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Vat photopolymerization 3D printing for advanced drug delivery and medical device applications

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Abstract

Three-dimensional (3D) printing is transforming manufacturing paradigms within healthcare. Vat photopolymerization 3D printing technology combines the benefits of high resolution and favourable printing speed, offering a sophisticated approach to fabricate bespoke medical devices and drug delivery systems. Herein, an overview of the vat polymerization techniques, their unique applications in the fields of drug delivery and medical device fabrication, material examples and the advantages they provide within healthcare, is provided. The outstanding challenges and drawbacks presented by this technology are also discussed. It is forecast that the adoption of 3D printing could pave the way for a personalised health system, advancing from traditional treatments pathways towards digital healthcare and streamlining a new cyber era.

Keywords

Additive manufacturing; Photopolymerisation; Stereolithography; Stereolithographic printing; 3D printed drug products; Personalized pharmaceuticals and medicines;

List of Abbreviations

2PP, two-photon polymerization;

3D, three-dimensional;

4D, four-dimensional;

ASTM, American Society for Testing and Materials;

BA, n-butyl acrylate;

BAPO, phenylbis (2,4,6-trimethylbenzoyl) phosphine oxide;

CAD, computer-aided design;

CE, cyanate ester;

CLIP, continuous light interface production;

CQ, camphorquinone;

CT, computed tomography;

DEF, diethyl fumarate;

DEGDA, di(ethylene glycol) diacrylate;

DLP, digital light processing;

DMD, digital micromirror device;

DMPA, dimethoxyacetophenone;

DSC, differential scanning calorimetry;

EDMAB, ethyl 4-dimethylaminobenzoat;

EMA, European Medicines Agency;

EPU, elastic polyurethane;

FDA, Food and Drug Administration;

FDM, fused deposition modelling;

FTIR, Fourier transform infrared;

GDMA, glycerol dimethacrylate;

GMP, Good Manufacturing Practice;

GRAS, generally recognised as safe;

HEMA, 2-hydroxyethyl methacrylate;

HPLC, high-performance liquid chromatography;

IPA, isopropyl alcohol;

LAP, lithium phenyl-2,4,6-trimethylbenzoylphosphinate

LCD, liquid crystal display;

MAOMS, (methacryloxypropyl)methylsiloxane;

MN, microneedle

MP_2MA, di (ethylene glycol) methyl ether methacrylate;

MRI, magnetic resonance imaging;

NIR, near-infrared;

NMR, nuclear magnetic resonance;

PCL, polycaprolactone;

PCLDMA, polycaprolactone dimethacrylate;

PCL-tMa, polycaprolactone trimethacrylate;

PEG, polyethylene glycol;

PEGDA, poly (ethylene glycol) diacrylate;

PEGDMA, poly (ethylene glycol) dimethacrylate;

PEGMA, poly (ethylene glycol) methacrylate;

PMA, n-propyl methacrylate;

PPF, poly (ethylene fumarate);

PPGDMA, poly (propylene glycol) dimethacrylate;

SA/V, surface area to volume;

SLA, stereolithography;

tBA, tert-butyl acrylate;

Tg, glass transition temperature;

TMPTA, trimethylolpropane triacrylate;

TPA, two-photon absorption;

TPO, diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide;

TPO-L, ethyl (2,4,6-trimethylbenzoyl) phenyl phosphinate;

UDMA, diurethanedimethacrylate;

UMA, urethan methacrylate;

UV, ultraviolet;

1. Introduction

Three-dimensional (3D) printing, also known as additive manufacturing, is a rapid prototyping technique that was first invented over 30 years ago by Charles Hull [1]. The term “stereolithography” (SLA) was coined in his patent in 1986, defining it as a method and apparatus for making solid objects by successively printing thin layers of a curable material, e.g., by ultraviolet (UV) laser irradiation, one on top of the other [1]. Later he founded 3D Systems in California, making 3D printing systems commercially available [2]. Nowadays, 3D printing is better known as a method for producing physical objects using a computer-aided design (CAD) software or an imaging technique. Because it fabricates in a layer-by-layer fashion, 3D printing has the potential to manufacture objects with novel structures unattainable with conventional (subtractive) manufacturing. It has applications in almost all areas of manufacturing from building moulds and small-scale tools through to the automotive, aviation, dental, biomedical [3, 4] and even the food industry [5, 6].

3D printing has been forecast as a disruptive and transformative technology in healthcare, moving medical treatments away from “one size fits all” towards personalised medicines (medicines with dose or dose combinations tailored to the specific needs of the patient) [7], because 3D printing technologies have the potential to fabricate small production batches of medications and drug-loaded medical devices on demand and in a clinical setting [8-10]. A variety of innovative treatment systems have been reported, including orally disintegrating formulations [11-15], controlled release formulations [16-22], formulations with novel designs [23-25] and specific functions [10, 26-33], multi-drug combinations [34-38], paediatric-friendly formulations [10, 39, 40], and medical devices [41-44]. In 2015, Spritam®

(Aprecia Pharmaceuticals), the first 3D-printed medicine approved by the United States Food and Drug Administration (FDA), established a significant milestone for the use of 3D printing in manufacturing medicines [45].

The American Society for Testing and Materials (ASTM) International classifies 3D printing technologies into seven main categories [46]: binder jetting, vat polymerization, powder bed fusion, material extrusion, material jetting, directed energy deposition, and sheet lamination [47]. SLA printing falls under the category of vat photopolymerization, and is one of the most promising technologies, as it allows high accuracy and superior resolution (layer thickness of 1 μm for microstereolithography versus 100 μm for fused deposition modelling (FDM) [48, 49]), enabling the fabrication of complex internal structures with intricate details. It also has a high production speed compared with other 3D printing technologies (e.g., extrusion- or melting-based techniques), so more objects can be produced within a given timeframe [50]. Since its introduction, vat polymerization has rapidly grown as a promising manufacturing approach, expanding its boundless applications in a variety of fields, ranging from aerospace [51], water filtration and automotive industries [52] to even the fashion industry with 3D printed shoes [53] and jewellery making [54]. Within medicine, coupling vat polymerization with medical imaging techniques enables the fabrication of patient-specific surgical tools, implants, and tissue engineering scaffolds [55-60].

In this paper, an overview of the recent healthcare applications of vat photopolymerization 3D printing, including medical devices, novel drug delivery systems and oral dosage forms, are discussed. An insight into the drawbacks and

challenges of the implementation of vat photopolymerization to prepare medicines and drug-loaded medical devices is also provided.

2. Vat photopolymerization-based 3D printing techniques

Vat photopolymerization is a generic term given to a number of 3D printing technologies. It is defined as a liquid to solid process, where computer-spatially-controlled photopolymerization is used to create solid objects from a vat of liquid resins under light irradiation. Some of the more common vat photopolymerization processes include SLA (Figure 1A and 1B), digital light processing (DLP) (Figure 1C), continuous light interface production (CLIP) (Figure 1D) and two-photon polymerization (2PP) (Figure 1E). The main distinctive characteristics of the different processes are outlined in **Table 1**.

