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EXPERT REVIEW

An Overview of 3D Printing Technologies for Soft Materials and Potential Opportunities for Lipid-based Drug Delivery Systems

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ABSTRACT

Purpose Three-dimensional printing (3DP) is a rapidly growing additive manufacturing process and it is predicted that the technology will transform the production of goods across numerous fields. In the pharmaceutical sector, 3DP has been used to develop complex dosage forms of different sizes and structures, dose variations, dose combinations and release characteristics, not possible to produce using traditional manufacturing methods. However, the technology has mainly been focused on polymer-based systems and currently, limited information is available about the potential opportunities for the 3DP of soft materials such as lipids.

Methods This review paper emphasises the most commonly used 3DP technologies for soft materials such as inkjet printing, binder jetting, selective laser sintering (SLS), stereolithography (SLA), fused deposition modeling (FDM) and semi-solid extrusion, with the current status of these technologies for soft materials in biological, food and pharmaceutical applications.

Result The advantages of 3DP, particularly in the pharmaceutical field, are highlighted and an insight is provided about the current studies for lipid-based drug delivery systems evaluating the potential of 3DP to fabricate innovative products. Additionally, the challenges of the 3DP technologies associated with technical processing, regulatory and material issues of lipids are discussed in detail.

Conclusion The future utility of 3DP for printing soft materials, particularly for lipid-based drug delivery systems, offers great advantages and the technology will potentially support patient compliance and drug effectiveness via a personalised medicine approach.

KEY WORDS additive manufacturing · 3D printed drug products · lipid-based drug delivery systems · personalised medicines · printing pharmaceuticals · soft materials

INTRODUCTION

Three-dimensional printing (3DP), also known as additive layer manufacturing, is a rapid prototyping technique which enables the production of a physical object from a computer-aided digital file (1). The first commercial 3DP technique was introduced in the mid-1980s. In 1986, the 3DP apparatus, known as stereolithography (SLA), was developed and patented for printing objects and the 3DP file format termed. STL (which can be obtained by computer-aided design (CAD) software) was developed by Charles W. Hull (2). Subsequently, selective laser sintering (SLS) and fused deposition modeling (FDM) were developed by Carl Deckard in the mid-1980s and Sachs *et al.* in 1990, respectively (3,4). Over the past few decades, several 3DP technologies have evolved and been utilised in numerous fields either to advance the functionality of the existing system or as a new manufacturing process (5,6).

In 3DP, a 3D object is produced by combining or depositing layers of material on a substrate. A 3D pattern of the object is digitally designed using a CAD program and transformed into a .STL file. The .STL file is the most commonly

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used file format for 3D printing and contains the raw information about the surface geometry of a 3D object. The 3D printer software converts the .STL file into G-code file (or other file extensions depending on the printer) where the raw information of the .STL divides into a series of layers of specific thickness. The process enables a 3D printer to print an object in three-dimensions in a layer-by-layer manner (7). Firstly, for most of the 3DP technologies, the base of the object is printed by depositing the first layer of materials on the build plate in X-Y planes, either by moving the nozzle or less commonly the build plate. Then, the build platform moves downwards along with Z-axis and the subsequent layer is deposited on the first layer. The process follows the computer drafting instructions and repeated until a 3D object is produced (5,8,9). 3DP technologies can be used with a wide range of materials such as metals, powders, pastes, solids, liquids, ceramics, polymers, plastics, as well as living tissues and it is relatively easy to produce geometrically intricate shapes and structures as the method provides unprecedented flexibility over designs and shapes (10–12). These 3DP technologies acquired substantial interest across numerous fields over the few years and have been employed in various disciplines including the steel and metal industry (13,14), medical applications (15–18), dentistry (19), tissue engineering (20–22), food industry (23–25), and more recently, in the pharmaceutical field (5,10,26).

In the pharmaceutical arena, 3DP offers the advantages of high production rates, greater control over the accuracy and precision of the deposition of active ingredients (which enables to accurately deposit small amount of potent drugs), ability to generate complex shapes and structures, reduction in waste material (which can potentially reduce the production cost), applicability to broad types of materials including poorly water-soluble drugs, proteins, peptides as well as narrow therapeutic index drugs and the capability to fabricate the dosage form with varying compositions to tune certain characteristics (5,10,26–28). Henceforth, the technology has been employed to develop drug delivery devices (29–31), controlled release dosage forms (32), orally disintegrating dosage forms (33), solid dosage forms in various geometrical shapes (34,35) and formulations containing combinations of multiple active ingredients with well-defined drug release profiles (28,36). This versatility can potentially cause a paradigm shift in the manufacture of pharmaceuticals. It is anticipated that 3DP will provide a novel approach for the development and fabrication of pharmaceutical formulations with unique and customised characteristics which will potentially enable the manufacture of personalised medicines with individualised dose strengths (5,10,37–39). The use of 3DP in the pharmaceutical field crossed an important milestone in 2015 when the US Food and Drug Administration (FDA) approved the first 3D-printed tablet, Spritam® (levetiracetam), for epilepsy treatment (40).

Despite the great potential of the technique in the pharmaceutical field, one area that remains unexplored by 3DP is lipid-based drug delivery systems (LBDDS). Lipids, which are generally comprise of fatty acids and fatty alcohols are water-insoluble molecules with high solubility in non-polar organic solvents (i.e. chloroform), are either highly viscous liquid or soft semi-solid/solid material (with low melting temperature) at ambient temperature. In pharmaceutics, LBDDS are widely used as a promising strategy to enhance the drug absorption and bioavailability of many poorly water-soluble lipophilic drugs (41,42). Here, we aim to review the 3DP technologies that have been used with soft materials beyond polymers which could potentially be utilised for LBDDS. In the context of this paper, we considered as soft materials the products that are deformed or structurally altered by means of applying mechanical stress or thermal fluctuations at ambient temperature, and more generally soft matter. This is intended to be in contrast to ceramics, metals and other classically 'hard' materials. These types of soft materials such as lipids, gels, colloids, biological materials (i.e. collagen, gelatine), food materials (chocolate, liquid dough, jams and gels) are more common in biological applications, food industry and pharmaceutical applications. This review article starts with an introduction of 3DP technologies with a brief description of the process of the most commonly used 3DP technologies. The focus of the review is to expand the potential opportunities for LBDDS in pharmaceutical applications. Therefore, the following section summarise the recent advances and research studies regarding soft materials using 3DP technologies in biological applications and in the food industry and provides a greater insight into its pharmaceutical applications. Lastly, the final section outlines the most recently reported literature studies using 3DP technologies for LBDDS and highlights the potential future opportunities for lipid-based systems.

3D PRINTING TECHNOLOGIES

3DP is an emerging technology with an enormous potential to make a significant impact on manufacturing by offering simple and rapid means of product fabrication. A greater emphasis on the adapted 3DP technologies for soft materials is necessary to better understand the current applications and potential opportunities for soft materials such as LBDDS. Herein, we summarised the most commonly utilised and researched 3DP technologies such as material jetting (MJ), binder jetting (BJ), selective laser sintering (SLS), fused deposition modeling (FDM), VAT photopolymerisation (including stereolithography (SLA) and semi-solid extrusion (SSE) printing with a special focus on their application for soft materials (Fig. 1). The primary difference between the different 3DP technologies is based on the process of how individual layers

