintering 3DP

Selective laser sintering 3DP (SLS 3DP) involves heating powder particles by laser leading to melt and fusion of powder particles.(Charoo et al, 2020a) As it would be expected the resolution of SLS 3DP depends on the laser diameter in the range of 0.3 mm(Berry et al, 1997b) to 0.02 mm (20μm).(Muzaffar et al, 2020) As a result SLS produced an impressive 1.79% dimensional error.(Ibrahim et al, 2009) It should be noted that a laser absorbing material such as Candurin gold sheen (a food ingredient) may be required to be added to the powder mixer.(Charoo et al, 2020b) This process includes formation of a powder layer on a powder bed, where a controlled scanning laser beam fuses powder particles and a 2D layer is formed. Then another powder layer is spread over the previous layer with the help of a roller and the laser beam builds another layer over the previous built. This process is iterated until the desired object is formed, which located within a bulk of powder mass. The object is recovered and cleaned from the residual powder. Nylon is the most common material for SLS 3DP.(Berry et al, 1997a) Other potential polymers are polyethylene both high and low density, polyvinyl chloride and polystyrene.(Asim et al, 2017) Generally, thermoplastic polymers should be suitable for SLS 3DP. A thermoplastic polymer can be melt and shaped at a specific temperature.(Asim et al, 2017) However, the powders used for pharmaceutical applications are: HPMC (grades 100 to 30),(Fina et al, 2018) Kollidon® VA 64 (grades 100 to 300)(Fina et al, 2018), Kollicoat IR,(Fina et al, 2017) Eudragit L100-55(Fina et al, 2017), poly (L-lactic acid),(Duan et al, 2010) polyethylene,(Salmoria et al, 2018) poly (lactic-acid),(Bai et al, 2017) polyetheretherketone (PEEK),(Tan et al, 2003) and polycaprolactone.(Leong et al, 2007) SLS 3DP has been applied to produce orally disintegrating tablets (printlets),(Fina et al, 2018) with outstanding disintegration time of 4 seconds when Kollidon® VA 64 grade 300 was employed.(Fina et al, 2018) Candurin gold sheen was also added to the

Table 1. Natural products that have been used in 3DP including 3DP of pharmaceutical dosage forms.

Compound	Origin	Dosage Form/shape	3DP	Remarks	Ref
Xanthan gum	*Xanthomonas campestris*	gummy	Paste extrusion 3DP	Eye catching objects were produced	(Herrada-Manchón et al, 2020)
Pectin	Fruits such as apple and carrot	Chewable tablet	Paste extrusion 3DP	Tablets were well accepted by paediatric patients	(Goyanes et al, 2019c)
Sodium alginate	Phaeophyceae	Multilayer mesh structure	Paste extrusion 3DP	Flexible structure were prepared and CaCl2 was used to cross link alginate	(Wang et al, 2021)
Chitosan	*Litopenaeus vannamei* Boone (de Queiroz Antonino et al, 2017)	Star/half moon	Direct ink writing	Shapes with high resolutions were produced	(Zhou et al, 2020)
Snakegourd root/Astragalus	*Trichosanthes anguina* L/Astragalus propinquus	Square, round, rectangle	Hot melt extrusion 3DP	Changing shape led to change in the drug release rate	(Yan et al, 2019)
sodium hyaluronate	bovine vitreous humor/ *Streptococcus equi/*	Composite scaffolds	Paste extrusion 3DP followed by layer-by-layer coating with sodium hyaluronate	Sodium hyaluronate reduced drug release from the scaffolds	(Chen et al, 2019)
Collagen	Bone/skin/connective tissue of animals (cattle, fish, horse)	Composite scaffolds	FDM 3DP using PLA followed by coating with collagen	Scaffolds provided a closer structural support approximation to native bone architecture	(Martin et al, 2019)
Chocolate	*Theobroma cacao*	Cartoon characters	Paste extrusion 3DP	80% of drug released within 30 minutes	(Karavasili et al, 2020)

formulation. This printlet produced the least breaking force (13 N) with the highest porosity (40%).(Fina et al, 2018) Applying x-ray crystallography found that paracetamol drug crystals could be identified in 3D printed tablets made by the SLS method. While DSC analysis failed to detect the drug crystals.(Fina et al, 2017) This would be expected as by melting the thermoplastic polymer, the drug crystal may not melt at the same time and molten plastic may encapsulate the drug crystal. Intrauterine devices were manufactured using SLS 3DP. It was found that laser power had little effects on the release of progesterone or 5-