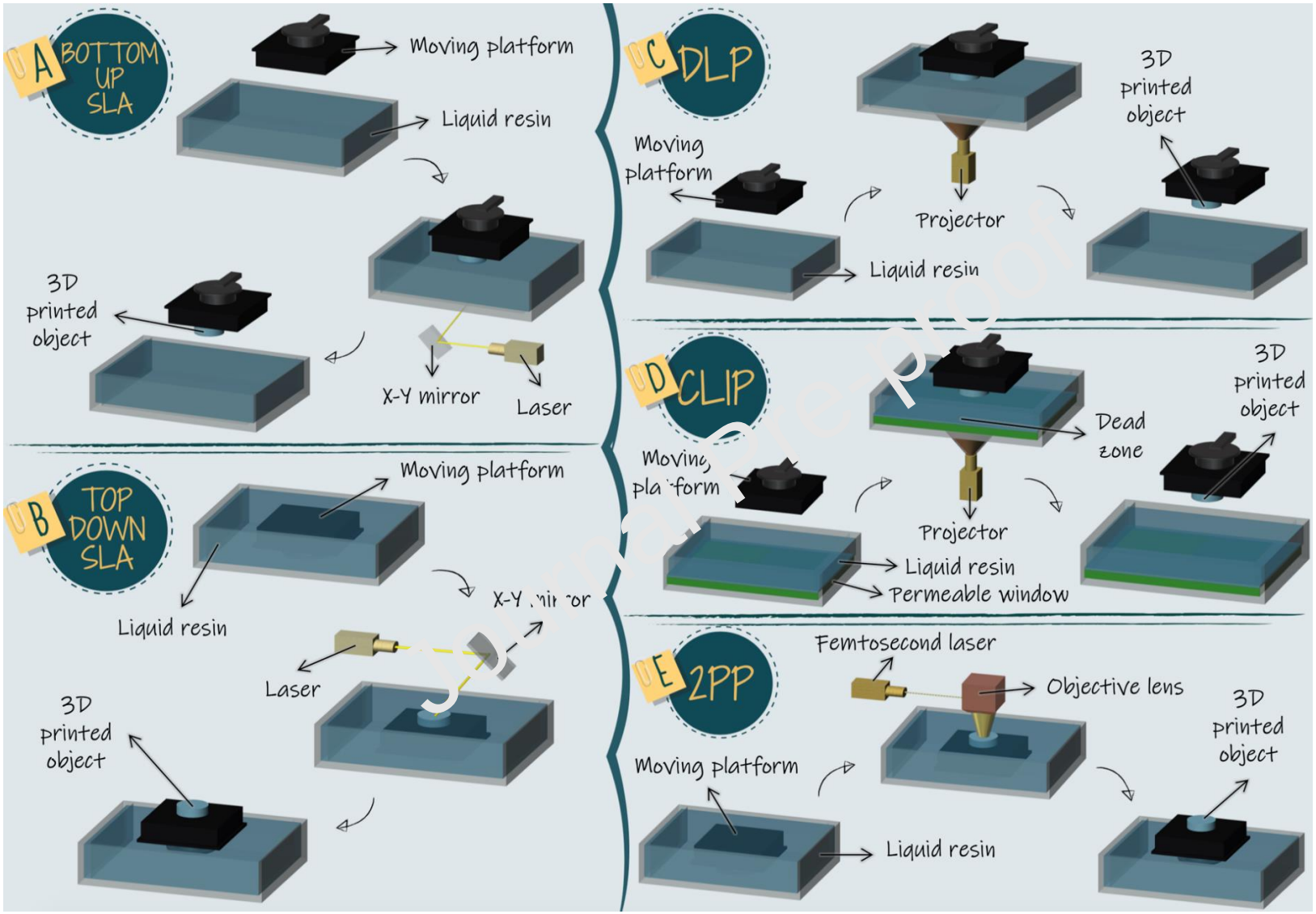

Figure 1. Schematic representation of a (A) bottom-up SLA, (B) top-down SLA, (C) DLP, (D) CLIP and (E) 2PP 3*D printing.*

Table 1. A summary highlighting the main differences between the vat photopolymerization technologies. *SLA: stereolithography; DLP: digital light processing; CLIP: continuous liquid interface production; 2PP: two-photon polymerization; DMD: digital micromirror device; LCD: liquid crystal display; TPA: two-photon absorption*.

Technology	Light source	Main feature(s)	Ref.
SLA	Laser beam	• The most commonly used vat photopolymerization technology. • It can be either bottom-up (laser sits underneath the resin tank) or top-down (the laser is positioned above the resin tank). • The bottom-up setup is more affordable than the top-down and has the advantage of small build volumes. • The laser points at two mirror galvanometers that direct the light in the X and Y axes to cure the layers	[61]
DLP	Digital light projector	• Due to the projector light source, the printing speed of DLP is considerably faster when compared with that of SLA. • Illumination is achieved by a DMD (a dynamic mask consisting of thousands of micromirrors) that can rotate rapidly and reflect light. • Instead of DMD, LCD panels can be used to directly shine light on the vat of photoreactive resins. • The image of each layer is made up of small square pixels, which creates layers that are composed of rectangular voxels in 3D space, known as the voxel effect.	[62-64]
CLIP	Digital light projector	• A relatively newer technique that was developed in 2015. • The fundamental concepts are similar to that of DLP. • It is up to 100 times faster than any other 3D printing technology. • A “dead zone” is created in the container between the oxygen-permeable window and the surface of the curing part, where photopolymerization is inhibited. In this way, the object being cured is continuously pulled out of the resin bath with a production rate of hundreds of millimetres per hour. • Ultimately yields printed objects with smooth surfaces without slicing	[65, 66]

		artefacts. • Variations of this technology have shown to enable continuous and rapid printing via the use of a mobile liquid interface (e.g., fluorinated oil) and dual-wavelength volumetric photopolymerization inhibition patterning.	
2PP	Titanium sapphire femtosecond laser	• A TPA-based fabrication process where the laser (λ = 780 nm; repetition rate = 80 MHz) is focused by an objective lens onto the photosensitive resin. • Used for fabricating microstructures with extremely high resolutions (< 100 nm). • Its main applications include microdevices, microfluidics, and microphotonics.	[67, 68]

3. Monomers and oligomers for healthcare applications

A wide range of advanced resins has been developed for vat photopolymerization and many are commercially available [69-71]. They are normally composed of multi-functional monomers based on methacrylates or acrylic esters [72]. However, the exact chemical compositions are often confidential and are not provided by manufacturers, which means the physicochemical and mechanical properties (e.g., tensile strength, elongation at break) and hazard identifications (cytotoxicity) remain unclear. Thus, there is a growing demand for the development of novel photocurable materials for medical and pharmaceutical applications. Examples of functional monomers or oligomers investigated for vat photopolymerization 3D printing are summarised in **Table 2**.

Table 2. Examples of photopolymers investigated for use with vat photopolymerization 3D printing for healthcare applications.

Material(s)	Function (s)	Technology	Ref.
Tert-butyl acrylate (tBA), di(ethylene glycol) diacrylate (DEGDA) crosslinker, phenylbis (2,4,6-trimethylbenzoyl) phosphine oxide (BAPO)	Thermally induced shape-memory	SLA	[73]
Methacryloxypropyl)methylsiloxane (MAOMS), commercially available methacrylate-based resins (Formlabs, USA), HNU-200L	Flexible	SLA	[74]
Poly(mercaptopropylmethylsiloxane-co-dimethylsiloxane), vinyl terminated polydimethylsiloxane, diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide (TPO)	Elastomer, biocompatible	SLA	[75]
Pluronic F127 dimethacrylate macromonomers, acrylic acid, ethyl (2,4,6-trimethylbenzoyl) phenyl phosphinate (TPO-L), vitamin E	pH induced shape-memory	SLA	[76]
Epoxidised vegetable oils, BAPO, iodonium salt, Sudan I	Sustainable	SLA	[77]
Soybean oil epoxidised acrylate, Irgacure 819	Sustainable, biocompatible	SLA	[78]
Acrylated waste cooking oil, Irgacure 819	Sustainable, biodegradable	SLA	[79]
Lignin, methacrylic anhydride, SR494 (Sartomer), Ebecryl 8210 (Allnex), Genomer 1122 (Rahn), TPO, Benetex OB Plus (Mayzo)	Sustainable, ductile	SLA	[80]
Methacrylated vanillin, glycerol dimethacrylate, TPO	Sustainable, high strength	SLA	[81]

Alkyne carbonate-based resins, TPO-L, Ivocerin, Sudan II	Tough, biocompatible	DLP	[82]
Ebecryl 8413 and 113 (Allnex), TPO	Highly stretchable	DLP	[83]
Acrylamide, PEGDA 575 and 700, TPO nanoparticles, Sudan I	Highly stretchable, biocompatible	DLP	[84]
(Mercaptopropyl)methylsiloxane]-dimethylsiloxane, iodobenzene diacetate, vinyl-terminated polydimethylsiloxanes, tributylphosphine, TPO, Sudan I	Self-healing	DLP	[85]
Methacrylated polycaprolactone (PCL), TPO, vitamin E, Orasol Orange G	Thermally induced shape-memory	DLP	[86]
PEGDA 700, PPGDMA, Irgacure 819, Sudan I	Water induced shape-memory	DLP	[87]
Bisphenol A ethoxylate diacrylate, bisphenol A ethoxylate dimethacrylate, methyl red, disperse red 1 methacrylate, Irgacure 819	Light induced shape-memory	DLP	[88]
Succinic acid, itaconic acid, glycidyl methacrylate, Irgacure 819	Sustainable, heat-resistant	DLP	[89]
Trimethylolpropane triacrylate (TMPTA), Ebecryl 8402 (Allnex), n-butyl acrylate (BA), TPO, Sudan I	Volatilisation-induced, shape-morphing	DLP	[90]
Elastic polyurethane (EPU) (Carbon3D, USA)	Highly stretchable	CLIP	[91]
Urethan methacrylate (UMA) (Carbon3D, USA)	Tough	CLIP	[92]
Cyanate Ester (CE) (Carbon3D, USA)	Stiff	CLIP	[93]

Methacrylate- and acrylate-based monomers are mostly used, demonstrating fast reaction rates, long-term stability and tuneable mechanical properties [95]. One major drawback of these monomers is that they exhibit volume shrinkage during the chain growth free radical polymerization, resulting in highly brittle printed parts, which limits their applications. The synthesis of alkyne carbonate-based compounds with enhanced toughness has shown to offer similar curing rates and much higher conversion with lower cytotoxicity over comparable acrylates [82].