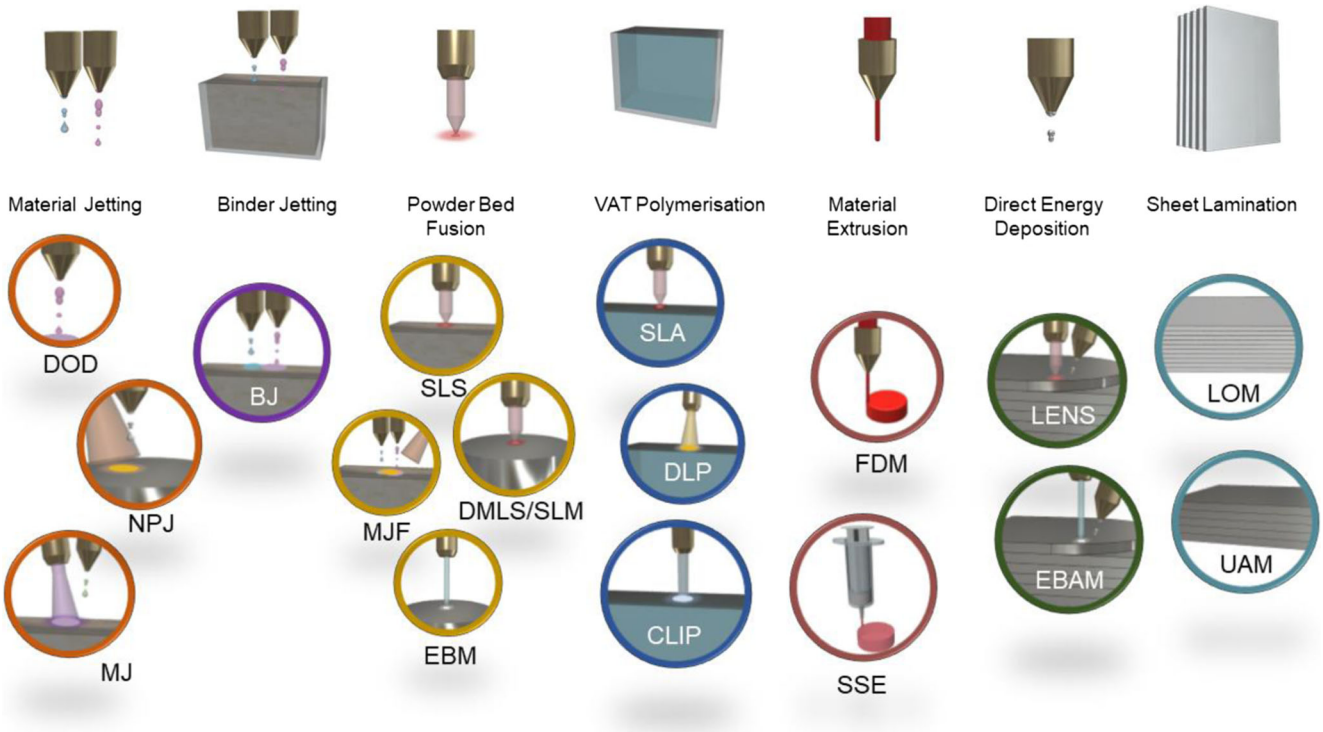

Fig. 1 Graphical representation of the different 3DP technologies. DOD: Drop-on-demand; MJ: Material jetting; NPJ: Nanoparticle jetting; BJ: Binder jetting; SLS: Selective laser sintering; DMLS/SLM: Direct metal laser sintering/selective laser melting; MJF: Material jet fusion; EBM: Electron beam melting; SLA: Stereolithography; DLP: Direct light processing; CDLP: Continuous digital light processing; FDM: Fused deposition modeling; SSE: Semi-solid extrusion; LENS: Laser engineering net shape; EBAM: Electron beam additive manufacturing; LOM: Laminated object manufacturing; UAM: Ultrasonic additive manufacturing. Figure adapted with permission from reference (26).

of material are formed and assembled to generate the finished product (43). The main benefits and drawbacks associated with each technology are summarised in Table I and the current published literature studies in the pharmaceutical field are summarised in Table II.

Material Jetting – Inkjet Printing

In the process of material jetting (MJ) a print head selectively deposits droplets of material on the build plate (Fig. 1). Drop-on-demand (DOD) inkjet printing is one of the types of MJ technologies, and the two most common actuation types of DOD print heads are thermal or piezoelectric. In the thermal print heads, a resistor produces heat which rapidly creates a vapour bubble in the material reservoir. Subsequently, a small volume of material is ejected from the nozzle in the form of the droplet. This process can potentially increase the local temperature of the material reservoir near the resistor, however for a short period of time and over a small contact area. This can potentially degrade thermo-labile active compounds. Thermal print heads are only applicable to high vapour pressure or volatile solvents thus these type of print heads are less common in pharmaceutical applications (37,44). On the other hand, piezoelectric print heads are embedded with piezoelectric elements (i.e. crystal or ceramic) which generate a mechanical movement upon the application of an electrical current. This deformation process produces the required pressure to push the liquid out of the nozzle in droplet form (59). The process can be conducted using less volatile liquid at room temperature, thus these type of print heads are more common in pharmaceutical applications (27,60).

In pharmaceutics, inkjet printing has been used with solutions (37,61–64), nanosuspensions (65) and melts (66,67) for 2D printing. For example, Buanz *et al.* demonstrated a robust technology based on a thermal inkjet print head and developed personalised-dose oral films of salbutamol sulfate. The liquid droplets of salbutamol sulphate solution were ejected onto the surface of the porous oral film made from potato starch (68). Subsequently, the technology expanded to print a combination product containing paclitaxel in a cyclodextrin inclusion complex and cidofovir encapsulated in polycaprolactone nanoparticle on bioadhesive film for the treatment of cervical cancer and studied the prolonged release behaviour (69). However, a limited number of studies have been conducted for soft materials and the literature examples are provided in the relevant application section in Tables III, IV and V.

Table I List of Benefits and Drawbacks or Limitations of Frequently Used 3DP Technologies

3DP technology	Benefits	Drawbacks or limitations	References
Material jetting – Inkjet printing	High spatial resolution can be attained by depositing very small volume	Requires drying step Long printing times	(44,45)
Binder jetting	Applicable to a broad range of materials Room temperature process Able to produce a highly porous matrix	Requires drying after printing Requires a specialised powder facility Sometimes the fast disintegrating tablets suffer from high friability and low hardness	(29,30,46–48)
Powder bed fusion – Selective laser sintering (SLS)	A single object can be produced with variable porosities and microstructures Porosity and microstructures are greatly controllable and reproducible	Limited sintering speed High energy may degrade materials Requires finishing after printing	(49–52)
VAT photopolymerisation - stereolithography (SLA)	High resolution and accuracy (superior to all other 3DP technologies) Able to produce submicron-sized objects and micron-sized layers	Requires curing after printing A limited number of resins are available Residual analysis would be necessary for pharmaceutical applications Long printing time if high resolution is selected	(53,54)
Material extrusion – Fused deposition modeling (FDM)	Widely available Low-cost units Provide high uniformity Does not requires post-printing solidification Mechanically resistant product with negligible friability	Requires production of filaments in advance High-temperature process may degrade active compounds Low-resolution control depending on the nozzle size	(35,55–58)
Material extrusion - Semi-solid extrusion	Possible to have high drug loading Able to produce multi-release profiles in a single tablet	Low-resolution control depending on the nozzle size Requires drying or solidification after printing Tablet properties might be compromised- low hardness and high friability Challenging to control material flow-rate through the nozzle	(28,32,36)

Binder Jetting 3D Printing

In the binder jetting (BJ) 3DP technology (also referred as powder bed inkjet printing), thin layers of powder are distributed layer-by-layer, either by a roller (powder layering system) or by a powder jetting reservoir (powder jetting system), and the layers are fused together via the drops of binder solution ejected from the printer heads (70–72). The first layer is printed on the build platform then the piston lowers to the thickness of the following layer, and subsequent layers are printed and fused together. The process is repeated several times until the pre-determined 3D object is produced. Nevertheless, the process sometimes requires additional drying steps to remove the residual moisture and to improve the physical and mechanical integrity of the product. BJ 3DP permits control over micro- and macrostructure of the objects enabling the production of complex and highly porous structures. However, sometimes it can be challenging to achieve high-resolution objects as the highly porous structure can lead to an increased friability and poor mechanical strength (71,73).

The important parameters of BJ printing are the diameter of the nozzle, droplet spacing, printing speed and the velocity and frequency of the droplets. The concentration of the binder can significantly affect the mechanical strength of the product. For instance, Patirupanusara *et al.* studied the effect of binder concentration (maltodextrin and polyvinyl alcohol (PVA)) on the formability and the properties of fabricated polymethyl methacrylate and reported that at least 10% w/w of the binder was required for a successful fabrication (74). Increasing binder concentration resulted in lower porosity and reduced strength (74). Additionally, the droplet size of the binder solution can also significantly affect the binder distribution and eventually the porosity and strength.

BJ is well established in tissue engineering and pharmaceutics (29,46,48,71,75–77). A pioneering example of this is Spiritam® (levetiracetam), the first 3D printed medicine approved by the US FDA, where the Zipdose® technology was employed to develop a highly porous tablet (40). The high porosity resulted in a rapid dispersion of the tablet upon contact with liquids, even at high dose (40). This technology has been less explored for soft materials and has limited applications into the food industry. The relevant literature examples for soft materials are presented in Table IV.