Fluorouracil.(Salmoria et al, 2018) The potential drawback of SLS 3DP is drug degradation during melting the polymers.(Fina et al, 2017) Furthermore, large quantities of powders are required and this may become costly for expensive drugs.(Awad et al, 2020)

Inkjet 3P

As explained in the previous section, inkjet 3DP has been employed for powder bed 3DP. Other applications of inkjet printing will be reviewed in this section. It should be noted that inkjet printing deposits liquid droplets and these can form solid objects, when the droplets themselves contain nanopatilces.(Saleh et al, 2017) In this approach the nanoparticles are joined by a curing or sintering process, which leaves a solid 2D layer behind. 3D objects were created with the height of 2 mm, following printing of 1000 layers.(Saleh et al, 2017) In another approach, the ink contained quantum dots and the inkjet printing was employed to uniformly deposit the quantum dots on transdermal microneedles.(Boehm et al, 2011) Uddin et al 20.15 applied this technique to coated transdermal microneedles with three anticancer drugs (curcumin, 5 fluorouracil, cisplatin).(Uddin et al, 2015) Inkjet printing have been employed to deposit salbutamol sulphate on oral films made of potato starch.(Buanz et al, 2011) In this approach, the ink contained aqueous solution of salbutamol sulphate, as well as glycerol, which was employed to increase the viscosity of the ink and prevent salbutamol sulphate crystallisation. Inkjet 3DP has been widely used in tissue engineering, where cells are deposited uniformly on a hydrogel scaffolding layer-by-layer with simultaneous photopolymerisation of the gel.(Cui et al, 2012; Gao et al, 2015; Tamay et al, 2019) Polymers such as the Soluplus, a co-polymer of polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol has been employed to coat the microneedles.(Uddin et al, 2015) The drug and polymers were dissolved in water or ethanol. Also, aqueous solution of quantum dot nanocrystals (Qtracker® 705) were used as ink for inkjet printing on microneedles.(Boehm et al, 2012) The ink may contain viscosity increasing agents and surfactants as well as nanoparticles.(Saleh et al, 2017) For cell printing, the ink contained cells, I-2959 photoinitiator, poly(ethylene glycol) dimethacrylate and gelatin methacrylate.(Gao et al, 2015) Blocking the inkjet nozzle is the main challenge. Clogging may happen for nanoparticles due to flow-induced aggregation at the nozzle or if the suspended nanoparticles are not sufficiently stabilised and aggregations form.(Lee et al, 2012)

CONCLUSIONS

Synthetic polymeric materials form most of excipients in 3DP. Thermoplastics form majority of the polymers. In certain SLS 3DPs photoinitiators are required to commence photopolymerisation. The cytotoxicity and safety of these chemicals should be investigated in pharmaceutical applications, in particular when these materials are used on a regular basis. Natural products may appear as active ingredient in the 3DP. However, they have been used as excipients in extrusion based 3DP and inkjet printing. Extrusion based 3DP have been employed to manufacture gummies containing APIs for paediatric use. Therefore, use of natural products may become desirable as natural products do not tend to carry synthetic additives. These advantages may also encourage parents and caregivers to maintain patient compliance. Shellac is a natural thermoplastic polymer with melting point in the range of 115-120°C. Shellac is used on candies as shiny shells. Furter investigations are required for the suitability of this material in 3DP, in particular in FDM 3DP.

Conflicts of Interest

The authors declare no personal or financial conflict of interest related to this work.

Authors contribution

REFERENCES

Amza, C. G., Zapciu, A. & Popescu, D. (2017) Paste Extruder—Hardware Add-On for Desktop 3D Printers. *Technologies*, 5(3), 50.

Asim, M., Jawaid, M., Saba, N., Ramengmawii, Nasir, M. & Sultan, M. T. H. (2017) 1 - Processing of hybrid polymer composites—a review, in Thakur, V. K., Thakur, M. K. & Gupta, R. K. (eds), *Hybrid Polymer Composite Materials*Woodhead Publishing, 1-22.

Awad, A., Fina, F., Goyanes, A., Gaisford, S. & Basit, A. W. (2020) 3D printing: Principles and pharmaceutical applications of selective laser sintering. *International Journal of Pharmaceutics*, 586, 119594.