On the other hand, the introduction of flexible oligomers presents another approach to overcome the limitations of acrylated-based resins (too tough, too brittle, too

hydrophobic) [74]. For instance, (methacryloxypropyl)methylsiloxane (MAOMS) was directly added into a commercial resin to form a siloxane-methacrylate composite for SLA 3D printing [83]. The hybrid material increased in tensile toughness, ductility and compression break yield and modulus, and decreased in glass transition temperature (T_g), tensile strength and surface energy. Another example is a family of highly stretchable and UV curable elastomer systems, which consist of epoxy aliphatic acrylate and aliphatic urethane diacrylate diluted with isobornyl acrylate. Printed parts created using these systems can be stretched by up to 1100%, which is more than five times the elongation at break of some commercial elastomers (e.g., Formlabs Flexible, Carbon EPU 40). This permits their use for 3D printing soft and deformable structures that require the adoption of temporary conformations.

Shape memory materials are a class of smart polymeric materials that are capable of changing their shapes in a predefined manner when subjected to an external stimulus such as heat, pH, light or moisture [47]. Compared with shape-memory alloys (e.g., metals with shape-memory effect), shape-memory polymers possess the advantages of lower cost, higher extent of elastic deformation, and potential biocompatibility and biodegradability [96, 97]. The 3D printing of shape-memory polymers paved the way for the emergence of four-dimensional (4D) printing, whereby the printed objects display dynamic transformation (e.g., change in shape, property, or functionality) over a fourth dimension, namely time [62, 98].

Thermally-induced shape-memory polymers exhibit a temporary state and a permanent state [47]. Following the manufacturing of an object using a smart material, it is heated above the polymer's T_g to enable its transformation to the

temporary state. This is followed by rapid cooling to fix the shape. Once exposed to a temperature above the T_g again, the polymer recovers to its permanent shape. In a recent study, methacrylated polycaprolactone (PCL) was formulated as a DLP printable resin with a shape-memory effect (Figure 2A), giving enormous potential for the fabrication of soft robotics, invasive medical devices, sensors and wearable electronics [86]. A novel hydrophilic/hydrophobic composite was also developed using poly (ethylene glycol) diacrylate (PEGDA) and poly (propylene glycol) dimethacrylate (PPGDMA). The resulting photopolymer was easily patterned using DLP 3D printing to fabricate water-responsive shape-shifting structures (Figure 2B) [87]. Examples of other stimuli-induced shape-memory polymers can be found in **Table 2**. The synthesis of self-healing elastomers was also reported. These materials not only can be 3D printed using photopolymerization-based techniques, but can also self-heal fatal fractures and restore mechanical strengths up to 100% (Figure 2D) [85].

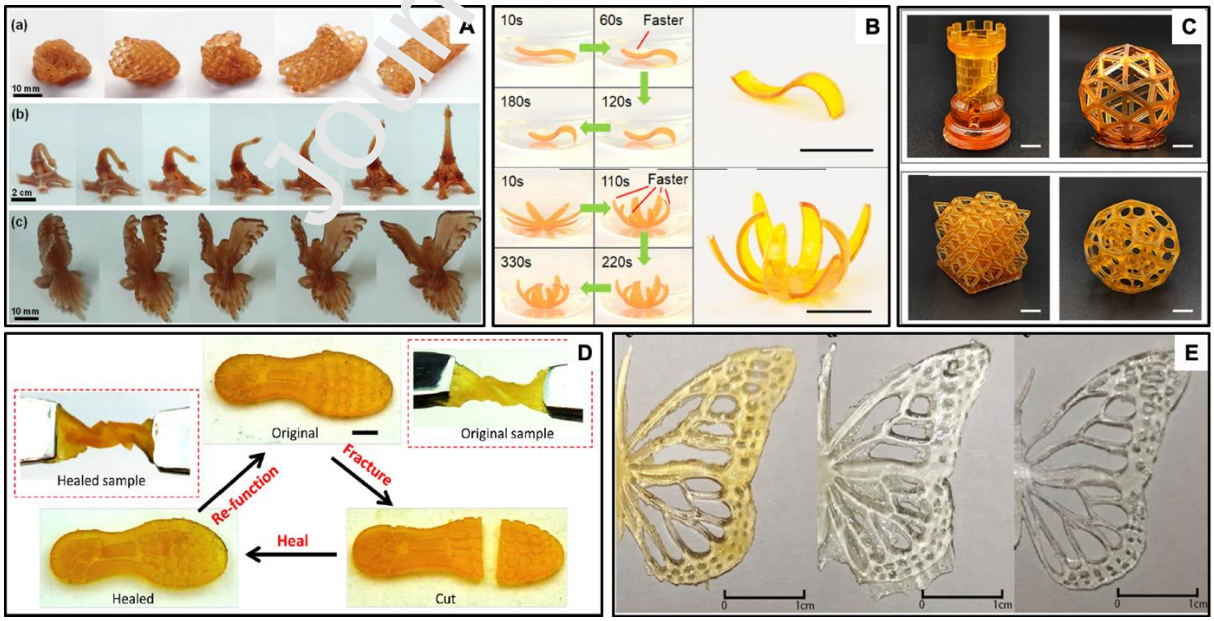

Figure 2. (A) DLP 4D printed model cardiovascular stent, Eiffel Tower model, and a bird reverting to their original shapes at 70°C. Reprinted with permission from [86]. (B) DLP 4D printed water-responsive “S” strip and flower. Reprinted with permission from [87]. (C) DLP 3D printed complex structures by bio-based heat-resistant resin. Reprinted with permission from [89]. (D) DLP 3D printed self-healing shoe pad sample. Reprinted with permission from [85]. (E) SLA 3D printed butterfly from (left to right) McDonald’s acrylated waste cooking oil, acrylated epoxidised soybean oil and commercial resin MiiCraft. Reprinted with permission from [79]

Interestingly, biomasses, such as vegetable oils and soybean oils, have lately gained attention as economical and renewable resources for the formulation of SLA/DLP monomers [77, 78]. Bio-based, heat-resistant resins synthesised from glycidyl methacrylate and succinic or itaconic acid were also reported as a sustainable and low-cost source for DLP 3D printing of complex structures (Figure 2C) [89]. Not long ago, the possibility of directly converting McDonald’s waste cooking oil into an SLA resin via acrylation was reported (Figure 2E) [79]. The formulated resin displayed high stability, homogeneity and biodegradability, wherein it was capable of producing parts with a high resolution (up to 100 µm). More recently, a range of bio-based photoactive acrylates derived from succinic acid or itaconic acid [89], lignin [80], vanillin [81] and lactose [94], were developed, demonstrating a great potential to substitute petrochemical-based polymers by being environmentally friendly and abundantly available. All of the above examples have demonstrated the potential of vat photopolymerization 3D printing as a sustainable and economical technology platform [99].

4. Progress within healthcare

The introduction of 3D printing within healthcare has revolutionised the way medicines and drug delivery devices can be made. Owing to its flexible and precise spatial control distribution of materials, 3D printing enables the production of small batches of medicines at the point of care with a tailored dosage, shape, size and release characteristic [47]. As such, advancing treatment from the traditional 'one-size-fits-all' approach towards personalised medications. Various vat photopolymerization technologies have demonstrated their suitability for the fabrication of drug delivery systems with high printing resolution and accuracy, offering diverse controlled or sustained release profiles. **Figure 3** provides a graphical illustration of the way drug-loaded devices can be fabricated via vat photopolymerization 3D printing. This can be achieved via two different approaches; either by directly incorporating the drug into the liquid resin before printing or by introducing the drug into a blank device after printing [100]. In the former scenario, the drug is fully dissolved or homogeneously dispersed in a resin, composed of a photoinitiator and a photopolymer, by magnetic stirring at room temperature. Following the printing process, the drug is physically entrapped in the crosslinked polymeric network. Once the device is dispersed into a dissolution medium, the drug is released via diffusion from the swollen matrix. In the case of blank devices, the drug can be incorporated via traditional drug loading techniques based on adsorption, such as dipping and spray coating. Alternatively, the drug can be absorbed into the polymer network by swelling the blank device in a drug-concentrated solution. Although post loading adds an additional manufacturing process, it prevents potential drug degradation during pre-printing or printing.