Powder Bed Fusion - Selective Laser Sintering 3D Printing

Selective laser sintering (SLS) is the most common type of powder bed fusion. It is similar to BJ 3DP except that it uses laser radiation to sinter (superficial melting) or fuse the powder materials and form a 3D object, instead of a liquid binder to glue the layers (50). In SLS printing, the first layer of the

Table II Summary of Literature Examples of 3DP Technologies Utilized in the Pharmaceutical Field

3DP technique	Type of dosage form	Ingredients	Summary	References
MJ - Inkjet printing	Microparticles	Paclitaxel and PLGA	Fabricated polymer-based microparticles in various geometrical shapes	(110)
	Coated stent	Fenofibrate and Zotarolimus	Inkjet printing demonstrated high coating efficiency for stents with the potential to deposit low dose with high precision	(111)
	Solid dispersion	Felodipine and PVP	Developed solid dispersion felodipine formulation capable of controlling the drug release	(64)
	Orthopedic implant	Rifampicin, PLGA and BCP	Demonstrated the feasibility of a piezoelectric print head to deposit microparticles of rifampicin onto the orthopedic implant	(112)
BJ	Tablets	Chlorpheniramine maleate, fluorescein disodium salt, EuE, EuRL and PVP	Developed delayed-release tablets with a varying polymer content	(71)
	Microporous bioceramic implants	Vancomycin, ofloxacin, tetracycline, hydroxyapatite, MDCPD and DCPA	Fabricated microporous bioceramic implants comprising antibiotics for the treatment of bone infections	(113)
	Tablets	Acetaminophen, HPMC, EuRS 100, SA, EC and SLS	Fabricated tablets with the complex inner structure to achieve zero-order drug release characteristics	(46)
	Orodispersible dosage forms	Levetiracetam, MCC, glycerine, Tween 80, MA, povidone, sucralose and colloidal silicon dioxide	Developed a rapidly disintegrating 3D printed dosage form containing a high drug dose in a porous matrix	(75)
	Extended-release tablet	Acetaminophen, EC and HPMC	Developed multi-layer controlled release doughnut-shaped drug-delivery device	(47)
	Implants	Levofloxacin, rifampicin and PLA	Fabricated the drug-loaded implants with complicated structure to control the drug release. This may potentially provide a new approach for the prophylaxis and therapy for bone diseases	(77)
	Implant containing multiple drugs	Rifampicin, isoniazid and PDLLA	Developed dose form containing multi-active drugs to achieve the programmed release of drugs for the treatment of tuberculosis	(30)
	FDT	Acetaminophen, methylene blue, PVP, MA and colloidal silica	Designed and fabricated FDTs with loose powders in their central regions	(76)
SLS	IR & MR tablets	Acetaminophen, KolR, EuL100-55 and Candurin gold sheen (for sintering)	Demonstrated the capability of SLS to formulate pharmaceutical oral solid dosage forms	(49)
	Shell core structure	PA and MB	Fabricated polymeric drug delivery devices utilizing SLS	(114)
	Cubic porous structure	Nylon powder and MB	Developed porous cylindrical disc of polymeric matrices and studied the influence of temperature on porosity and on dense wall	(52)
	Tablets with different drug loading and shapes	Acetaminophen, EuL100-55, HPMC and Candurin gold sheen (for sintering)	PAT used to quantify the drug content in the printed tablets	(115)
	ODT	Acetaminophen, HPMC E5, KoVA 64 and Candurin gold sheen (for sintering)	Demonstrated the SLS feasibility for pharmaceutical applications and developed ODT with accelerated drug release	(33)
	Lattice structures	Acetaminophen, PEO, EuL100-55, EuRL and EC	Modulated the drug release profiles by developing the gyroid lattice structures	(116)
SLA	Anti-acne patch	Salicylic acid, PEG and PEGDA	Developed salicylic acid patches for the treatment of acne	(92)
	Tablets	4-aminosalicylic acid, acetaminophen, PEGDA, diphenyl(2,4,6-trimethyl benzoyl)phosphine oxide and PEG 300	Fabricated drug-loaded tablets to achieve tailor drug release profiles	(93)
FDM	Capsular device for oral pulsative release	HPC and PEG	Produced HPC filaments using HME and fabricated hollow structures using FDM	(117)
	Tablets	HPC	Patient acceptability of 3D printed formulations depending on size, shape and colour	(118)
	Tablets	Acetaminophen and PVA	Fabricated drug-loaded tablets into geometrical shapes	(34)

Table II (continued)

3DP technique	Type of dosage form	Ingredients	Summary	References
	Tablets loaded with nanocapsules	Deflazacort nanocapsules, PCL and EuRL 100	Developed multi-functional solid dosage form containing drug-loaded nanocapsules, by coupling FDM and nanotechnology, for customized drug delivery.	(119)
	Tablets	Theophylline, EuRL, EuRS, EuE and HPC	Developed flexible-dose tablets with immediate and/or extended release profiles	(101)
	Tablets	Prednisolone and PVA	Fabricated extended-release tablet and controlled its dose	(120)
	Tablets	5-aminosalicylic acid, captopril, theophylline, prednisolone, EuEPO, TCP and processed lactose	Developed IR tablets using non-melting filler possessing the excellent mechanical strength	(121)
	An intrauterine system and subcutaneous rods	Indomethacin and EVA copolymers	Demonstrated the feasibility of EVA polymer grades for FDM and fabricated T-shaped intrauterine systems and subcutaneous rods using most appropriate grades of EVA	(122)
	Tablets printed in capsule shapes	Budesonide and PVA	Developed capsule-shaped tablets using FDM and coated using the fluid bed, and compared the release kinetics with commercially available budesonide products	(123)
	Tablets	Ramipril, KoVA 64 and Ko12 PF	Low-temperature printing for thermo-labile Ramipril	(55)

Abbreviations: MJ (material jetting), BJ (binder jetting), SLS (selective laser sintering), SLA (stereolithography), FDM (fused deposition modeling) PLGA (poly lactic-co-glycolic acid)), PVP (polyvinylpyrrolidone), PAT (process analytical technology), BCP (biphasic calcium phosphate), EuE (Eudragit® E), EuRL (Eudragit® RL), MDCPD (microporous dicalcium phosphate dehydrate), DCPA (dicalcium phosphate anhydrous), hydroxypropyl methylcellulose (HPMC), EuRS-100 (Eudragit® RS 100), SA (stearic acid), EC (ethyl cellulose), SLS (sodium lauryl sulfate), MCC (microcrystalline cellulose), PLA (polylactic acid), PDLLA (poly-DL-lactic acid), MA (mannitol), FDT (fast disintegrating tablet), IR (immediate release), MR (modified release), KoIR (Kollicoat® IR), EuL 100-55 (Eudragit® L100-55), PA (polyamide), MB (methylene blue), KoVA 64 (Kollidon® VA 64), ODT (orally disintegrating tablet), PEO (polyethylene oxide), PEG (polyethylene glycol), PEGDA (polyethylene glycol diacrylate), HPC (hydroxypropyl cellulose), PCL (polycaprolactone), EuEPO (Eudragit® EPO), TCP (tribasic calcium phosphate), EVA (ethylene vinyl acetate), Ko12 PF (Kollidon® 12PF), HME (hot melt extrusion)

Table III Literature Examples of 3D Bioprinting Performed Using Soft Materials for Biological Applications

3DP technique	Biomaterials	Summary	References
MJ - Inkjet	PEG, collagen and PDL mixture	Demonstrated the feasibility of inkjet printing to create neuron adhesive patterns	(134)
	Gelatine and MTG	Developed printable gelatine with encapsulated cell and use as bioink	(135)
	Fibrin gels	Fabricated 3D scaffolds structures	(136)
	Decellularised adipose tissue bioink	Prepared a precisely defined dome-shaped adipose tissue structures using decellularised adipose tissue matrix bioink that has viability over 2 weeks	(137)
SLS	PCL and HC	Developed novel protocol to produce micro-sphere based bone scaffolds with multi-scaled porosity and good biocompatibility	(138)
	PCL and gelatine or collagen	Fabricated scaffolds with gelatine or collagen and studied the mechanical and biological properties	(139)
	PCL and HC	Fabricated tissue engineering scaffolds	(140)
SLA	Photopolymerisable PEG-based hydrogel scaffolds	Developed hydrogel scaffolds within the open channels of scaffolds 3D structures	(141)
	Photo-polymerisable PEGDA	Fabricated the complex inner structures of cell encapsulating hydrogels	(142)
	PCL oligomers, biodegradable resins, Irgacure 369 photoinitiator and dye	Developed designed porous 3D scaffolds	(143)
	PDLLA-PEG-PDLLA-based macromer, visible light photo-initiator, and dye	Prepared porous biodegradable hydrogel structures with well-defined internal structures and good mechanical properties	(144)