Bai, J., Goodridge, R. D., Hague, R. J. M. & Okamoto, M. (2017) Processing and characterization of a polylactic acid/nanoclay composite for laser sintering. *Polymer Composites*, 38(11), 2570-2576.
Ball, D. J., Norwood, D. L. & Nagao, L. M. (2012) Overview of Leachables and Extractables in Orally Inhaled and Nasal Drug Products, *Leachables and Extractables Handbook*, 1-19.
Barui, S., Ding, H., Wang, Z., Zhao, H., Marathe, S., Mirihanage, W., Basu, B. & Derby, B. (2020) Probing Ink-Powder Interactions during 3D Binder Jet Printing Using Time-Resolved X-ray Imaging. *ACS Appl Mater Interfaces*, 12(30), 34254-34264.
Berry, E., Brown, J. M., Connell, M., Craven, C. M., Efford, N. D., Radjenovic, A. & Smith, M. A. (1997a) Preliminary experience with medical applications of rapid prototyping by selective laser sintering. *Med Eng Phys*, 19(1), 90-6.
Berry, E., Brown, J. M., Connell, M., Craven, C. M., Efford, N. D., Radjenovic, A. & Smith, M. A. (1997b) Preliminary experience with medical applications of rapid prototyping by selective laser sintering. *Medical Engineering & Physics*, 19(1), 90-96.
Boehm, R. D., Miller, P. R., Hayes, S. L., Monteiro-Riviere, N. A. & Narayan, R. J. (2011) Modification of microneedles using inkjet printing. *AIP advances*, 1(2), 22139-22139.
Boehm, R. D., Miller, P. R., Singh, R., Shah, A., Stafslien, S., Daniels, J. & Narayan, R. J. (2012) Indirect rapid prototyping of antibacterial acid anhydride copolymer microneedles. *Biofabrication*, 4(1), 011002.
Boniatti, J., Januskaite, P., Fonseca, L. B. D., Viçosa, A. L., Amendoeira, F. C., Tuleu, C., Basit, A. W., Goyanes, A. & Ré, M. I. (2021) Direct Powder Extrusion 3D Printing of Praziquantel to Overcome Neglected Disease Formulation Challenges in Paediatric Populations. *Pharmaceutics*, 13(8).
Buanz, A. B. M., Saunders, M. H., Basit, A. W. & Gaisford, S. (2011) Preparation of Personalized-dose Salbutamol Sulphate Oral Films with Thermal Ink-Jet Printing. *Pharmaceutical Research*, 28(10), 2386.
Charoo, N. A., Barakh Ali, S. F., Mohamed, E. M., Kuttolamadom, M. A., Ozkan, T., Khan, M. A. & Rahman, Z. (2020a) Selective laser sintering 3D printing - an overview of the technology and pharmaceutical applications. *Drug Dev Ind Pharm*, 46(6), 869-877.
Charoo, N. A., Barakh Ali, S. F., Mohamed, E. M., Kuttolamadom, M. A., Ozkan, T., Khan, M. A. & Rahman, Z. (2020b) Selective laser sintering 3D printing – an overview of the technology and pharmaceutical applications. *Drug Development and Industrial Pharmacy*, 46(6), 869-877.
Chen, S., Shi, Y., Luo, Y. & Ma, J. (2019) Layer-by-layer coated porous 3D printed hydroxyapatite composite scaffolds for controlled drug delivery. *Colloids and Surfaces B: Biointerfaces*, 179, 121-127.
Chia, H. N. & Wu, B. M. (2015) Recent advances in 3D printing of biomaterials. *Journal of Biological Engineering*, 9(1), 4.
Cho, H. W., Baek, S. H., Lee, B. J. & Jin, H. E. (2020) Orodispersible Polymer Films with the Poorly Water-Soluble Drug, Olanzapine: Hot-Melt Pneumatic Extrusion for Single-Process 3D Printing. *Pharmaceutics*, 12(8).
Cordeiro, A. S., Tekko, I. A., Jomaa, M. H., Vora, L., McAlister, E., Volpe-Zanutto, F., Nethery, M., Baine, P. T., Mitchell, N., McNeill, D. W. & Donnelly, R. F. (2020) Two-Photon Polymerisation 3D Printing of Microneedle Array Templates with Versatile Designs: Application in the Development of Polymeric Drug Delivery Systems. *Pharmaceutical Research*, 37(9), 174.
Cui, X., Breitenkamp, K., Finn, M. G., Lotz, M. & D'Lima, D. D. (2012) Direct human cartilage repair using three-dimensional bioprinting technology. *Tissue engineering. Part A*, 18(11-12), 1304-1312.
de Queiroz Antonino, R. S. C. M., Lia Fook, B. R. P., de Oliveira Lima, V. A., de Farias Rached, R. Í., Lima, E. P. N., da Silva Lima, R. J., Peniche Covas, C. A. & Lia Fook, M. V. (2017) Preparation and Characterization of Chitosan Obtained from Shells of Shrimp (Litopenaeus vannamei Boone). *Marine drugs*, 15(5), 141.
Do, A.-V., Worthington, K. S., Tucker, B. A. & Salem, A. K. (2018) Controlled drug delivery from 3D printed two-photon polymerized poly(ethylene glycol) dimethacrylate devices. *International Journal of Pharmaceutics*, 552(1), 217-224.
Dorival-García, N., Carillo, S., Ta, C., Roberts, D., Comstock, K., Lofthouse, S., Ciceri, E., D'Silva, K., Kierans, G., Kaisermayer, C., Lindeberg, A. & Bones, J. (2018) Large-Scale Assessment of Extractables and Leachables in Single-Use Bags for Biomanufacturing. *Anal Chem*, 90(15), 9006-9015.
Duan, B., Wang, M., Zhou, W. Y., Cheung, W. L., Li, Z. Y. & Lu, W. W. (2010) Three-dimensional nanocomposite scaffolds fabricated via selective laser sintering for bone tissue engineering. *Acta Biomaterialia*, 6(12), 4495-4505.