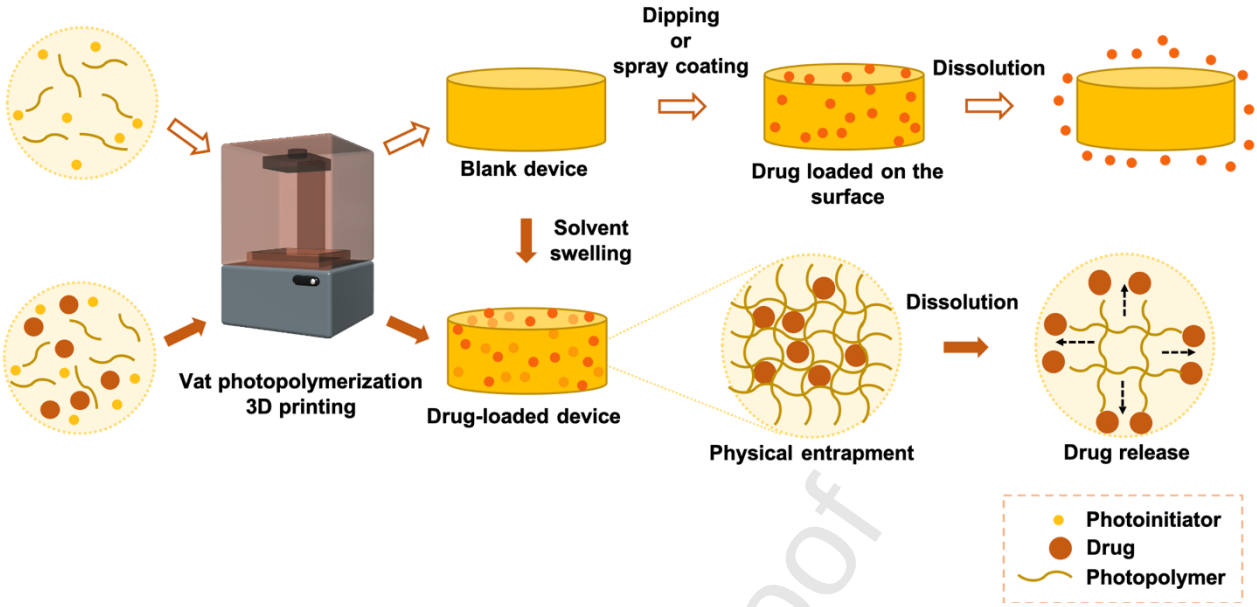

Figure 3. Vat photopolymerization 3D printing for fabrication of drug delivery systems.

As previously mentioned, 3D printing employs 3D models to create physical objects. The 3D models used can be created using a CAD software or obtained from imaging techniques (e.g., 3D scanner, computed tomography (CT), magnetic resonance imaging (MRI)) that capture real-time images, detailing the anatomical features of the patient [101]. As such, by coupling 3D printing with imaging data, patient-specific drug delivery devices can be fabricated. Examples of drug delivery devices manufactured via vat photopolymerization are outlined in **Table 3** and can be described as follows:

Table 3. Examples of drug delivery systems manufactured via vat photopolymerization 3D printing technologies; MN: microneedle.

Technology	Drug(s)	Device	Material(s)	Ref.
SLA	-	MN mould	Clear Resin V4 (Formlabs, USA)	[102]
	Insulin	MN arrays	Dental SG Resin (Formlabs, USA)	[103, 104]
	Cisplatin	MN arrays	Class I biocompatible resin	[105]
	Rhodamine B	MNs with barb	PEGDA 250, Irgacure 819, Sudan I	[106]
	-	Microfluidic-enabled hollow MN device	Dental LT Clear Resin (Formlabs, USA)	[107]
	Salicylic acid	Nose patch	PEGDA 700, polyethylene glycol (PEG) 300, TPO	[101]
	Acetylsalicylic acid	Scaffolds	PEGDA 700, Irgacure 2959	[108]
	Lidocaine	Scaffolds	PCL macromers, Omnirad TPO-L, Orasol orange G	[109]
	Ovalbumin	Microjet device	E-Shell 300 Resin (EnvisonTEC Inc., USA)	[110]
	-	Dental splint	Diurethanedimethacrylate (UDMA), glycerol dimethacrylate (GDMA), quaternary ammonium methacrylate, camphorquinone (CQ), ethyl 4-dimethylaminobenzoat (EDMAB), Irgacure 819	[111]
	Glucagon	Rapid reconstitution packages	VisiJet Clear (3D Systems, Inc.)	[112]
	-	MN arrays	Castable resin (Formlabs, USA)	[113]
DLP	Diclofenac sodium	MN array on finger splints	Castable Resin (Kudo3D Inc., USA)	[114]

	Dacarbazine	MN arrays	Poly (ethylene fumarate) (PPF), diethyl fumarate (DEF), BAPO	[115]
	Rhodamine B	Hydrogel MNs	PEGDA 400, Irgacure 819	[116]
	Lidocaine, ibuprofen sodium, diclofenac sodium, ketoprofen	Non-dissolving suppository moulds	Castable Resin (Kudo3D Inc., USA)	[117]
	Diclofenac sodium, ibuprofen	Implants with various shapes	PEGDA 400, TPO	[118]
	-	Microreservoir device	HTM 140 M V2 (EnvisionTEC, Germany)	[119]
	-	Scaffolds	Acid-cleavable crosslinker, poly (ethylene glycol) methacrylate (PEGMA), dimethoxyacetophenone (DMPA), avobenzone UV blocker	[120]
	doxycycline, vancomycin, cefazolin	Implants	PEGDA, PEG, diphenyl phosphine oxide	[121]
CLIP	Rhodamine B & fluorescein	MN arrays	TMPTA, poly (ethylene glycol) dimethacrylate (PEGDMA 500), polycaprolactone trimethacrylate (PCL-tMa 1100), acrylic acid, TPO	[122]
	Bovine serum albumin	MN arrays	PEGDMA 350, TPO	[123]
	Rhodamine B, docetaxel, dexamethasone-acetate	Geometrically complex model devices	PEGMA, di(ethylene glycol) methyl ether methacrylate (MP_2MA), 2-hydroxyethyl methacrylate (HEMA), n-propyl methacrylate (PMA), polycaprolactone dimethacrylate (PCLDMA), PEGDMA, TPO	[100]
	-	Vascular stents	Methacrylated poly (1,12 dodecamethaylene citrate), Irgacure 819	[124]

	-	Intravaginal rings	Urethane-methacrylated (Carbon3D, USA), methacrylated silicone-poly(urethane) (SIL 30 - Carbon3D, USA)	[125]
2PP	Gentamicin sulphate	MN arrays	PEGDA 600, Irgacure 369	[126]
	-	MN arrays	Ormocer (Fraunhofer-Gescllschaft, Germany), Irgacure 369	[127]
	Rhodamine B	Drug delivery device	PEGDMA 575, Irgacure 369	[128]
	Doxorubicin	Microswimmer	Methacrylamide chitosan, lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP)	[129]

4.1. Hearing aids

Hearing aids are a remarkable example of medical devices that benefit from the development of vat photopolymerization 3D printing. In fact, more than 99% of patient-oriented hearing aids are manufactured using 3D printing nowadays [130]. Before 3D printing was introduced into this domain, the production of hearing aids took longer than a week. Today, the whole process, involving scanning, modelling and 3D printing, could take less than a day [131]. EnvisionTEC is one of the leading companies for the manufacturing of hearing aids, providing large scale production and offering over 16 biomedically approved materials, including soft and hard materials, ranging from transparent for ear moulds to skin colours for ear shells [132].

4.2 Microneedles

Microneedles (MNs) have been extensively studied as a minimally invasive approach to enhance transdermal drug delivery [133]. These miniaturised structures are capable of facilitating drug delivery by means of overcoming the stratum corneum barrier without reaching the nerve endings that elicit pain [134]. A wide range of materials have been used for MN fabrication, such as silicon, metal, glass, ceramic and various polymers [135]. Polymeric MNs are gaining attention due to their biocompatibility, biodegradability, strength and optical clarity. Fabrication of these polymeric MNs is commonly accomplished by mould-based techniques (e.g., casting, injection moulding), which allows the use of master templates several times [136]. However, these approaches are generally complicated, time-consuming, difficult to scale up and could be expensive when it comes to new design screening. Although FDM 3D printing has been previously employed to fabricate MNs using biocompatible materials, such as polylactic acid, its poor resolution hindered the

feasibility of producing sharp MNs [136]. By utilising vat photopolymerization, the fabrication of MNs becomes a one-step process, time- and cost-effective without compromising the printing resolution. Previously, an indirect “Print & Fill” fabrication method of customisable MN master was reported for mould-making using SLA 3D printing [102]. Although it is a two-step approach, the fabricated MNs had sharp tips within the sub-millimetre range.

The direct fabrication of personalised MN arrays on curved surfaces via DLP 3D printing was also reported [114]. The MNs fully conformed the undulating surface of the finger and ensured complete insertion for effective drug delivery. Compared to the control of intact skin, enhanced penetration of diclofenac diethylamine gel was observed after treatment with the MN finger splint. Similarly, bioinspired MNs with backward-facing barbs were created to enhance tissue adhesion (Figure 4A) [137].