Abbreviations: MJ (material jetting), SLS (selective laser sintering), SLA (stereolithography), PEG (polyethylene glycol), PDL (poly-D-lysine), MTG (microbial transglutaminase), PCL (polycaprolactone), HC (hydroxyapatite composite), PEGDA (polyethylene glycol diacrylate), PDLLA (poly-DL-lactic acid))

Table IV Summary of Literature Studies Carried out for Soft Materials in the Food Industry Using 3DP Technologies

3DP technique	Ingredients	Summary	References
MJ - Inkjet	Chocolate, solid desserts, liquid dough, jams, gels, cheese, sugar icing and meat paste	Developed FoodJet printing technology for the disposition of liquid food layers on top of solid food substrate	(150)
BJ	Chocolate	Printed chocolate on basis of the chemical reaction providing adhesive forces between powder and binder	(151,152)
	Sugars and flavour binders	Fabricated the sculptural cakes for a wedding or other special occasions	(153)
SLS	Sugar and Nesquik	Developed a multi-layer food matrix. Each layer contained different food materials	(154,155)
SSE	Cake frosting and processed cheese	Printed cake frosting and processed cheese at room temperature	(156)
	Turkey, scallop and celery	Demonstrated the feasibility of semi-solid extrusion process for food printing with complex internal structures	(23)
	Pasta recipe (Durum wheat semolina with water and without additives)	Prepared 3D printed pasta	(157)
	Chocolate and confection	Printed chocolates at a working temperature between 28°C and 40°C	(158)
	Xanthan and gelatine	Printed food materials containing protein, starch etc. in different texture and flavours	(159)

Abbreviations: MJ (material jetting), BJ (binder jetting), SLS (selective laser sintering), SSE (semi-solid extrusion)

powder is uniformly distributed via a roller on the build plate. Thereafter, the powder is heated up to the softening point (just below the melting point) by a source of laser beam to fuse the powder particles together and form a layer following the cross-section profiles from the controlling computer software. The subsequent layers follow the similar process of adding, levelling and sintering at the desired locations until a 3D object is produced. The unused materials provide a mechanical support during the printing and are removed via post-processing.

SLS permits great control over internal microstructure and porosity in forming a porous single object. However, the technology has limited sintering speed and sometimes the printed objects show shrinkages or deformations due to thermal heating from laser irradiation (52). SLS is applicable to a broad range of materials such as polymers, polyesters, ceramic powders, metals, glass and presumably, it could be extended to high melting point lipids (78). SLS is well established in tissue engineering and other non-medical manufacturing

Table V Summary of Literature Examples Carried Out Using Soft Materials in Pharmaceutical Applications Using 3DP Technologies

3DP technique	Ingredients	Summary	References
MJ - Inkjet	Fenofibrate with beeswax	Fabricated honeycomb architectures in intricate and flexible shapes for controlled drug-loading and drug-release characteristics	(45)
	Naproxen, PEG 3350 and PIF38	Printed melt-based dosage forms onto edible HPMC polymeric films	(67)
SLA	Ibuprofen, PEG, and riboflavin	Fabricated drug-loaded hydrogels from cross-linkable resins	(53)
SSE	Captopril, nifedipine and glipizide with HPMC	Developed multi-active ingredient tablets with well-defined SR profiles for nifedipine and glipizide and an osmotic pump for captopril	(28)
	Hydrochlorothiazide, aspirin, atenolol, pravastatin sodium, ramipril, cellulose acetate, D-mannitol and PEG 6000	Developed multi-active ingredient tablets with the functionally of more than one release profile (IR sections of aspirin and hydrochlorothiazide and SR compartments of pravastatin, atenolol and ramipril)	(36)
	Guaifenesin, HPMC, PAA, and MCC	Developed bilayer tablet with SR and IR profiles, and compared the release profiles with commercial tablet	(32)
	Dexamethasone-21-phosphate disodium, PLGA and PVA	Encapsulated active-component between printed polymer layers to develop CR drug delivery systems for the treatment of chronic inflammatory disorders	(106)
	Metformin hydrochloride, glyburide, acarbose, PIF 127 and red dye	Fabricated the polypill for type II diabetes and studied the relationship between programmed profiles and resultant temporal profile	(166)
	Paracetamol, PVP K25, sodium phosphate monobasic and dibasic and NaCCS	Developed IR paracetamol tablets with high drug loading, suitable for personalized medicine	(109)
	Dipyridamole, HPMC K4M, HPMC E15 and MCC PH 101	Fabricated gastro-floating tablets to prolong the gastric residence time to improve the drug release	(167)

Abbreviations: MJ (material jetting), SLA (stereolithography), SSE (semi-solid extrusion) PEG (polyethylene glycol), HPMC (hydroxy propyl methyl cellulose), PIF38 (Pluronic® F38), PEGDA (polyethylene glycol diacrylate), SR (sustained release), IR (immediate release), PAA (polyacrylic acid), MCC (microcrystalline cellulose), PLGA (poly lactic-co-glycolic acid), PVA (polyvinyl alcohol), CR (controlled release), PIF 127 (Pluronic® F 127), NaCCS (croscarmellose sodium)

industries (79–82). The high energy laser used in some 3D printers may potentially degrade the active compounds thus, the technology had limited applications in the pharmaceutical arena. However, more recently, the technology has been employed to prepare an immediate release and modified release tablets of acetaminophen, and the feasibility of the method for the pharmaceutical field has been demonstrated (49). In case of soft materials, the technology has been utilised in the bioprinting for tissue engineering and in the food industry. Hence, the literature examples of reported studies for soft materials are provided at a later stage in the relevant sections (see Tables III and IV).

VAT Photopolymerisation

In VAT photopolymerisation, a vat with liquid photopolymer resin is used to construct the layers. A 3D object is produced by curing a photosensitive resin in a process called 'photopolymerisation'. VAT photopolymerisation includes different types of 3DP process such as stereolithography (SLA), digital light projection (DLP), continuous liquid interface production(CLIP) or two-photon photopolymerisation (83). Each technique produces the object based on similar chemical reactions but they slightly differ in the initiation process and source of light (84,85).

In this technique, the print head focusses a laser beam or light into a vat of resin to a specific depth. The laser causes localized photopolymerisation of the resin and forms a matrix of cross-linked polymers. The process hardens the materials and forms a solid layer. The build platform lowers into a vat of resin to the equivalent depth of the polymerised layer thickness where the UV light cures the resin. The second polymerised layer is cured as the penetration of the UV lights depth exceeds the thickness of the layer. The build platform continues to lower and the subsequent layers are formed on top of the previous layers and a 3D object is generated in layer-by-layer fashion (84). The formed object is further processed for the curing of the final product, improving the mechanical strength and polish or removal of unattached material (84).

The important parameters of the SLA process are scanning speed, laser power, exposure time, the selection of resin and the amount of polymer and photoinitiator (86). SLA offers a great efficiency, versatility, high level of accuracy and resolution. An object can be produced at a resolution down to 0.2 μm, making SLA a superior technique compared to other 3DP technologies (84). SLA has been extensively applied in tissue engineering (87,88), tissue scaffolding (89,90), into the fabrication of implantable devices (91) and more recently in the pharmaceutical field (92,93). For pharmaceutical applications, the active compounds are incorporated with resin and they get trapped into the matrix during cross-linking process. The localised heating is minimal during printing thus SLA is suitable for thermo-labile active compounds. Wang *et al.* developed modified release tablets of 4-aminosalicylic acid (4-ASA) and paracetamol (acetaminophen) using polyethylene glycol diacrylate (PEGDA) as a monomer avoiding drug degradation that was observed for 4-ASA using FDM 3D printing (93).