Ehtezazi, T., Algellay, M., Islam, Y., Roberts, M., Dempster, N. M. & Sarker, S. D. (2018) The Application of 3D Printing in the Formulation of Multilayered Fast Dissolving Oral Films. *Journal of Pharmaceutical Sciences*, 107(4), 1076-1085.
Elbl, J., Gajdziok, J. & Kolarczyk, J. (2020) 3D printing of multilayered orodispersible films with in-process drying. *International Journal of Pharmaceutics*, 575, 118883.
Fanous, M., Gold, S., Muller, S., Hirsch, S., Ogorka, J. & Imanidis, G. (2020) Simplification of fused deposition modeling 3D-printing paradigm: Feasibility of 1-step direct powder printing for immediate release dosage form production. *International Journal of Pharmaceutics*, 578, 119124.
Fina, F., Goyanes, A., Gaisford, S. & Basit, A. W. (2017) Selective laser sintering (SLS) 3D printing of medicines. *International Journal of Pharmaceutics*, 529(1), 285-293.
Fina, F., Goyanes, A., Rowland, M., Gaisford, S. & A, W. B. (2020) 3D Printing of Tunable Zero-Order Release Printlets. *Polymers (Basel)*, 12(8).
Fina, F., Madla, C. M., Goyanes, A., Zhang, J., Gaisford, S. & Basit, A. W. (2018) Fabricating 3D printed orally disintegrating printlets using selective laser sintering. *Int J Pharm*, 541(1-2), 101-107.
Gao, G., Schilling, A. F., Hubbell, K., Yonezawa, T., Truong, D., Hong, Y., Dai, G. & Cui, X. (2015) Improved properties of bone and cartilage tissue from 3D inkjet-bioprinted human mesenchymal stem cells by simultaneous deposition and photocrosslinking in PEG-GelMA. *Biotechnol Lett*, 37(11), 2349-55.
Gorkem Buyukgoz, G., Soffer, D., Defendre, J., Pizzano, G. M. & Davé, R. N. (2020) Exploring tablet design options for tailoring drug release and dose via fused deposition modeling (FDM) 3D printing. *International Journal of Pharmaceutics*, 591, 119987.
Goyanes, A., Allahham, N., Trenfield, S. J., Stoyanov, E., Gaisford, S. & Basit, A. W. (2019a) Direct powder extrusion 3D printing: Fabrication of drug products using a novel single-step process. *International Journal of Pharmaceutics*, 567, 118471.
Goyanes, A., Buanz, A. B., Hatton, G. B., Gaisford, S. & Basit, A. W. (2015) 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. *Eur J Pharm Biopharm*, 89, 157-62.
Goyanes, A., Madla, C. M., Umerji, A., Duran Piñeiro, G., Giraldez Montero, J. M., Lamas Diaz, M. J., Gonzalez Barcia, M., Taherali, F., Sánchez-Pintos, P., Couce, M.-L., Gaisford, S. & Basit, A. W. (2019b) Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: First single-centre, prospective, crossover study in patients. *International Journal of Pharmaceutics*, 567, 118497.
Goyanes, A., Madla, C. M., Umerji, A., Duran Piñeiro, G., Giraldez Montero, J. M., Lamas Diaz, M. J., Gonzalez Barcia, M., Taherali, F., Sánchez-Pintos, P., Couce, M. L., Gaisford, S. & Basit, A. W. (2019c) Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: First single-centre, prospective, crossover study in patients. *Int J Pharm*, 567, 118497.
Gültekin, H. E., Tort, S. & Acartürk, F. (2019) An Effective Technology for the Development of Immediate Release Solid Dosage Forms Containing Low-Dose Drug: Fused Deposition Modeling 3D Printing. *Pharm Res*, 36(9), 128.
Hammond, M., Nunn, H., Rogers, G., Lee, H., Marghitoiu, A. L., Perez, L., Nashed-Samuel, Y., Anderson, C., Vandiver, M. & Kline, S. (2013) Identification of a leachable compound detrimental to cell growth in single-use bioprocess containers. *PDA J Pharm Sci Technol*, 67(2), 123-34.
Harinarayana, V. & Shin, Y. C. (2021) Two-photon lithography for three-dimensional fabrication in micro/nanoscale regime: A comprehensive review. *Optics & Laser Technology*, 142, 107180.
Hermabessiere, L., Receveur, J., Himber, C., Mazurais, D., Huvet, A., Lagarde, F., Lambert, C., Paul-Pont, I., Dehaut, A., Jezequel, R., Soudant, P. & Duflos, G. (2020) An Irgafos® 168 story: When the ubiquity of an additive prevents studying its leaching from plastics. *Science of The Total Environment*, 749, 141651.
Herrada-Manchón, H., Rodríguez-González, D., Alejandro Fernández, M., Suñé-Pou, M., Pérez-Lozano, P., García-Montoya, E. & Aguilar, E. (2020) 3D printed gummies: Personalized drug dosage in a safe and appealing way. *Int J Pharm*, 587, 119687.
Ibrahim, D., Broilo, T. L., Heitz, C., de Oliveira, M. G., de Oliveira, H. W., Nobre, S. M., Dos Santos Filho, J. H. & Silva, D. N. (2009) Dimensional error of selective laser sintering, three-dimensional printing and PolyJet models in the reproduction of mandibular anatomy. *J Craniomaxillofac Surg*, 37(3), 167-73.
Ibrahim, M., Barnes, M., McMillin, R., Cook, D. W., Smith, S., Halquist, M., Wijesinghe, D. & Roper, T. D. (2019) 3D Printing of Metformin HCl PVA Tablets by Fused Deposition Modeling: Drug Loading, Tablet Design, and Dissolution Studies. *AAPS PharmSciTech*, 20(5), 195.
Ilyés, K., Kovács, N. K., Balogh, A., Borbás, E., Farkas, B., Casian, T., Marosi, G., Tomuță, I. & Nagy, Z. K. (2019) The applicability of pharmaceutical polymeric blends for the fused deposition modelling (FDM) 3D