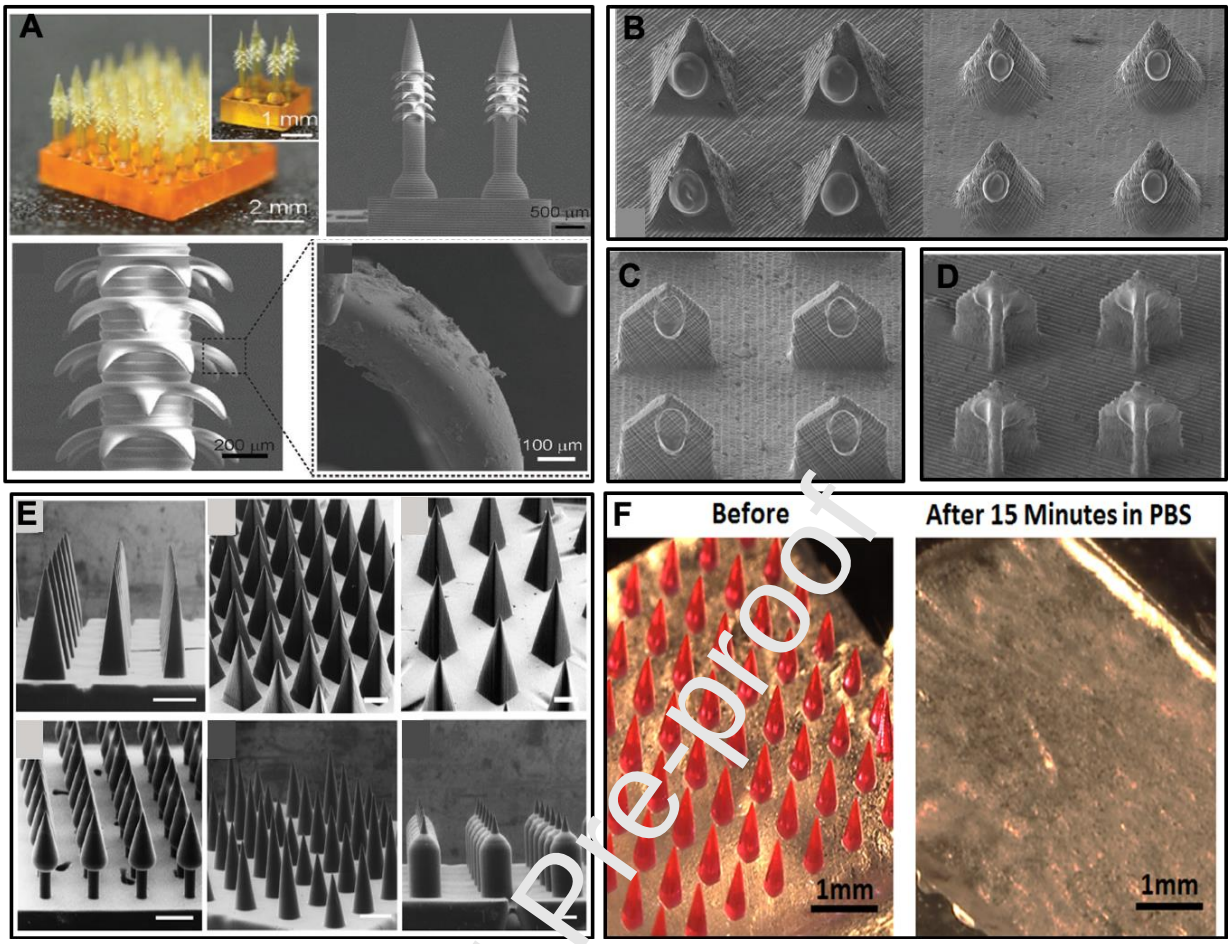

Figure 4. (A) Images and SEM images of SLA 4D printed MN array with backward-facing barbs. Reprinted with permission from [137]. (B) SLA 3D printed MNs with pyramid and cone-shaped design. Reprinted with permission from [103]. (C) SLA 3D printed MNs with spear-shaped design. Reprinted with permission from [104]. (D) SLA 3D printed MNs with cross-shaped design. Reprinted with permission from [105]. (E) CLIP 3D printed MNs of different shapes. Reprinted with permission from [122]. (F) dissolution of rhodamine B containing CLIP 3D printed polyacrylic acid MNs. Reprinted with permission from [122].

Pyramid- and cone-shaped MN patches were also prepared using an SLA 3D printer, followed by their coating with insulin using ink-jet printing (Figure 4B) [103]. All the fabricated MN arrays demonstrated successful insertion into porcine skin, with the

cone design requiring less force to achieve penetration through the skin. *In vitro* drug release studies showed 90-95% of insulin was released within 30 min. Later on, animal studies also revealed that lower glucose levels was achieved using the insulin-coated SLA 3D printed MN arrays compared to subcutaneous injections (Figure 4C) [104]. Similarly, cisplatin (e.g., anticancer drug) was incorporated onto the surface of MN arrays featuring a cross-shaped design with the same SLA 3D printing method (Figure 4D) [105]. Rapid cisplatin release was shown within 1 h and *in vivo* studies with mice demonstrated remarkable anti-cancer activity and complete tumour regression following the MNs treatment.

In the studies described above, drugs were loaded on the surface of the MNs following their fabrication. Using a single step process, MN arrays were developed via DLP 3D printing, encapsulating 1-2% dacarbazine directly in the poly (propylene fumarate) and diethyl fumarate solutions [115]. In this regard, the preparation of drug-loaded MNs was easier and more convenient. The release of dacarbazine from the MN arrays extended over five weeks, wherein it was well controlled and matched the therapeutic requirements. In another study, rhodamine B and fluorescein were incorporated as surrogate drugs in various photopolymers using the CLIP technique (Figure 4E) [122]. Interestingly, the polyacrylic acid MNs manufactured were water-soluble, where all the loaded rhodamine was released within 30 min in phosphate buffered saline (Figure 4F).

4.3 Tuneable and personalised devices

Vat photopolymerization technologies have also been used to produce patient-specific drug-loaded devices. For example, SLA 3D printed personalised nose-

shaped anti-acne devices containing salicylic acid were previously reported (Figure 5A) [101]. Compared to the same devices manufactured by FDM, the SLA devices showed a better printing resolution and higher drug loading, as well as faster drug diffusion rate.

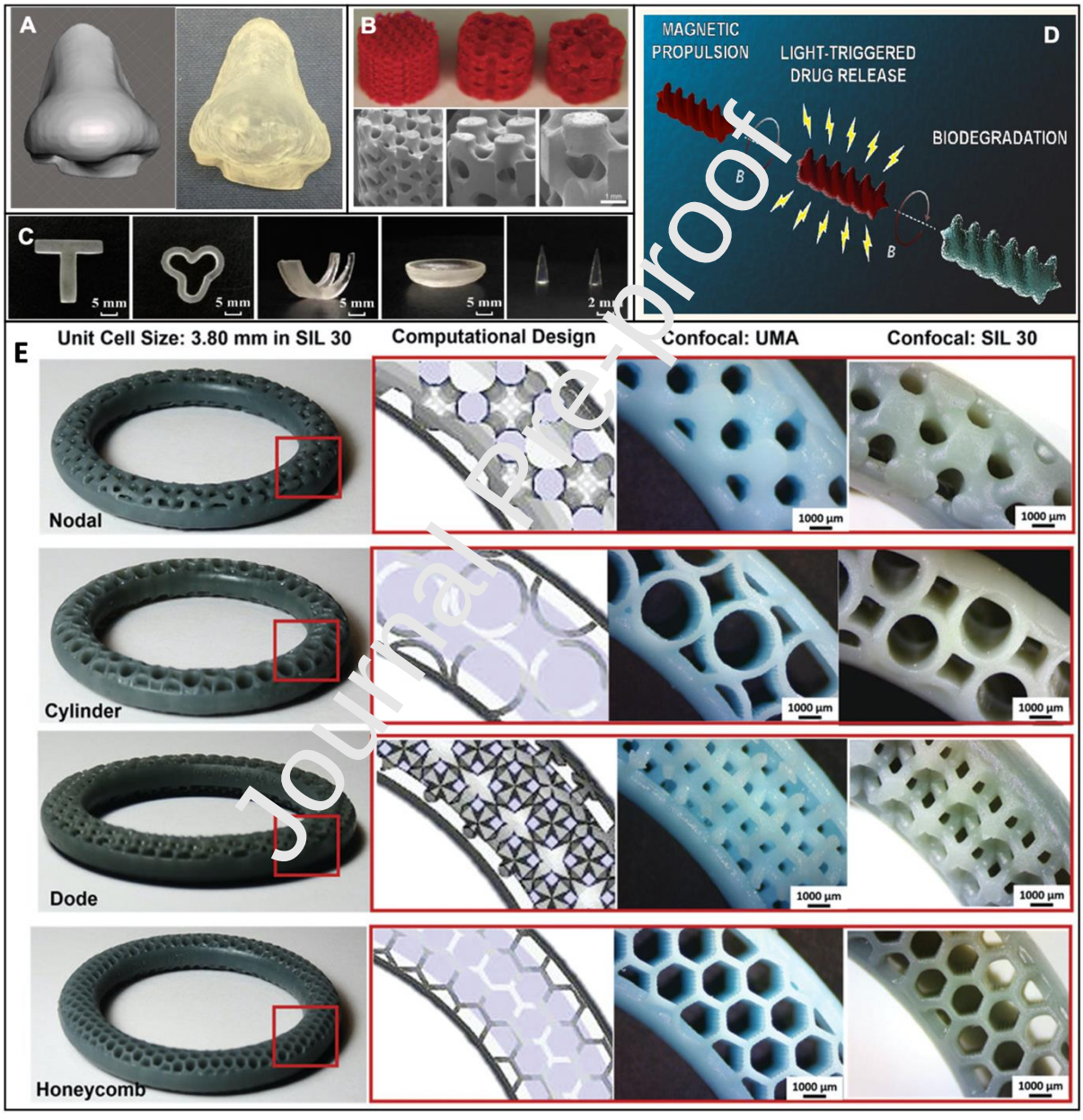

Figure 5. (A) 3D model and image of an SLA 3D printed personalised nose-shaped patch containing salicylic acid. Reprinted with permission from [101]. (B) Visible light photograph and SEM images of CLIP 3D printed model devices of 1, 2, and 3 mm