The technology has limited applications in pharmaceutics due to the limited availability and compatibility of photocrosslinkable polymers since only the FDA approved resin for human use can be used for pharmaceutical applications. In general, low-molecular-weight polyacrylate macromers are the most suitable and broadly used materials for photopolymerisation. However, the major drawback of them is the potential residual monomers that can remain in the object after the printing and the potential hazards associated with them, which can lead to regulatory challenges and stability issues (94). Typically, VAT photopolymerisation printing processes are time-consuming. However, the recent advancement of the methods led to the evolution of continuous liquid interface production technique (CLIP), the fastest 3DP technology to date, which can be applied for different materials in order to produce diverse type of objects with high pace and superior resolution (95). The use of SLA for soft materials printing is limited and the reported literature examples are summarised in Tables III and V.

Material Extrusion - Fused Deposition Modeling 3D Printing

Fused deposition modeling (FDM) is the most broadly used low-cost 3DP technique across many fields. In FDM, thermoplastic polymers, in form of a filament, are extruded through the printer head at a specific temperature at definite directions and the semi-molten material is deposited on the build plate to form the layers (96–98). The FDM process can be divided into three parts - (i) the extrusion of molten material, (ii) the deposition of material layers and (iii) the solidification of the layers (generally the cooling of the printed layers). Briefly, the thermoplastic polymeric filaments (printing materials) are fed through the nozzle tip of the printer head where the filaments are melted just above the softening point via heating elements. These semi-molten materials are extruded through the nozzle tip of the printer head on the build plate and form a thin layer of material. Usually, the outer layer is printed first and then the internal structures printed layer-by-layer with the degree of internal space filled with an extruded polymer known as the 'infill'.

FDM has been broadly used for commercially available pre-processed filaments (for easy and rapid processing) with different types of polymeric materials such as polylactic acid (PLA), polyvinyl alcohol (PVA), acrylonitrile butadiene styrene (ABS), thermoplastic polyurethane (TPU) and high-impact polystyrene (HIPS) or aliphatic polyamides (nylon).

FDM enables the production of complex objects with high accuracy and with different substances via using multi-nozzle printing systems (35).

The versatile user control over the fabrication of the object by controlling printing parameters enables FDM to produce hollow and porous objects with good mechanical strength (1,86). For instance, the technique has been employed to fabricate the pharmaceutical tablets with varying infill density from 0 -100% in order to investigate the impact of infill density on the tablet characteristics (35). The tablets with 0% infill density formed a complete hollow structure (with high porosity) whereas 100% infill density tablets created a totally solid object (high mechanical strength), indicating the pronounced effect of infill density on porosity and mechanical strength on the final product (35). The materials should possess appropriate heat transfer characteristics and rheological properties as these factors can significantly influence the performance of the printing process in addition to other processing variables such as nozzle diameter, pressure drop, feed rate and thermal properties of the feed (11).

In pharmaceutics, the drugs were initially loaded via incubation of filaments in drug-loaded organic solutions (35). Usually, the incubation process is expensive and time-consuming as the drug loading is achieved via passive diffusion thus, the process requires the use of highly concentrated drug solution for a long time to incorporate a small mass of drug into the filaments. Additionally, the drug-loading via incubation is not efficient and the process may be limited to low-dose drugs. Thus, hot melt extrusion (HME) has been used as an alternative method to obtain the drug-loaded filaments (34). In HME, the materials (i.e. polymer, drug and additives such as plasticizer) are homogeneously mixed and extruded at elevated temperature to produce the polymeric filaments (31,99). This approach enhanced the potential of FDM to expand the range of suitable polymers for FDM with the capability to achieve higher drug loading and to design multi-active drug delivery systems (100). For example, Goyanes *et al.* produced paracetamol-loaded polyvinyl alcohol (PVA) filaments with the use of a single-screw filament extruder and printed solid dosage forms in five unique geometrical shapes: cube, pyramid, cylinder, sphere and donut-like. The study reported dependency of the kinetics of the drug release profiles on the surface area to volume ratio of the printed dosage forms (34). In another study, Pietrzak *et al.* developed instantaneous and prolonged release theophylline caplets primarily based on cellulose or methacrylic polymeric filaments with a yield of nearly 100% drug loading, and demonstrated the use of plasticizer in order to modulate the melting temperatures to restrict the thermal degradation of active ingredient and polymer (101). Subsequently, the use of FDM expanded for the development of numerous types of pharmaceutical dosage forms and the published literature studies are summarised in Table II.

The high processing temperature during extrusion can degrade active pharmaceutical compounds and/or excipients. However, the issue can be avoided by using novel polymers that print at lower temperatures (55,56) or including the drug inside the formulation without incorporation into the filament (102–104). A way to avoid the incorporation of the drug in the filament is to print the shell of the tablet using FDM and to include the drug in the middle in liquid, powder or semi-solid form (Figure 2). The concept of printing formulations with drug-free filaments using FDM printing with pharmaceutical grade polymers have been already tested *in vivo* incorporating radiotracers and antituberculosis drug combinations (103,104). As shown in Figure 2, the process can be completely automatic and it would be feasible to modify the kinetics of drug release of the incorporated drugs in the core by selecting the appropriate polymers for the shell of the formulations.

Material Extrusion - Semi-Solid Extrusion 3D Printing

Another major type of 3DP technique that could be highly relevant to soft materials is extrusion-based semi-solid extrusion (SSE) printing. In this process, the starting materials (usually semi-solid mixture) are extruded via a syringe-based tool-head nozzle to create the 3D object (105). The starting materials, more commonly gels or pastes, are prepared by means of mixing the ideal ratio of substances with solvents in order to attain an optimum viscosity appropriate for printing (32,106). The chemical, physical and mechanical properties, such as rheological properties, viscosity and miscibility of materials, can significantly impact on the processing (i.e. excess material flow at low viscosity or insufficient material flow at high viscosity). The printing parameters such as material flow rate, processing temperature and printing speed have to be optimal and carefully controlled to achieve a decent finished product with good mechanical properties. Generally, the printed product requires post-processing steps of drying or cooling.

The main advantage of SSE compared to FDM is that the process does not require high temperature thus it is suitable for thermo-labile active compounds. However, the physical state of the starting material (gels or paste) may affect the drying process that can potentially lead to the shrinkage or deformation of the product or the collapse of the object in the case of the insufficient hardness. The resolution of this method is sometimes lower than FDM as the process uses larger size orifices with a dimension of 0.5 – 0.8 mm, which can potentially affect the reproducibility. The use of soft materials is more common in the food industry (24) and the biological applications (bioprinting) thus the technique has been extensively implemented for tissue engineering (107),

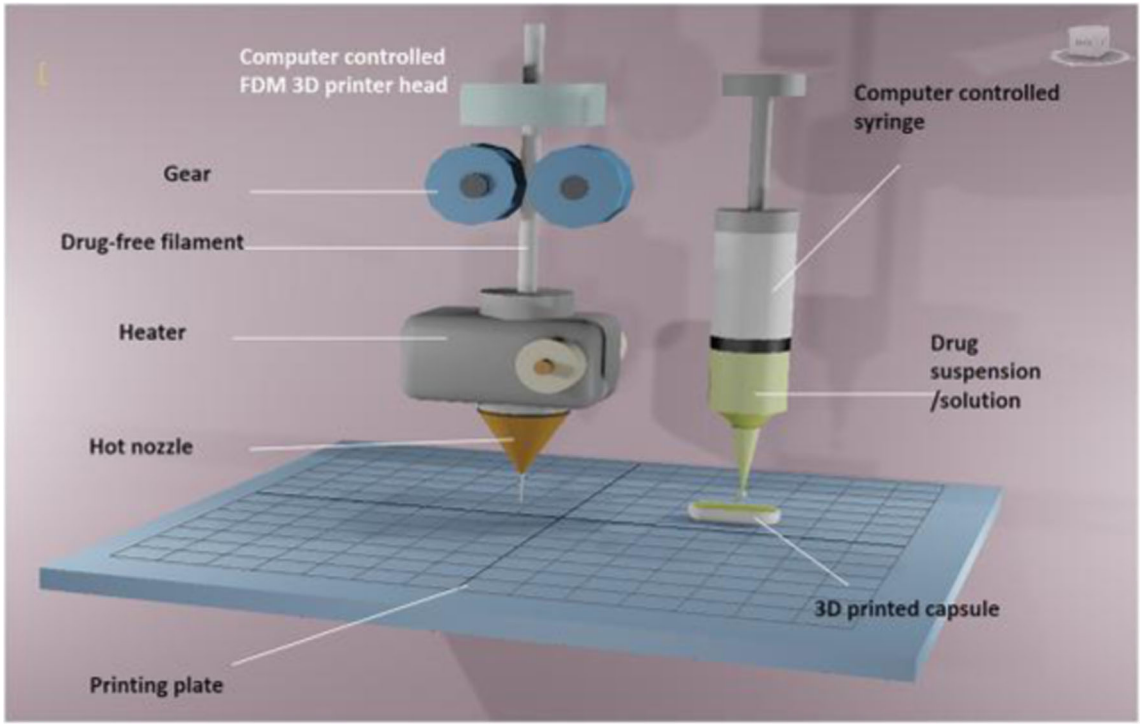

Fig. 2 Schematic illustration of the manufacture of a 3D printed liquid capsule. A dual head 3D printer was modified by replacing the right-hand nozzle with a syringe dispenser. The FDM nozzle head was loaded with HME processed drug-free filament whilst drug solution or suspension is incorporated inside the formulations using a syringe dispenser. Figure adapted with permission from reference (102).