technique: Material considerations-printability-process modulation, with consecutive effects on in vitro release, stability and degradation. *Eur J Pharm Sci*, 129, 110-123.
Infanger, S., Haemmerli, A., Iliev, S., Baier, A., Stoyanov, E. & Quodbach, J. (2019) Powder bed 3D-printing of highly loaded drug delivery devices with hydroxypropyl cellulose as solid binder. *International Journal of Pharmaceutics*, 555, 198-206.
Jem, K. J. & Tan, B. (2020) The development and challenges of poly (lactic acid) and poly (glycolic acid). *Advanced Industrial and Engineering Polymer Research*, 3(2), 60-70.
Karavasili, C., Gkaragkounis, A., Moschakis, T., Ritzoulis, C. & Fatouros, D. G. (2020) Pediatric-friendly chocolate-based dosage forms for the oral administration of both hydrophilic and lipophilic drugs fabricated with extrusion-based 3D printing. *European Journal of Pharmaceutical Sciences*, 147, 105291.
Katstra, W. E., Palazzolo, R. D., Rowe, C. W., Giritlioglu, B., Teung, P. & Cima, M. J. (2000) Oral dosage forms fabricated by Three Dimensional Printing™. *Journal of Controlled Release*, 66(1), 1-9.
Kempin, W., Domsta, V., Grathoff, G., Brecht, I., Semmling, B., Tillmann, S., Weitschies, W. & Seidlitz, A. (2018) Immediate Release 3D-Printed Tablets Produced Via Fused Deposition Modeling of a Thermo-Sensitive Drug. *Pharm Res*, 35(6), 124.
Kempin, W., Franz, C., Koster, L.-C., Schneider, F., Bogdahn, M., Weitschies, W. & Seidlitz, A. (2017) Assessment of different polymers and drug loads for fused deposition modeling of drug loaded implants. *European Journal of Pharmaceutics and Biopharmaceutics*, 115, 84-93.
Kim, S. J., Lee, J. C., Ko, J. Y., Lee, S. H., Kim, N. A. & Jeong, S. H. (2021) 3D-printed tablets using a single-step hot-melt pneumatic process for poorly soluble drugs. *International Journal of Pharmaceutics*, 595, 120257.
Kjar, A. & Huang, Y. (2019) Application of Micro-Scale 3D Printing in Pharmaceutics. *Pharmaceutics*, 11(8).
Lee, A., Sudau, K., Ahn, K. H., Lee, S. J. & Willenbacher, N. (2012) Optimization of Experimental Parameters to Suppress Nozzle Clogging in Inkjet Printing. *Industrial & Engineering Chemistry Research*, 51(40), 13195-13204.
Leong, K. F., Wiria, F. E., Chua, C. K. & Li, S. H. (2007) Characterization of a poly-epsilon-caprolactone polymeric drug delivery device built by selective laser sintering. *Biomed Mater Eng*, 17(3), 147-57.