unit cells (from left to right) loaded with rhodamine B as a surrogate drug. Reprinted with permission from [100]. (C) DLP 3D printed T-, ring-, U-, arc-, and needle-shaped implants (from left to right). Reprinted with permission from [118]. (D) 2PP 3D printed magnetic chitosan microswimmer. Reprinted with permission from [129]. (E) Images, 3D designs and confocal images of intravaginal rings fabricated using a urethane-methacrylated resin (UMA) prototyping resin and a silicone-based resin (SIL 30) with varying unit cell designs, including (from top to bottom) nodal, cylinder, dode and honeycomb, with the unit cell size kept constant at 3.80 mm and band parameters of height = 4.0 mm and thickness = 0.6 mm. Reprinted with permission from [125].

CLIP technology has been employed to fabricate biocompatible drug-loaded scaffolds with controlled release properties (Figure 5B) [100]. In the study, 0.2% (w/w) rhodamine B was first incorporated as a surrogate drug, where *in vitro* release studies showed that different release rates could be obtained by changing the 3D design of the devices. Essentially, the smaller the unit cell of the device, the higher surface area, and hence, the more rapid the drug release. Subsequently, two clinically relevant small molecules, docetaxel and dexamethasone-acetate, were loaded in five different resin formulations based on polycaprolactone dimethacrylate (PCLDMA) and PEGDMA. The release behaviours of both drugs followed the same trend of rhodamine B, wherein it was demonstrated that a tuneable release can be achieved by changing the crosslink density and polymer network compositions. DLP was also employed to fabricate various implants including the T- and ring-shaped samples that can be applied for intrauterine drug delivery, while the U-and arc-shaped devices can be used as femoral cartilage and contact lens (Figure 5C) [118]. On the other hand, the needle-shaped device had a potential application as a

minimally invasive implant. All of the devices mentioned above exhibited sustained release of diclofenac sodium and ibuprofen over 24 h. Similarly, the fabrication of intravaginal rings using the CLIP technology was investigated for the delivery of hormones and microbicides [125]. This novel approach involved designing and creating lattice ring structures with varying internal architectures (e.g., nodal, cylinder, dode and honeycomb) (Figure 5E), permitting the engineering and fine-tuning of the drug release.

Another recent example of precise and effective drug delivery was demonstrated by the use of microswimmers [129]. In this study, magnetically actuated biodegradable chitosan-based microswimmers were fabricated via 2PP 3D printing to achieve on-demand light-triggered release of a chemotherapeutic drug, doxorubicin (Figure 5D). More recently, the fabrication of microreservoir devices featuring anchor-like surface structures for oral drug delivery was reported (Figure 6A) [119]. The surface texture of the microreservoir was found to increase mucoadhesion to the intestinal mucosa by up to two-folds compared to a non-structural control, offering a promising solution to enhance the mucoadhesive performance and potentially, increasing the drug uptake.

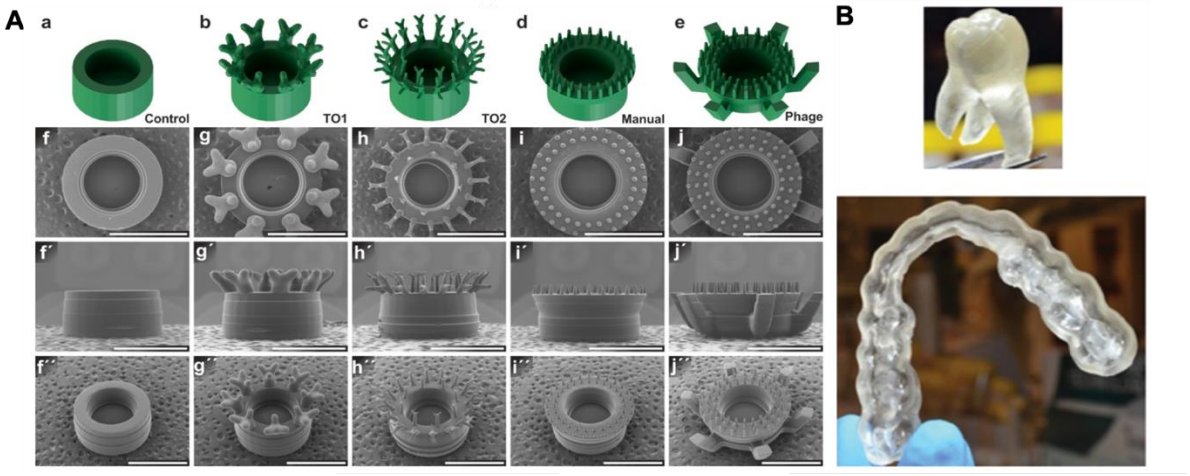

Figure 6. (A) Designs and SEM images of DLP 3D printed microreservoirs with various geometries. Scale bar correspond to 2mm. Reprinted with permission from [119]. (B) SLA 3D printed molar tooth model (top) and clear dental splint (bottom). Reprinted with permission from [111].

4.4 Dental applications

Vat photopolymerization has also been extensively explored within the dental industry for the fabrication of prosthetics and orthodontic applications [138]. Dentca™ Denture Base II was the first FDA approved "light-cured resin indicated for the fabrication and repair of full and partial removable dentures and baseplates" in 2015 [139]. Similarly, in 2017, NextDent™ Denture was approved by the FDA in as a Class- II 3D printing material for the manufacturing of denture bases [140]. Since then, a wide range of biocompatible resins have been commercialised for different applications, including trays, drilling templates, dental models, temporary crowns and bridges, and surgical guides [141, 142]. Compared with mouthguards produced using FDM [41], those fabricated using vat photopolymerization have a higher printing resolution, providing an enhanced fitting and more comfort to the patient. Apart from commercial resins, Yue et al. described SLA 3D printable antimicrobial resins containing diurethanedimethacrylate (UDMA), glycerol dimethacrylate (GDMA), and quaternary ammonium methacrylate, with potential to be used for dental and orthopaedic applications (Figure 6B) [111].

4.5 Printed moulds

Vat photopolymerization 3D printing has also been utilised for the on-demand fabrication of customised moulds, where drug delivery systems can be subsequently

produced to meet the individual needs of patients. This method has shown to be more cost-effective in comparison to other manufacturing technologies, such as injection moulding, especially when the production volume is low [49]. DLP 3D printing was also used to manufacture personalised moulds for non-dissolving suppositories of drug-laden elastomers aimed at rectal and vaginal drug delivery [117]. The geometrical features of the suppositories can be designed to meet the needs of female patients, especially those that suffer from different degrees of vaginal relaxation syndrome or posterior prolapse.

4.6 Oral dosage forms

Although its remarkable resolution and excellent surface finish makes vat photopolymerization more suited for the fabrication of patient-specific medical devices, its applications have also extended to oral drug delivery. A wide range of personalised oral dosage forms has been previously prepared to provide tailored release profiles to suit the individual needs of each patient. Examples of such are summarised in **Table 4.**

Table 4. Examples of oral dosage forms using vat photopolymerization 3D printing technologies

Technology	Drug(s)	Oral dosage form	Material(s)	Ref.
SLA	Paracetamol & 4-Aminosalicylic acid	Tablets	PEGDA 700, PEG 300, TPO	[143]
	Paracetamol & Aspirin	Tablets	PEGDA 700, PCL Triol, TPO	[144]
	Paracetamol	Tablets with different geometries	PEGDA 700, TPO	[145]
	Ibuprofen	Hydrogels	PEGDA 700, PEG 300, TPO, Riboflavin, TEOHA	[146]
	Ascorbic acid	Hydrogels	PEGDMA 550, riboflavin, triethanolamine	[147]

	Naproxen, Aspirin, Paracetamol, Caffeine, Chloramphenicol, Prednisolone	Polypills	PEGDA 575, PEG 300, TPO	[34]
	Atenolol, Hydrochlorothiazide, Irbesartan, Amlodipine	Polypills	PEGDA 575, PEG 300, TPO	[148]
	Capsaicin	Moulds for capsaicin candies	Commercial LCD-type resins (GODSAID Science and Technology Co., Ltd., China)	[149]
	Bovine serum albumin	Specimens	PEGDA 700, LAP	[150]
DLP	Theophylline	Tablets	PEGDA 400, PEGDMA 1000, Irgacure 2959	[151]
	Ibuprofen	Tablets	PEGDA 700, PEG 400, Riboflavin	[152]
	Paracetamol	Tablets	PEGDA 700, PEG 400, TPO, sodium chloride, mannitol	[153]
	Atomoxetine hydrochloride	Tablets	PEGDA 700, PEG 400, TPO	[154]
	Sulforhodamine B	Responsive hydrogels	Acrylic acid, PEGDA, TPO nanoparticles	[155]