tissue scaffolding (108). The current application of SSE printing in the pharmaceutical field is limited. However, interesting formulations incorporating high drug loading or multiple drugs have been manufactured for research purposes (28,109) and the published literature studies based on this technology for soft materials are described in the relevant sections (see Tables III, IV and V).

CURRENT 3DP APPLICATIONS FOR SOFT MATERIALS

Materials such as liquids, lubricants, foams, adhesives, gels, paints, food additives (such as chocolate, cheese and jams), liquid crystals, lipids, colloids and biological materials (such as collagen and gelatine) are soft materials that show a large degree of internal freedom with weak internal interactions between molecules. These types of materials are more commonly used in the biological applications, food industry and pharmaceutical field. Thus, this section briefly outlines the most recently used 3DP technologies for soft materials in the biological application and food industry with greater emphasis into pharmaceutical applications. As mentioned earlier, the focus of the manuscript is on drug delivery thus the biological and food industry section are described superficially. However, the interested reader can retrieve detailed information by referring references (24, 25, 124).

Current 3D Bioprinting Applications for Soft Materials

3DP is a broadly used tool in tissue engineering with the aim to develop new tissues and organs in order to regenerate, restore or replace the functionally of defective or injured organs (125,126). To achieve this aim, the biological scaffolds are produced from natural or synthetic polymers in tissue engineering. However, these biological scaffolds must have a highly porous 3D structure in order to achieve the biological functionality and to use as a tissue or organ (127). 3D bioprinting has the capability to meet this unique requirement by producing highly porous 3D structures with the biological functions such as cell affinity, migration, attachment and differentiation (108,128). Thus, 3D bioprinting has been employed to produce 3D porous structures with controlled cell pattern in order to retain the cell functionality and viability. Briefly, in 3D bioprinting, tissue-like structures are generated by means of the layer-by-layer deposition of biomaterials recognised as bioinks and a 3D highly porous structure containing living tissue and biomaterials are generated in the desired shape. The bioinks (a mixture of cells, matrix and nutrients) are printed from the printer cartridge and placed in an incubator where this cell-based matrix matures into a tissue. The technique is highly dependent on the precise deposition of biomaterial layers and living tissues.

3D bioprinting offers the advantages of rapid-fabrication, high-precision and customised manufacturing of biocompatible

scaffolds (129,130). The recent advancement in the technology enabled the accurate control of the distribution of the pore size, pore volume and interconnectivity of the pores to form a biocompatible scaffold (108,128). Among other 3DP technologies, three most commonly researched 3D bioprinting techniques for soft materials are MJ-inkjet printing (131), SLS (132) and SLA (133). Some literature examples of 3D bioprinting applications using soft materials are summerised in Table III.

Despite the advantages, the technology has only been implemented into some laboratories and wider adoption of the technology can potentially develop new models. 3D bioprinting still has many challenges to overcome, such as the selection of appropriate biomaterials, development of bacteria free-environment during printing, blood supply and moulding and prolonged survival of the printed structures. The most important resources of bioprinting are bioinks and printable biomaterials. Currently, the range of biocompatible materials is very small and the catalogue of the bioinks is restrained to collagen, fibrin, thermoplastics, gelatine, fibrin, ceramics and mild curable composites. Therefore, there is a need to develop new printable biomaterials with the properties of biocompatibility, easy manufacturing process and sufficient mechanical strengths to form cell supports and to secure 3D structures (20). The application of bioprinting is not limited to produce scaffold structures but the technology also has been extended to medical applications to produce bone implants that can accurately match with the body parts (145). It is forecasted that in the future, it may be possible to manufacture a whole human organ and transplant it into the human body.

Current 3DP Applications for Soft Materials in the Food Industry

In recent times, awareness about food ingredient metabolism and consciousness about healthy food has prompted public interest on the concept of personalised nutrition food which is customised to individual requirements (25,124). The current food production process is unable to meet this unique requirement as the production of customised food can be complex, slow, and expensive and require handmade skills.

In food 3D printing, premixed food ingredients are deposited into layers where the food products can be designed and fabricated via controlling the amount of printing material and nutrition content to meet the individual needs. 3DP has the capability provide a platform to meet the unique requirement of customised food production while offering creativity, sustainability and customisation (24). 3DP permits the control over design and fabrication of food with customised colour, shape, flavour, texture, characteristics and optimisation of nutrition content which can potentially provide a new kind of food with high dietary values (25,124). 3DP can potentially serve as a new way of cooking that can bring the food production process to the digital stage.

In the food industry, 3DP has been utilised for three primary reasons – (i) to design the layout of food with unique textures (ii) to enhance the appearance of the food by designing the food in complex structures by way of controlling the construction of structures at micro- and macro levels and (iii) to develop new nutrient-dense food materials (25). Thus far, the technologies have been researched to meet the unique requirement of distinctive consumer categories such as children, elderly, athletes and expectant mother via varying the food component levels such as protein and fat (24,146). For example, the 3D printed smooth foods have been prepared for elderly populations who suffer from difficulty in chewing and swallowing (147,148). More recently, the 3D printing company (BeexHex, USA) developed a 3D printer for the NASA (National Aeronautics and Space Administration) astronauts to produce food while they are on missions (149). This would enable astronauts to avoid the drudgery of pre-processed food and permit them to eat high nutritional value interesting food every day. Similarly, 3D food printing was also proposed to be used in isolated areas or during natural disasters, since the technology can be used to meet specific food requirements.

Different 3DP technologies have been applied to process the additives, flavours and vitamins to advance food properties with tailor-made chemical, structural characteristics and extended shelf-life which can satisfy the unique need of individuals. It is anticipated that 3DP will change the manufacturing process of certain types of foods such as chocolates, cookies, cakes and ice creams. To date, inkjet, BJ, SLS and SSE have been applied for food-related applications and several reported literature studies for printing food using soft materials are provided in Table IV.

The printing of food is a far more complex and challenging process than it may appear. Numerous parameters such as mechanical force, the layout of digital recipes and processing pressures need to be optimised. The process of optimisation is challenging and the process requires the evaluation of the customised needs to meet the individual requirements. For instance, in semi-solid extrusion, the diameter and size of the nozzle can significantly affect the deposition rate and resolution. Sometimes, dense oil material can block the printer nozzle which may lead to the short fall of printing material in forming the desired shape. Other important parameters of the process include the line distance, the size and diameter of the nozzle, quantity of layers, the thickness of layers and shapes, laser power, printing temperature and cooling temperature (25). And more importantly, the properties of the materials need to satisfy the requirements for printability.

In the clinical practice, it is a common approach to administer medicines with food in order to facilitate swallowing and/or to enhance the absorption and oral bioavailability of the poorly water-soluble drugs (160). Considering the progression of 3DP technology, it is easily envisaged that 3D printing of

food may be utilized as a novel tool to delivery drugs by incorporating active compounds during the food printing process. It is anticipated that this approach will open new avenues in near future for bespoke food-based pharmaceutical drug delivery systems.