Li, K., Rogers, G., Nashed-Samuel, Y., Lee, H., Mire-Sluis, A., Cherney, B., Forster, R., Yeh, P. & Markovic, I. (2015) Creating a Holistic Extractables and Leachables (E&L) Program for Biotechnology Products. *PDA J Pharm Sci Technol*, 69(5), 590-619.
Limongi, T., Susa, F., Allione, M. & di Fabrizio, E. (2020) Drug Delivery Applications of Three-Dimensional Printed (3DP) Mesoporous Scaffolds. *Pharmaceutics*, 12(9), 851.
Liu, S., Zhao, P., Wu, S., Zhang, C., Fu, J. & Chen, Z. (2019) A Pellet 3D Printer: Device Design and Process Parameters Optimization. *Advances in Polymer Technology*, 2019, 5075327.
Maibohm, C., Silvestre, O. F., Borme, J., Sinou, M., Heggarty, K. & Nieder, J. B. (2020) Multi-beam two-photon polymerization for fast large area 3D periodic structure fabrication for bioapplications. *Scientific Reports*, 10(1), 8740.
Martin, V., Ribeiro, I. A., Alves, M. M., Gonçalves, L., Claudio, R. A., Grenho, L., Fernandes, M. H., Gomes, P., Santos, C. F. & Bettencourt, A. F. (2019) Engineering a multifunctional 3D-printed PLA-collagen-minocycline-nanoHydroxyapatite scaffold with combined antimicrobial and osteogenic effects for bone regeneration. *Materials Science and Engineering: C*, 101, 15-26.
Martinez, P. R., Goyanes, A., Basit, A. W. & Gaisford, S. (2017) Fabrication of drug-loaded hydrogels with stereolithographic 3D printing. *Int J Pharm*, 532(1), 313-317.
Melocchi, A., Uboldi, M., Cerea, M., Foppoli, A., Maroni, A., Moutaharrik, S., Palugan, L., Zema, L. & Gazzaniga, A. (2020) A Graphical Review on the Escalation of Fused Deposition Modeling (FDM) 3D Printing in the Pharmaceutical Field. *Journal of Pharmaceutical Sciences*, 109(10), 2943-2957.
Musazzi, U. M., Selmin, F., Ortenzi, M. A., Mohammed, G. K., Franzé, S., Minghetti, P. & Cilurzo, F. (2018) Personalized orodispersible films by hot melt ram extrusion 3D printing. *International Journal of Pharmaceutics*, 551(1), 52-59.
Muzaffar, A., Ahamed, M. B., Deshmukh, K., Kovářík, T., Křenek, T. & Pasha, S. K. K. (2020) Chapter 4 - 3D and 4D printing of pH-responsive and functional polymers and their composites, in Sadasivuni, K. K., Deshmukh, K. & Almaadeed, M. A. (eds), *3D and 4D Printing of Polymer Nanocomposite Materials*Elsevier, 85-117.
Norwood, D. L., Paskiet, D., Ruberto, M., Feinberg, T., Schroeder, A., Poochikian, G., Wang, Q., Deng, T. J., DeGrazio, F., Munos, M. K. & Nagao, L. M. (2008) Best practices for extractables and leachables in

orally inhaled and nasal drug products: an overview of the PQRI recommendations. *Pharm Res*, 25(4), 727-39.
Oh, B.-C., Jin, G., Park, C., Park, J.-B. & Lee, B.-J. (2020) Preparation and evaluation of identifiable quick response (QR)-coded orodispersible films using 3D printer with directly feeding nozzle. *International Journal of Pharmaceutics*, 584, 119405.
Okwuosa, T. C., Soares, C., Gollwitzer, V., Habashy, R., Timmins, P. & Alhnan, M. A. (2018) On demand manufacturing of patient-specific liquid capsules via co-ordinated 3D printing and liquid dispensing. *European Journal of Pharmaceutical Sciences*, 118, 134-143.
Oliveira, M., Santos, E., Araújo, A., Fechine, G. J. M., Machado, A. V. & Botelho, G. (2016) The role of shear and stabilizer on PLA degradation. *Polymer Testing*, 51, 109-116.
Ong, J. J., Awad, A., Martorana, A., Gaisford, S., Stoyanov, E., Basit, A. W. & Goyanes, A. (2020) 3D printed opioid medicines with alcohol-resistant and abuse-deterrent properties. *International Journal of Pharmaceutics*, 579, 119169.
Prasad, L. K. & Smyth, H. (2016) 3D Printing technologies for drug delivery: a review. *Drug Development and Industrial Pharmacy*, 42(7), 1019-1031.
Reddy Dumpa, N., Bandari, S. & M, A. R. (2020) Novel Gastroretentive Floating Pulsatile Drug Delivery System Produced via Hot-Melt Extrusion and Fused Deposition Modeling 3D Printing. *Pharmaceutics*, 12(1).
Rindelaub, J. D., Baird, Z., Lindner, B. A. & Strantz, A. A. (2019) Identifying extractable profiles from 3D printed medical devices. *PLOS ONE*, 14(5), e0217137.
Rycerz, K., Stepien, K. A., Czapiewska, M., Arafat, B. T., Habashy, R., Isreb, A., Peak, M. & Alhnan, M. A. (2019) Embedded 3D Printing of Novel Bespoke Soft Dosage Form Concept for Pediatrics. *Pharmaceutics*, 11(12).
Saleh, E., Zhang, F., He, Y., Vaithilingam, J., Fernandez, J. L., Wildman, R., Ashcroft, I., Hague, R., Dickens, P. & Tuck, C. (2017) 3D Inkjet Printing of Electronics Using UV Conversion. *Advanced Materials Technologies*, 2(10), 1700134.
Salmoria, G. V., Vieira, F. E., Muenz, E. A., Gindri, I. M., Marques, M. S. & Kanis, L. A. (2018) Additive Manufacturing of PE/fluorouracil/progesterone intrauterine device for endometrial and ovarian cancer treatments. *Polymer Testing*, 71, 312-317.
Sánchez-Guirales, S. A., Jurado, N., Kara, A., Lalatsa, A. & Serrano, D. R. (2021) Understanding Direct Powder Extrusion for Fabrication of 3D Printed Personalised Medicines: A Case Study for Nifedipine Minitablets. *Pharmaceutics*, 13(10).
Selimis, A., Mironov, V. & Farsari, M. (2015) Direct laser writing: Principles and materials for scaffold 3D printing. *Microelectronic Engineering*, 132, 83-89.
Sjöholm, E. & Sandler, N. (2019) Additive manufacturing of personalized orodispersible warfarin films. *International Journal of Pharmaceutics*, 564, 117-123.
Solanki, N. G., Tahsin, M., Shah, A. V. & Serajuddin, A. T. M. (2018) 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*, 107(1), 390-401.
Stults, C. L., Ansell, J. M., Shaw, A. J. & Nagao, L. M. (2015) Evaluation of extractables in processed and unprocessed polymer materials used for pharmaceutical applications. *AAPS PharmSciTech*, 16(1), 150-64.
Tagami, T., Ito, E., Kida, R., Hirose, K., Noda, T. & Ozeki, T. (2021) 3D printing of gummy drug formulations composed of gelatin and an HPMC-based hydrogel for pediatric use. *International Journal of Pharmaceutics*, 594, 120118.
Tagami, T., Kuwata, E., Sakai, N. & Ozeki, T. (2019) Drug Incorporation into Polymer Filament Using Simple Soaking Method for Tablet Preparation Using Fused Deposition Modeling. *Biol Pharm Bull*, 42(10), 1753-1760.
Tamay, D. G., Dursun Usal, T., Alagoz, A. S., Yucel, D., Hasirci, N. & Hasirci, V. (2019) 3D and 4D Printing of Polymers for Tissue Engineering Applications. *Frontiers in Bioengineering and Biotechnology*, 7.
Tan, K. H., Chua, C. K., Leong, K. F., Cheah, C. M., Cheang, P., Abu Bakar, M. S. & Cha, S. W. (2003) Scaffold development using selective laser sintering of polyetheretherketone–hydroxyapatite biocomposite blends. *Biomaterials*, 24(18), 3115-3123.
Trenfield, S. J., Goyanes, A., Telford, R., Wilsdon, D., Rowland, M., Gaisford, S. & Basit, A. W. (2018) 3D printed drug products: Non-destructive dose verification using a rapid point-and-shoot approach. *International Journal of Pharmaceutics*, 549(1), 283-292.

Uddin, M. J., Scoutaris, N., Klepetsanis, P., Chowdhry, B., Prausnitz, M. R. & Douroumis, D. (2015) Inkjet printing of transdermal microneedles for the delivery of anticancer agents. *International Journal of Pharmaceutics*, 494(2), 593-602.
Wang, J., Goyanes, A., Gaisford, S. & Basit, A. W. (2016) Stereolithographic (SLA) 3D printing of oral modified-release dosage forms. *International Journal of Pharmaceutics*, 503(1), 207-212.
Wang, J., Liu, Y., Zhang, X., Rahman, S. E., Su, S., Wei, J., Ning, F., Hu, Z., Martínez-Zaguilán, R., Sennoune, S. R., Cong, W., Christopher, G., Zhang, K. & Qiu, J. (2021) 3D printed agar/ calcium alginate hydrogels with high shape fidelity and tailorable mechanical properties. *Polymer*, 214, 123238.
Wei, C., Solanki, N. G., Vasoya, J. M., Shah, A. V. & Serajuddin, A. T. M. (2020) Development of 3D Printed Tablets by Fused Deposition Modeling Using Polyvinyl Alcohol as Polymeric Matrix for Rapid Drug Release. *Journal of Pharmaceutical Sciences*, 109(4), 1558-1572.
Wu, B. M., Borland, S. W., Giordano, R. A., Cima, L. G., Sachs, E. M. & Cima, M. J. (1996) Solid free-form fabrication of drug delivery devices. *Journal of Controlled Release*, 40(1), 77-87.
Xu, X., Robles-Martinez, P., Madla, C. M., Joubert, F., Goyanes, A., Basit, A. W. & Gaisford, S. (2020) Stereolithography (SLA) 3D printing of an antihypertensive polyprintlet: Case study of an unexpected photopolymer-drug reaction. *Additive Manufacturing*, 33, 101071.
Yan, J., Wang, Y., Zhang, X., Zhao, X., Ma, J., Pu, X., Wang, Y., Ran, F., Wang, Y., Leng, F. & Zhang, W. (2019) Snakegourd root/Astragalus polysaccharide hydrogel preparation and application in 3D printing. *International Journal of Biological Macromolecules*, 121, 309-316.
Yu, D.-G., Branford-White, C., Ma, Z.-H., Zhu, L.-M., Li, X.-Y. & Yang, X.-L. (2009) Novel drug delivery devices for providing linear release profiles fabricated by 3DP. *International Journal of Pharmaceutics*, 370(1), 160-166.
Zhou, L., Ramezani, H., Sun, M., Xie, M., Nie, J., Lv, S., Cai, J., Fu, J. & He, Y. (2020) 3D printing of high-strength chitosan hydrogel scaffolds without any organic solvents. *Biomaterials Science*, 8(18), 5020-5028.