The first study to demonstrate the feasibility of SLA 3D printing for the fabrication of oral dosage forms comprised tablets with modified-release characteristics [143]. Paracetamol and 4-aminosalicylic acid loaded 3D printed tablets, thereafter termed Printlets^{TM}, were prepared in a torus shape (Figure 7A). By increasing the concentration of PEGDA in the resin formulation, drug release rates were reduced. This was due to a higher degree of crosslinking, resulting in less molecular mobility in the core of the Printlet and slower drug diffusion through the polymer matrix. Other excipients have been added to manipulate the drug release rates from Printlets, including water [146], poly(caprolactone) Triol [144], mannitol and sodium chloride [153]. Unlike other oral dosage forms prepared from biodegradable or water-soluble polymers, the structure of Printlets made of photocrosslinkable materials, such as PEGDA and PEGDMA, remains intact after the drug release. As such, the Printlets do no degrade and instead will be eliminated from the body in their solid, intact

forms, which may pose risks of intestinal blockage or raise concerns for some patients.

The drug release rate can also be tuned by changing the geometry of the Printlets. Interestingly, Printlets with different shapes but similar surface area to volume (SA/V) ratio do not exhibit significant difference in their release properties (Figure 7B - top). On the other hand, increasing the SA/V ratio of a torus Printlet, increases the drug release rate (Figure 7B - bottom) [145]. Similarly, the drug release rate can also be controlled by adjusting the number of perforations in the printlets (Figure 7C and E) [151, 156].

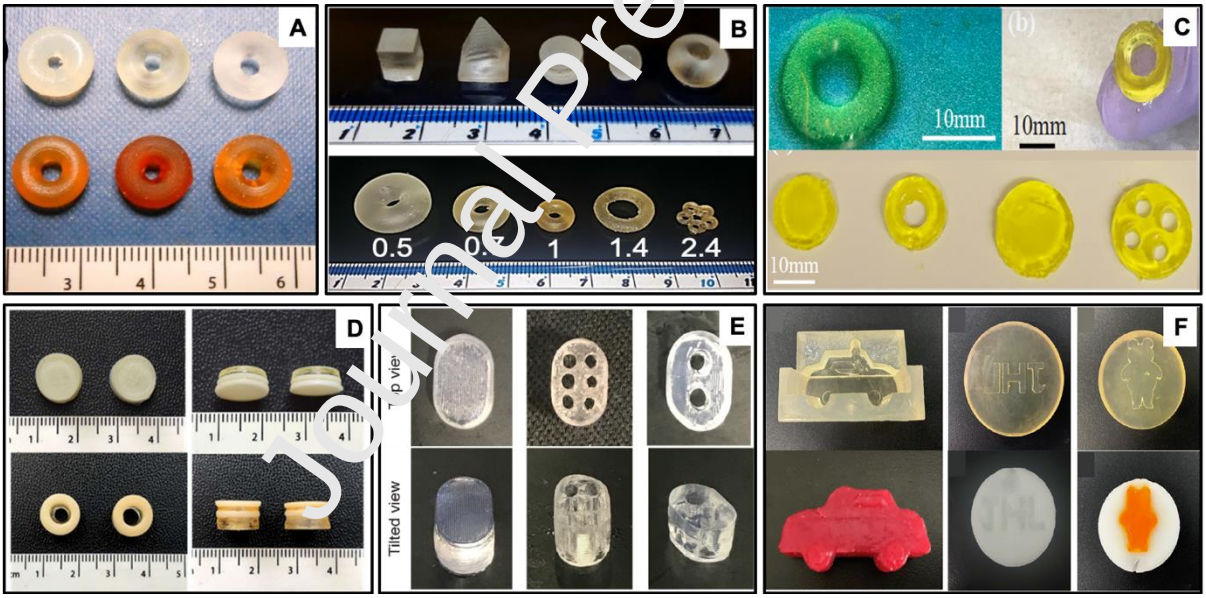

Figure 7. (A) SLA torus Printlets containing paracetamol (top) and 4-ASA (bottom). Reprinted with permission from [143]. (B) SLA Printlets with similar SA/V ratios (top) and SLA torus Printlets with different SA/V ratios (bottom). Reprinted with permission from [145]. (C) SLA 3D printed ascorbic acid-loaded hydrogel tablets in various shapes. Reprinted with permission from [156]. (D) SLA Polyprintlets with cylinder shape (top) and ring shape (bottom) incorporating naproxen, aspirin, paracetamol,

caffeine, chloramphenicol and prednisolone from top to bottom. Reprinted with permission from [34]. (E) DLP Printlets containing no holes, two or six holes (from left to right). Reprinted with permission from [151]. (F) SLA 3D printed moulds with different shapes (top) and the capsaicin candies made from the mould (bottom). Reprinted with permission from [149].

Polypharmacy (the concurrent use of more than five medications) has been an ongoing consideration linked to patient non-adherence and increasing risk of medication errors due to the high pill burden [7]. As such, the concept of polypills was introduced to overcome such challenge where more than one drug is incorporated into a single dosage form. In recent research, SLA 3D printing has shown to be beneficial for the development of 3D printed polypills (herein termed Polyprintlets) owing to its precise and flexible spatial distribution of materials. It was demonstrated that it is possible to produce a Polyprintlet containing six different drugs (naproxen, aspirin, paracetamol, caffeine, chloramphenicol and prednisolone) in separate layers of cylindrical or ring-shaped formulations (Figure 7D) [34]. In the study, the printer software was modified to enable control over the position of the build platform following the pausing of the printing process. This permitted the manual changing of the resin formulation tray during the fabrication process. As such, a polypill Printlet can be easily prepared, whereby the order of the drugs is controlled using the resin formulation in the tank at any particular point. In another study, a Polyprintlet incorporating four antihypertensive drugs, including atenolol, hydrochlorothiazide, irbesartan and amlodipine, was manufactured to deliver a quarter-dose combination therapy, which has been previously shown to have additive therapeutic effects when compared with the standard dose of each

medication alone [148]. Other oral dosage forms examples include hydrogels for drug delivery purposes. pH responsive hydrogels loaded with sulforhodamine B were fabricated using DLP 3D printing [155]. The printed hydrogel tablets exhibited high swelling and faster drug release at higher pH, which could be useful for targeted and delayed release in the small intestines. Furthermore, SLA 3D printing was utilised for the fabrication of personalised moulds for capsaicin candies aimed at the treatment of oral ulcers (Figure 7F) [149].

5. Challenges

5.1 unreacted monomers

Despite photopolymerization-based 3D printing techniques gaining popularity in the medical and pharmaceutical fields, concerns relating to the safety of the resins remains a major drawback. These printing materials are typically composed of (meth)acrylate-based monomers, which are currently not on the generally recognised as safe (GRAS) list [143]. To put this in context, the double-bond conversion rates are usually low (60-90%) but the residue monomers in the uncured state may leach out from the printed parts, causing allergic reactions and cytotoxicity when in direct contact with the human cells [82, 157]. Additionally, the formation of (meth)acrylic acid from the hydrolytic degradation of the (meth)acrylate network may decrease local pH and negatively affect the surrounding tissues [62, 158].

To overcome this challenge, a logical approach would involve the removal of the residual monomers after printing, which can be achieved by post-washing and post-curing. Isopropyl alcohol (IPA) is the most common organic solvent used to wash out uncured liquid resin off the printed parts. However, it is highly volatile and flammable

[159]. Moreover, both IPA and its metabolite, acetone, act as central nervous system depressants, wherein the absorption of IPA can occur through oral, nasal or topical routes, posing high risks of poisoning. Recently, tripropylene glycol monomethyl ether has been proposed as a viable alternative, due to its non-flammability and non-toxicity. Yet, it requires longer periods of time to fully dry. Post-washing can be a concern when the drug delivery system is directly fabricated with drug incorporated in the printing resin. This is because the drug on the surface or within the printed parts can be washed away, resulting in inaccurate drug loading and hence the loss of therapeutic efficacy. In recent years, extensive research has been undertaken to evaluate the effect of exposure to SLA 3D printed parts, wherein zebrafish embryos have been used in *in vivo* studies due to their genetic relevance to humans. It was shown that the degree of conversion and the survival rates of embryos increased when the SLA printed parts were treated with ethanol or UV light [157, 158].