Current 3DP Pharmaceutical Applications for Soft Materials

In pharmaceutics, the dosage forms are prepared to administer the active pharmaceutical compounds with the aim to deliver them to the biological sites of action in order to achieve a therapeutic effect. The inter-individual differences in patients (e.g. race, gender, age, weight, disease condition and pharmacokinetic characteristics) lead to variability in the therapeutic effects. Henceforth, in recent times, the approach of personalised medicines, unique for the patient, is in considerable demand and is rapidly growing with an increased emphasis on the patient-specific dosage form. In personalised medicines, the drug dose and dose combinations are tailored to meet the patient's individual need. Despite the fact that traditional manufacturing techniques are cost-efficient and allow large-scale production, they can be labour intensive, and time-consuming. Conventional manufacturing do not provide the appropriate flexibility particularly in the dose variations or dose combinations required for personalised medicine and they are not suitable to produce complex geometries to meet the therapeutic requirement of the individual, hence, limiting their use in the manufacture of 'personalised medications' (5,32,64).

3DP shows the potential to meet these needs, and revolutionise the manufacturing of medicines by providing simple and rapid means of a fabrication customised dosage form (10). The technology offers the benefits of the production of small batches (even only one tablet) with tailored dosages, sizes, shapes and release characteristics. The process also offers novel approaches and tactics for the development of novel drug delivery units and thereby it is turning into a very popular technique in the pharmaceutical field (10–12,26,29,30,37). Over the past few years, 3DP received an increasing interest within the pharmaceutical industry and the technology has been employed to develop various kinds of unique pharmaceutical dosage forms such as tablets, implants, microchips, circular discs and hydrogels, with special characteristics (i.e. complicated inner structures, complex geometries, surface texture controlled release profiles) (28,34,48,53,71,100,161–165). This is changing the perception of how medicines will be designed, manufactured and used. The most commonly used 3DP technologies in the pharmaceutical field are inkjet, BJ, SLS, SLA, FDM and SSE printing. The comprehensive review about the literature examples of the developed different type of formulations using 3DP technologies are summarised in Table II. Since most of the evaluated formulations are polymer-based systems, our purpose here is to provide an insight of 3DP technologies for pharmaceutical applications for soft materials, thus, the reported literature examples associated with soft materials are provided in Table V.

3DP offers many benefits including streamlining the production process and the possibility to create personalised medicines. The major therapeutic and technical benefits of 3DP in the pharmaceutical field are related to personalised medicines (10,12,26). The ability to produce small batches of individualised dosage forms directly at the point of care where not only the dose is regarded in the design of the customised medicines but also the patient's individual characteristics, needs and preferences (36,72). This is not attainable with the use of conventional manufacturing methods due to mass manufacturing of dosage forms designed for desirable effect on the majority of the population. The advantages of 3DP include:

- Dose flexibility: Flexibility in the formation of the dosage form with varying dose where the dose can be controlled effortlessly and rapidly with the aid of adjusting dimensions or infill density of the dosage forms (100).
- Reduce labour and capital investment: A platform that can potentially partially replace conventional manufacturing methods like tableting and reducing labour and capital investment in processes like compounding pharmacy.
- Unique characteristics: Capability to produce a large array of dosage forms with unique characteristics (shape, colour, size, flavour) by controlling the accurate deposition of materials (118).
- Pediatric and geriatric formulations: Ability to produce more acceptable dosage forms containing specific doses for pediatric or geriatric populations which can considerably enhance therapy efficacy and clinical adherence while reducing the hazard of unfavourable effects.
- Dosage forms with complex dosage regimes: Production of complex dosage forms incorporating different sections or drug release regimes. It permits to create dosage forms with the exact amount of drugs with easy administration process and low risk of dose deviation, providing an effective treatment (165,168,169).
- Drug combinations: Production of a single dosage form containing multi-active ingredients by accurately controlling the spatial distribution of materials resulting in the improvement of patient adherence (28,36,165).

LIPIDS AND POTENTIAL OPPORTUNITIES FOR LIPID-BASED DRUG DELIVERY SYSTEMS

Lipids are based on fatty acids and fatty alcohols, and derivatives thereof, and are broadly used as carriers to deliver poorly water-soluble lipophilic drugs. Many active pharmaceutical compounds possess low water

solubility and high membrane permeability (classified as Class II compounds in Biopharmaceutical Classification System) (170,171). These lipophilic compounds often suffer from low absorption due to low solubility and/or limited dissolution rate in the gastrointestinal (GI) tract. It has been reported that lipid species can potentially provide a beneficial effect on the absorption and bioavailability of these lipophilic compounds (42,172). Briefly, the lipids can potentially enhance the absorption of these poorly water-soluble lipophilic compounds by presenting the drugs in the solubilised state in the GI tract thereby overcoming the drug dissolution step, delaying the gastric emptying, promoting lymphatic transport and attenuating the protein efflux activity at the surface of the enterocytes, leading to enhancement in the oral bioavailability (42). Additionally, the digestion of lipids leads to the formation of free fatty acids and monoglycerides which can interact with the endogenous amphiphilic components (such as bile salts, phospholipid and cholesterol) and form liquid crystalline colloidal phases. The lipophilic drugs can reside into these formed liquid crystalline phases resulting into further enhancement in drug solubilisation and drug absorption (42,173). As a result, over the past two decades, lipid-based drug delivery systems (LBDDS) have received an increased interest and it is a well-known approach to co-administer the lipophilic drug with natural or synthetic lipids in order to improve the absorption and oral bioavailability of poorly water-soluble lipophilic drugs. Lipid-based drug delivery systems comprise a broad range of formulations from simple oil solutions to complex combinations of oils, surfactants, co-surfactants and sometimes co-solvents in addition to active compounds. Pouton classified LBDDS into four different classes based on their compositions and likely behavior on dispersion and digestion (174,175). Briefly, type I formulations are simple oil solutions (i.e. mono, di or triglycerides), type II formulations are mixture of oils and water-insoluble surfactants (referred as self-emulsifying drug delivery system (SEDDS)), type III are mixture of oils, water soluble or water insoluble surfactants and co-solvents (referred as self-microemulsifying (SMEDDS)/nanoemulsifying drug delivery systems (SNEDDS)) and type IV formulations are mixture of water-soluble surfactants and co-solvents without oils (174,175).

To date, the applications of 3DP in the pharmaceutical field have been mainly focussed on polymer-based systems and much less is known for the LBDDS. Lipids are low-temperature melting soft materials and the use of 3DP technologies to modify and to tune certain characteristics of lipid-based systems can be promising. However, lipid offers the benefits of processing at low-temperature thus they are highly beneficial for thermo-labile compounds. Due to the low processing temperature, the drugs can retain their crystalline or amorphous form which can be advantageous for some active compounds. Additionally, the lipids can enhance the solubility of lipophilic drugs during processing which can potentially offer the possibility of manufacture of high drug-loading formulations.

To the best of our knowledge, there are only three studies reported for LBDDS using 3DP technologies. Firstly, Içten *et al.* proposed custom made dropwise additive manufacturing technique for the development of amorphous self-emulsifying drug delivery system (SEDDS) (176). The group developed custom-made DOD inkjet printing and used as a tool for a small-scale manufacturing process to distribute the individualised dose of celecoxib. A melt-based solid oral dosage form containing 90% w/w Gelucire® 44/14 and 10% w/w celecoxib was prepared on hydroxypropyl methylcellulose (HPMC) film using custom-made DOD as shown in Fig. 3. The final dosage form exhibited spontaneous emulsification upon contact with water. The amorphous form of model drug celecoxib into the final dosage form resulted in an enhanced dissolution behaviour. The team proposed a custom-made DOD as a viable technique to tailor the regimen of the dosage form for individual patients. On the other hand, Kyobula *et al.* validated the use of beeswax as a carrier to produce fenofibrate-loaded solid dosage forms in bespoke geometries (honeycomb structures) with the usage of hot-melt inkjet printing (45). The group demonstrated the feasibility of hot-melt inkjet printing in order to achieve desired drug release profiles by implementing the geometrical capability in combination with predictive computation techniques (45).

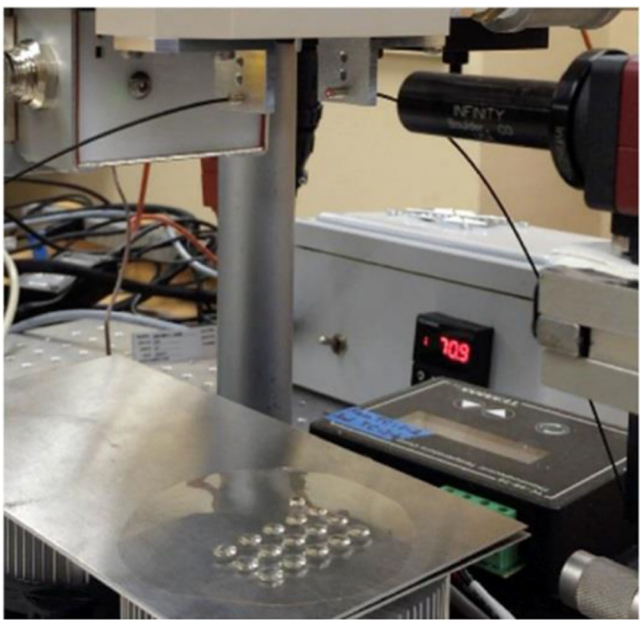

Fig. 3 Preparation of amorphous self-emulsifying drug delivery system (SEDDS) melt-based formulation on hydroxypropyl methylcellulose (HPMC) films using a custom-made DOD inkjet printing. Figure adapted with permission from reference (176).

More recently, Vithani *et al.* developed fenofibrate and cinnarizine-loaded solid self-microemulsifying drug delivery system (SMEDDS) into various geometrical shapes without a solid phase carrier using syringe-based extrusion 3DP and studied the effect of geometry on performance. Solid SMEDDS with four geometrical shapes - cylinder, prism, cube and torus, with different surface area and surface area to volume ratio were prepared (Fig. 4). The result of this study showed that the kinetics of dispersion was dependent on surface area to volume ratio values and the kinetics of digestion was initially partially affected by the geometries. The team proposed an alternative way of preparing solid SMEDDS formulations without the need of a solid-phase carrier to circumvent the drawbacks of dose dilution, toxicity, dose uniformity and tolerability associated with an additional solid-phase carrier. This was the first study where 3DP technology was applied to develop solid LBDDS (i.e. solid SMEDDS formulations) without using a solvent or a solid-phase carrier (177) and it was anticipated to open new avenues for the development of novel solid LBDDS prepared by 3DP technologies.

The above described three literature studies demonstrated the feasibility of 3DP technologies for LBDDS and indicated 3DP as a promising platform with an immense capability to develop modified or tailored characteristics LBDDS. These promising studies are anticipated to promote the adoption of 3DP technologies for lipid-based systems which can potentially lead to a whole new class of LBDDS. Inkjet and SSE 3DP process are seen as the most suitable technologies for the lipid-based systems. 3DP can potentially make the manufacturing of solid LBDDS as a single-step process by eliminating the solidification steps and the associated drawbacks. However, the use of 3DP for lipids and LBDDS is still in its infancy and the area is wide open for new approaches. The future directions for LBDDS encompass the identification and characterisation of additional lipid materials amendable to 3DP process. Due to its high degree of control and flexibility, 3DP may be appropriate to develop personalised lipid-based medicines with customised dispersion and digestion kinetics and subsequently drug solubilisation profiles for an optimal drug delivery.

Fig. 4 3D printed fenofibrate-loaded solid SMEDDS formulations in various geometrical shapes prepared using semi-solid extrusion 3DP technology. Figure adapted with permission from reference (177).

CURRENT CHALLENGES

Despite the enormous potential, 3DP technology shows numerous technical issues and regulatory hurdles to be overcome in order to achieve significant adoption in the pharmaceutical field for LBDDS. This section highlights the current outstanding technical challenges (including formulation and processing parameters), regulatory challenges and the material issues of lipid species that are needed to be overcome in order to develop the real potential of 3DP in the pharmaceutics.

General challenges affecting all the 3D printed formulations include, the reproducibility, especially for nozzle based 3DP technologies (i.e. binder jetting and semi-solid extrusion based), as the printing process goes through multiple start-stop steps throughout printing of single or multiple objects. Additionally, many 3DP technologies (i.e. inkjet, binder jetting and semi-solid extrusion) require post-processing treatment which can obviate the apparent benefits of 3DP technology in the first place. The appearance of the final product can impact on the patient compliance as sometimes the deposition of the layers are imperfect and may be visible (96). Sometimes the production of highly porous structures can lead to poor mechanical resistance such as higher friability values. However, this can be improved by creating more resistant shell structures in a core-shell tablet design (76). The optimisation of processing parameters and the selection of materials are basic to ensure the quality of the printed products. Additionally, many of the used materials in the printing process are non-pharmaceutical grade substances and the current 3D printers for pharmaceuticals are not good manufacturing practice (GMP) compliant thus, the process and products must be validated as safe for human consumption.

Regarding LBDDS, two important challenges for printing are (i) finding the appropriate pharmaceutical grade lipid or lipidic species that are feasible for printing and (ii) maintaining the properties of the printed product. Lipids or lipidic substances are non-toxic biodegradable species that are either in a liquid state at ambient temperature or solid materials having low-melting temperatures. This physical state of lipid species suggests that substances are more likely to be compatible for droplet-based or extrusion-based 3DP technologies. The physical and chemical properties of lipids may make them less appropriated for printing, for instance, the poor thermoplastic behaviour of lipid species may result in the poor or imperfect binding of layers which may results in the poor physical property and mechanical strength of the printed product. The high viscosity of the substances may further lead to poor resolution

and less controlled deposition of materials. Therefore, the use of lipids with low melt viscosity and high binding capabilities may be most efficient in the printing process. Lastly, the availability of 3D printing lipid materials, colours and surface finishes are limited in comparison to conventional materials for printing (72). Despite the challenges, lipids offer distinct advantages of low-printing temperature and the possibility of incorporating high-drug loading, so we forecast that the existence of new lipid-based drug delivery systems is just a matter of time.

The stability and shelf-life of LBDDS are important aspects of the printed formulations which can significantly affect the performance of the printed formulations. The stability is significantly affected by the physicochemical properties of the selected lipids and sometimes by the process. In 3DP, similar to other melting-based methods, lipids are processed at below or above the melting point of lipid species, thus, theoretically, the implementation of 3DP is just a new technology with identical process conditions so it should not dramatically affect the stability of the 3D printed products. It is important to highlight that the printing of LBDDS at the point of care can potentially remove the stability issue out of the equation, as the freshly printed products are extemporaneous formulations expected to be used by the patients within a short period of time.

Indeed, the 3DP technology and its immense potential to revolutionise drug development and manufacturing has caught the attention of regulatory bodies. However, it is challenging to meet the traditional regulations for the introduction of 3D printed products. Thus, the FDA is currently working on developing an understanding of 3DP process via its own research (178). In May 2016, the FDA released a final guidance on Technical Considerations for Additive Manufactured Devices for the regulation of 3D-printed medical devices for industry and FDA staff, which was focussed on design, manufacturing and testing of the devices (179). Several medical devices and implantable products have been granted clearance based on proving the effect of 3D printed products is substantiality equivalent to the marketed device. It has been proposed that similar kind of approach can be applied for pharmaceutical products by approving the 3D printed drug products that show the bioequivalent to the approved product. However, a specific guideline and a clear regulatory pathway are very much needed and a new pathway and guidelines should likely to be developed by the FDA and other regulatory bodies that also includes the pathway for an approval of personalised medicines.

CONCLUDING REMARKS

The evolution and implementation of the different 3DP technologies are rapidly happening in many manufacturing areas. Regarding the use of soft materials, several types of 3DP technologies have been employed in (i) bioprinting application to produce scaffolds to regenerate, replace or restore the functionality of injured tissue or organs, (ii) the food field to design the food products with better texture and high nutritional values and (iii) the pharmaceutical area to prepare novel solid dosage forms. 3DP has enabled the preparation of complex dosage forms with accurate deposition of materials, with greater spatial control and geometric flexibility. These features can enhance control, uniformity and the safety of low dose and potent active compounds. Despite the substantial use of varied "soft" material for 3DP-based pharmaceutical applications, the application of lipids or LBDDS remains almost unexplored. The literature studies for soft materials in the biological application, food industry and pharmaceutical field shows the great potential of 3DP for soft materials. The most current application of 3DP in the preparation of drug-loaded solid SMEDDS without a solid-phase carrier can boost the use of lipids for 3DP applications. This technology can provide a whole new option for solid LBDDS and it can potentially resolve engineering problems associated with the physicochemical properties of lipids. The commercialisation of 3DP printed novel dosage forms is challenging, however, this innovative technology will make a significant impact on the modern pharmaceutical industry where novel personalised solid dosage forms are demanded.

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