Apart from the washing, post-curing is also necessary to ensure the full conversion of the photoreactive monomers [160]. However, the drug release rate might be altered when this step is applied as the crosslinking density is increased, making more difficult for the drug to diffuse out of the formulation [143, 151]. Recently, a study reported the conversion rates of epoxy groups can be significantly increased from ~75-80% to 94-95% after 2 h of thermal dark curing treatment at 120°C and 140°C [161]. In the case of acrylate groups, the conversion rates were only ~65-70% after UV curing. However, 8 h of thermal treatment can boost the final conversions to 85-95%. Previously, potential toxic residues (e.g., monomers, low molecular weight oligomers, etc.) were removed from the polymer composites by treatment with supercritical carbon dioxide [162]. The biocompatibility of the material was

dramatically enhanced and at the same time, the supercritical fluid processing provided a novel approach to introduce interconnected microporosity required for bone implants. Alternatively, reduced cytotoxicity can be achieved using high temperature heating in a nitrogen atmosphere, resulting in the sublimation of unreacted materials and their diffusion out of the cured polymer [163].

Fourier transform infrared (FTIR) is one of the widely applied techniques for the quantification of conversion rates. Spectroscopically, the decrease of aliphatic carbon-carbon double (C=C) would cause a decrease in the peak at 1637 cm^{-1} [164]. The degree of conversion (DC) can then be calculated as the ratio between the peaks of the aliphatic C=C (peak at 1637 cm^{-1}) to the aromatic C-C (peak at 1610 cm^{-1}), before and after curing [165, 166]. There are also other approaches that have been previously reported for the quantification of the extent of conversion. Examples of such include differential scanning calorimetry (DSC) [167, 168], high-performance liquid chromatography (HPLC) [169, 170], near-infrared (NIR) spectroscopy [171], Raman spectroscopy [172, 173], and solid state nuclear magnetic resonance (NMR) [174].

5.2 Drug-photopolymer reactions

As discussed above, when directly incorporating a drug into a liquid resin for printing, the drug-loaded devices or oral dosage forms manufactured via vat photopolymerization 3D printing are only effective when the drug remains intact and effective before it is released. In a recent study, it was revealed that an unexpected chemical reaction occurred between the model drug and the photopolymer [148]. FTIR and NMR spectroscopy confirmed the presence of a Michael addition reaction

between the primary amine group of amlodipine and the diacrylate group of the photoreactive monomer, PEGDA, thus, highlighting the importance of polymer screening towards the development of drug-loaded drug delivery systems using vat photopolymerization techniques. It should be noted though that there could be other drugs or monomers serving as Michael donors or receptors, having the potential to undergo Michael reactions, or even other types of chemical reactions. As such, additional tests should be performed to ensure the drug stability in the resin mixture prior, during and following the printing process.

5.3 Unintended temperature increase

The exothermic nature of the photopolymerization reaction and heat transmitted from the light source to the materials may trigger a rise in temperature during printing [175]. When the exothermic heat released during photopolymerization was measured in-situ, it was found that a temperature surge occurs during the first 3 s of light curing, reaching up to around 55°C [176]. In addition to that, although most of the vat photopolymerization 3D printers operate at room temperature, due to their extended operation times, it is possible that the area around the resin tank may undergo a rise in temperature. This is critical in the case of thermolabile drugs or biologicals, particularly when they are directly incorporated into the resin mixture for the preparation of drug delivery systems [42]. Nonetheless, there were no reports on drug degradation thus far and vat photopolymerization is still considered as a suitable 3D printing technology for thermosensitive drugs [143].

5.4 Printing optimisation

Unlike powder bed-based 3D printing techniques, such as binder jetting and selective laser sintering, where a bed of powder serves as the inherent support material, it is challenging to use vat photopolymerization 3D printing to fabricate overhanging parts or objects (e.g., structures that extend outwards and over low levels without being supported by a previous layer) [177]. As a result, this might often lead to the warping or collapsing of structures during the printing process. Therefore, re-orientation and temporary supports need to be incorporated into the CAD design to minimise the overhung area. However, this increases the materials required for printing and makes the process more costly. Furthermore, the removal of the supports makes the process labour-intensive and time-consuming, wherein undesired marks can remain on the surface of the object, reducing its overall quality [178].

On the other hand, when fabricating objects with internal voids, for example microfluidics or hollow microneedles, the liquid resin trapped within the hollow cavity could solidify and block the space [179]. This is because the trapped uncured material could receive and absorb light during the printing of subsequent layers. Thus, the overall dimensions of the void could be affected. As such, the void space should be properly designed for a given resin, followed by adequate flushing with an appropriate solvent immediately after the end of the fabrication process and prior to the post-curing step.

5.5 Regulatory challenges

Regulatory approval remains another barrier that may hinder healthcare applications of vat photopolymerization 3D printing. Although a number of biocompatible 3D

printing resins have been cleared by the FDA for dental applications, thus far, no resins have been approved for use within medicinal products [180]. However, it is unlikely that a resin can be approved for the universal use with any drug. Instead, it is anticipated that the approval of a resin to be used to print medicines will require a case-by-case review approach, wherein the approval should be granted specific to each drug product, under specific printing and post-processing conditions (e.g., washing and post-curing). To date, FDA regulations are based on mass production, standardisation and batch validation, which do not apply to the manufacturing of personalised medicines [181]. Therefore, there is a need for establishing appropriate requirements for 3D printed medical devices and drug products in terms of various technical aspects, including material controls, process development (hardware and software) and final product validation.

In 2017, the FDA issued a guidance on technical considerations for medical devices manufactured using additive manufacturing/3D printing [182]. The guidance outlines design and manufacturing process considerations including, device design, material controls, post-processing, and process validation and recommendations for testing and characterising the 3D printed products. However, technical considerations relating to 3D printed devices derived from or incorporating biological, cellular, or tissue-based products were not addressed. Therefore, additional regulations concerning 3D printed products for drug delivery purposes are expected to be issued in the future.

Furthermore, due to the absence of concordance between the FDA and the European Medicines Agency (EMA), the regulatory burden on manufacturers to

satisfy different sets of regulatory frameworks inflates. As such, it is crucial to bridge these regulatory gaps to progress this technology into clinical practice.

6. Conclusion and future outlook

Since its conception nearly 30 years ago, 3D printing has been forecast to transform the industrial world. Its integration into clinical practice could introduce a digital transformation within healthcare, reshaping the medicine design and production system. Within healthcare, the high feature resolution and excellent surface finish obtained using vat photopolymerization 3D printing makes it particularly beneficial for the development of novel drug delivery approaches and medical devices. Vat photopolymerization enables the creation of drug laden products with exceptional structural and functional designs, which cannot be produced using conventional production methods or other printing technologies.

Within pharmaceutics, the most valuable use of vat photopolymerization could include the design and engineering of drug delivery devices for organ targeted treatments. This could be achieved by combining 3D scanning to obtain real-time images of patient organs and utilising them for the fabrication of patient-specific systems. In doing so, the tailored systems could provide superior action within the site of action, improving the efficacy of treatment. Furthermore, by personalising the drug dose and dosing regimen, the additional benefit of improved medication adherence could also be attained. The technology can be further enhanced by integrating novel principles such as 4D printing and artificial intelligence [28, 29, 183], wherein the functionality of the Printlets could be uplifted by performing timely actions. Due to the ability of vat photopolymerization to create objects in different

sizes, ranging from the microscale all the way to full organs, it can provide a novel and practical way to treat tumours or complex medical conditions. As an example, robotic drug reservoirs can be 3D printed in dimensions suitable for insertion into the body, after which they are controlled remotely or are biologically mediated into the site of action. Once in the site of action, the drug reservoirs release all their content and are evacuated or release part of their content in a timely manner and reside in the body until they fulfil their action.

This technology can also be implemented throughout the drug development timeline, including preclinical development and clinical trials. As an example, within the early phases multi-drug iterations could be produced, enabling easy and rapid fine-tuning of the formulation in the drug development phase. Similarly, Printlets can be easily modified to meet the specification and requirements of different animal models, enabling them to be tested efficiently and providing more representative data. Within clinical studies, this technology can be used for blinding (e.g., a practice that is used to prevent a clinical trial participant from being aware which medicine they are taking) and taste-masking (e.g. a method used to conceal bitter or unpleasant tastes of medicines) purposes.

Although large-scale production using vat photopolymerization is currently not feasible, its importance in the field of personalised medicines should not be overlooked. Moreover, with the continuous growth in the fields of medical and pharmaceutical 3D printing, it is becoming evident that further action is needed to transform the notional benefits of this technology into reality. One main outstanding challenge relates to the availability of photocurable biomaterials, which limits the

exploitation of vat photopolymerization in healthcare applications. However, as the exploration of advanced materials is constantly growing, the development of novel biocompatible resins with superior performance will perhaps be foreseeable in the near future. Furthermore, current commercial 3D printers do not abide by Good Manufacturing Practice (GMP) requirements, which are the minimum standard guidelines recommended by medical agencies that a manufacturer must meet to ensure the quality of the final product. The regulation of utilising 3D printers to fabricate healthcare products remains another unmet need that should be addressed and resolved. Only after overcoming these major barriers to the integration of vat photopolymerization within clinical practice, its true potential within healthcare will be realised.

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Graphical abstract: