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Polymeric drug delivery systems by additive manufacturing

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ABSTRACT

Additive manufacturing (AM) is gaining interests in drug delivery applications, offering innovative opportunities for the design and development of systems with complex geometry and programmed controlled release profile. In addition, polymer-based drug delivery systems can improve drug safety, efficacy, patient compliance, and are the key materials in AM. Therefore, combining AM and polymers can be beneficial to overcome the existing limitations in the development of controlled release drug delivery systems. Considering these advantages, here we are focusing on the recent developments in the field of polymeric drug delivery systems prepared by AM. This review provides a comprehensive overview on a holistic polymer–AM perspective for drug delivery systems with discussion on the materials, properties, design and fabrication techniques and the mechanisms used to achieve a controlled release system. The current challenges and future perspectives for personalized medicine and clinical use of these systems are also briefly discussed.

1. Introduction

A drug delivery system can be defined as a method or process using the principles of chemistry, engineering and biology for administering of pharmaceutical compounds with high therapeutic effects. Currently, there are high demands for designing modified release drug delivery systems for reducing frequency of dosing and increasing the efficiency of the drug at the required site to minimize its side effects [1,2]. Until now, considerable advances have been made in the development of different sustained and controlled drug delivery systems based on polymers [3,4]. Advancement in drug delivery systems have been significantly achieved by using polymers, enabling both hydrophilic and hydrophobic drugs to be delivered over an extended period of time to the site of action [5]. Improved drug safety and efficacy and patient compliance can be obtained using polymer-based drug delivery systems. These systems are designed to maintain the therapeutic levels of the drug, reduce the side-effects and drug dosage, and to facilitate the delivery of drugs with short *in vivo* half-lives [6].

Several methods have already been used for providing sustained or controlled release polymeric drug delivery systems, such as polymer encapsulation and polymer bound drug systems [4,7]. However, there is still a need towards developing more controlled and even tailored release profiles. Layer-by-layer additive manufacturing (AM) techniques enable rapid production of novel personalized drug delivery systems, where conventional manufacturing is impractical due to cost and design limitations. AM is one of the emerging megatrends that has progressed remarkably in the last few years. With the ability of mass customization, on demand supply, individualized dosing, and flexibility with drug combinations, AM offers great potential for the pharmaceutical sector. Through AM, various drug delivery systems

Abbreviations: 5-FU, 5-fluorouracil; APIs, Active Pharmaceutical Ingredients; ASS, Acetylsalicylic acid; AM, Additive manufacturing; ASTM, American Society for Testing and Materials; CBZ, Carbamazepine; CLIP, Continuous liquid interface production; CAD, Computer-aided design; CIJ, Continuous Inkjet; CT, Computer tomography; DPE, Direct powder extrusion; DLC, Diode laser curing; DLP, Digital light processing; DoD, Drop-on-demand; EC, Ethyl cellulose; EVA, Ethylene vinyl acetate; FIH, First in human; FDA, Food and drug administration; FDM, Fused deposition modeling; FFF, Fused filament fabrication; GIT, Gastrointestinal tract; HME, Hot melt extrusion; HPC, Hydroxypropyl cellulose; HPMC, Hydroxypropyl methylcellulose; ISO, International Organization for Standardization; IUS, Intrauterine system; LEV, Levetiracetam; MRI, Magnetic resonance imaging; MNs, Microneedles; MHDS, Multi-head deposition system; MJF, Multi jet fusion; HPMAM, N-(2-hydroxypropyl)methacrylamide; PDEA, Poly((2-diethylamino)ethylmethacrylate); PAA, Polyacrylic acid; PCL, Polycaprolactone; PDLA, Poly(D-lactic acid); PDLLA, Poly(D,L-lactic acid); PDMS, Polydimethylsiloxane; PEG, Poly(ethylene glycol); PEGDA, Polyethylene glycol diacrylate; PLA, Poly(lactic acid); PLLA, Poly(L-lactic acid); PLGA, Poly(lactic-co-glycolic acid); pNIPAM, Poly(N-isopropylacryalamide; PU, Polyurethane; PVP, Polyvinyl pyrrolidone; PBF, Powder bed fusion; PAM, Pressure assisted microsyringe; SLS, Selective laser sintering; SLA, Stereolithography; SSE, Semi-solid extrusion; SA/V, Surface area/volume; TBP, Tribasic phosphate sodium; 2PP, Two-photon polymerization; VA, vinyl acetate.

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can be fabricated with several predesigned sizes, shapes, material and drug combinations [8–10].

Various AM methods, such as binder jetting, fused deposition modeling (FDM), selective laser sintering (SLS), and stereolithography (SLA) enable the production of high resolution and complicated drug delivery systems with custom-designed geometries, which were not easy to obtain with conventional techniques [11,12]. In addition, multi-component AM under mild conditions has become possible. Approval of first binder jetting AM printed oral tablet formulation (Spritam® by Aprecia) for anti-epileptic drug levetiracetam by Food and Drug Administration (FDA) for commercial markets, represented introduction of AM technologies in the pharmaceutical sector [13].

AM can enable customization, enhancing system flexibility and adaptability right from the early product development phase to the 'first in human (FIH)' stages [14], enhancing product optimization, decreasing lead times and related costs. Traditional formulation processes are labor intensive, slow and rigid for development of investigational dosage forms. In contrast, AM enables rapid product development and optimization, allowing high flexibility in developing early phase experimental dosage forms to analyze solubility, stability, bioavailability, drug combinations, dose flexibility, and release kinetics of drugs [15,16]. In addition, AM allows for the preparation of drug delivery systems with shapes, sizes, colors and flavors which are optimized to the preference of patients, potentially increasing patient compliance [17–19].

Recently, researchers have explored AM to achieve release of multiple drugs from a single tablet (multilets), and to obtain a programmed drug release profile, by combining FDM and injection molding [20], directly printing specific architectures [21,22]. Depending on the drug properties, physiological and environmental factors, these architectures can be readily customized to achieve a required release profile. The release of pharmaceutical agents must be based on the understanding of the underlying release mechanisms and their specific phenomena.

This review provides a comprehensive overview of the topic discussing the chemical, physical and fabrication aspects and their importance for AM pharmaceutical delivery systems. After the initial introduction on the basic requirements of polymeric drug delivery systems and the mechanisms to achieve controlled release of the drugs, the design aspects of the AM approaches are highlighted. Next, the most extensively and recently used AM techniques for development of polymeric drug delivery devices are presented by discussing the materials, design and fabrication techniques and some prominent case studies regarding different delivery systems. Furthermore, the challenges faced by AM drug delivery systems and the future perspectives on the possibilities for more advanced polymer-based drug delivery systems utilizing AM techniques and the technological developments required to provide more patient friendly, safe, efficient, and personalized therapies in clinics are discussed.

2. Polymeric drug delivery systems

2.1. Design of a polymeric modified release system

In a polymer based drug delivery system, a polymer is used to achieve a predicted controlled (zero order) or sustained (first order) drug release from the system [23], maintaining persistent therapeutic levels of drug systemically, minimizing the dosing frequency. These systems can be categorized into: (i) matrix, (ii) reservoir, and (iii) conjugated systems.

Matrix based systems are most simple to generate, making them one of the largest explored systems in AM based drug release systems. In a matrix system, the drug can be either in a dissolved or in a dispersed (amorphous/crystalline) phase, depending on the polymer-drug solubility and concentration of the drug. In addition to drug-polymer interactions, and drug concentration, drug release from a matrix-based system, can be governed by the geometric design of the system. The multiplexity and flexibility of AM can provide more precise control over the release profile from a delivery system [24–26].

The reservoir-based systems differ from matrix-based systems in their basic design, containing drug as a solid core enclosed by a polymeric membrane. The drug diffusion rate across the membrane governs the release profile. Unlike the matrix-based systems, as the dimension of these systems doesn't change significantly with time, they provide almost zero-order constant release. However, concern of membrane rupture induced dose dumping, and post-usage system retrieval limits their usability.

Covalently conjugating the drugs with the polymers is another approach employed to control the release profile and prolong the residence time of a drug in the body. Poly(ethylene glycol)-drug conjugates increase the overall circulation time, reducing both dose and the frequency of administration [27,28]. The conjugation/sequestration of drugs with self-assembling polymeric nanoparticles (e.g. cyclodextrins, block copolymers) [29] leads to drug loaded micellar and nanoparticles. A diffusion or degradation-based mechanism can provide controlled release of the entrapped drug from these systems. Additionally, the linker chemistry (e.g. "S-S" disulfide) of active agents conjugated to polymeric nanocarriers enables predefined loading and release kinetics from nanoparticle-drug conjugates. By employing a stimuli responsive (smart) polymer (poly(*N*-isopropylacryalamide (pNIPAM), poly((2-diethylamino)ethylmethacrylate) (PDEA)) an intelligent controlled release system can be generated [30,31].

2.1.1. The matrix and geometric design

In addition to the nature of the drug and the polymer matrix properties, 3D geometric design of the release system plays an important role in governing the release of a drug from a system. These dimensional parameters of a system also play a deciding role in the route and site of delivery. Several mathematical models, such as Higuchi [32], Korsmeyer [33], Peppas [34], and Korsmeyer-Peppas (Power-law) [33] models, are available to predict drug release from polymeric systems. These models can be easily extrapolated to predict drug release from complex 3D architectures. With AM more complicated geometries with better control over the pore size, pore architecture, and wall thickness, exposed surface area, pore interconnectivity, the diffusion/erosion rates can be generated. This enables better control over the release profile. Using AM, structures with predefined and programmed drug release at a defined rate over a specified timeframe can be developed. Sun et al. demonstrated that drugs can be released in an increasing, decreasing or pulsatile pattern, using specifically designed drug loaded 3D polymeric architectures [18]. In another preliminary study, Goyanes et al. [8] observed that the release kinetics were independent of the exposed surface area of the structure (cube, pyramid, cylinder, sphere and torus), but dependent on the surface area to volume ratio from FDM printed eroding matrices. More complex 3D printed geometries were evaluated to achieve a programmed drug release in an increasing, decreasing or pulsatile manner [21,22]. In another study, Kadry et al. [35] investigated the effect of the geometry on drug release profiles from FDM printed hydroxypropyl methylcellulose (HPMC) tablets. By varying the geometric parameters, patterns and infill densities of a drug containing core, they achieved an increasing/decreasing and pulsatile- release profiles from the tablets. It was observed that an increase in either porosity (low infill density), or an increased surface area, enhanced the release rates. Infill architecture also influenced the release kinetics. Additionally, printing a core with

alternating drug containing and drug free polymer layers in a radial diametric fashion lead to tablets with pre-programmed release profiles [35]. Using AM and smart design, patient specific desired drug release profiles can be achieved as a personalized approach.

Moreover, the size of drug carriers influences *in vivo* performance, often determining the mode of drug administration, which depends on the site of use. In addition, from the AM process point of view, the size of printed structures is important and can affect the process of printing and drug release rate. AM techniques provide dimensional flexibility, the size of AM drug delivery systems can be easily manipulated to achieve the intended action. Awad et al. [36], prepared dual miniprintlets in two different sizes by SLS: 1 mm and 2 mm. The time needed to print one batch of 100 dual miniprintlets with the size of 1 mm was lower than that of dual miniprintlets with the size of 2 mm and the 1 mm miniprintlets displayed a higher precision in weight when compared to the 2 mm miniprintlets. In addition, by increasing the diameter of the miniprintlets the drug release rate was decreased. This confirms that the size of drug delivery systems can also influence the release profile [37].

2.2. Mechanisms of controlled release from polymeric matrices

Drug release strategies are designed depending on chemical, physical, biological, and engineering aspects, controlling the spatiotemporal release. Considering the physical and chemical properties of both the drug and the matrix, the major mechanism used are diffusion, erosion, swelling, and osmosis. Fig. 1 displays few of these processes.

2.2.1. Diffusion

Diffusion is a concentration gradient driven mass transfer process. In a diffusion controlled release system, post-solubilization the diffusion kinetics of a drug molecule is the rate limiting step [38,39]. In a diffusion mediated controlled release system, the drug can either be dispersed or dissolved in the polymeric matrix itself forming a monolith system (Fig. 2a). Or a drug containing core is enclosed by a polymeric membrane, generating a reservoir (Fig. 2b) system. In a monolithic system, if the drug is already dissolved in the matrix, it can lead to initial burst release from the surface. Additionally, as the mean diffusion distance before release increases with time in monolithic systems, the device geometry plays important role in drug release. On other hand, in a reservoir system, diffusion across polymeric membrane enclosing drug saturated core governs release rate. Drugs can be present either in a dispersed or dissolved phase within the reservoir. A constant concentration gradient is maintained in the membrane until the reservoir gets depleted, maintaining zero order release kinetics [40]. However, these devices pose a great risk; if the membrane gets damaged it will lead to a highly undesired dose dumping situation.

Polymer-drug permeability plays important role in both monolithic (Fig. 2a) and reservoir type controlled drug release systems (Fig. 2b) [40]. Factors such as change in temperature, composition of matrix (i.e. by additives), size of the molecule, and the presence of water molecules affect diffusivity [41,42].

2.2.2. Swelling

Swelling as a drug release mechanism can be used both in polymer matrices and crosslinked polymer networks [43]. Drugs are dissolved or dispersed in a matrix where it has limited diffusivity. When the polymeric matrix is surrounded with a suitable solvent, the solvent penetration into the polymeric network induces change in the matrix volume [44,45]. Forces such as entropy changes, hydrophilic/hydrophobic interactions, electrostatic/ionic interactions, and osmotic stress influence solvent diffusion into the polymer network, leading to solvation and polymer chain disentanglement and polymer swelling. In a crystalline polymeric network, this leads to a transition of the network from glassy state to an expanded rubbery state referred to as gel. The expansion in polymer volume generates gaps between polymer chains consequently increasing the mass flow of the solvent, and drug diffusivity. The release rate from these systems depends on surface area and degree of swelling. If the solvation leads to a complete dissolution of the matrix, these are called swellable-soluble matrices [46,47]. Using a combination of glassy polymers, additives and incorporation of crosslinks, dynamic swelling and drug release from a system can be appropriately modulated.

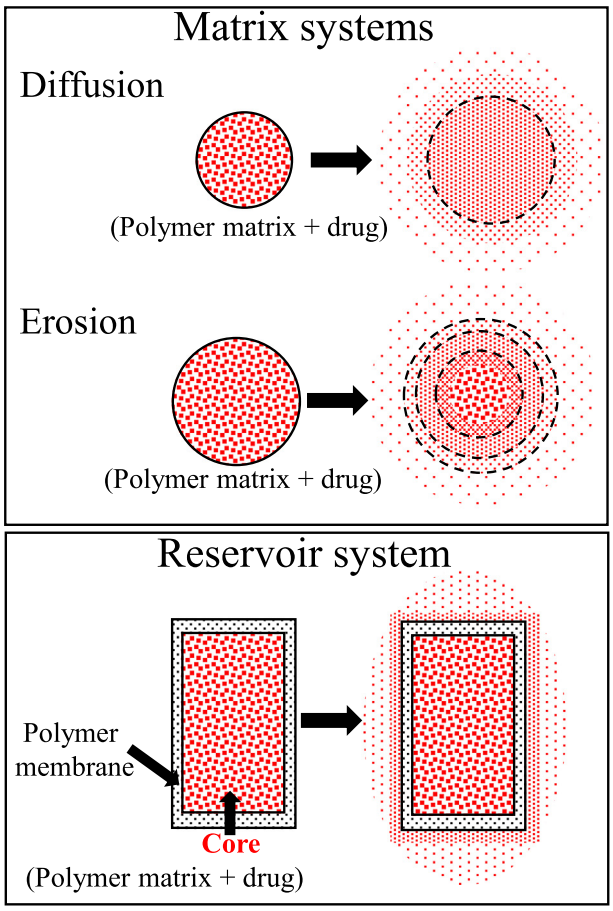

Fig. 1. Schematic representation of drug release mechanisms involved in different release systems.

2.2.3. Erosion

An eroding polymer matrix is preferred for implantable controlled release system [48]. As the matrix get eliminated by erosion, there is no need of retrieval post implantation. However, issues such as resorbability and toxicity of the degrading products also become important. Another advantage provided by eroding matrices is their ability to deliver large biomacromolecules in the form of an implantable system [49,50]. A drug molecule embedded in an eroding matrix only gets released upon hydrolytic degradation of the matrix. The degradation of a polymer matrix depends on both the rate of water penetration into the matrix and the rate of hydrolytic cleavage [51]. If water cannot readily penetrate into the matrix (e.g. polyanhydrides), a surface erosion behavior is observed [43,52]. Whereas if water penetrates more rapidly than the degradation rate of the matrix it induces bulk erosion and collapse of the network [53]. For certain polymers, for instance poly (lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA), the

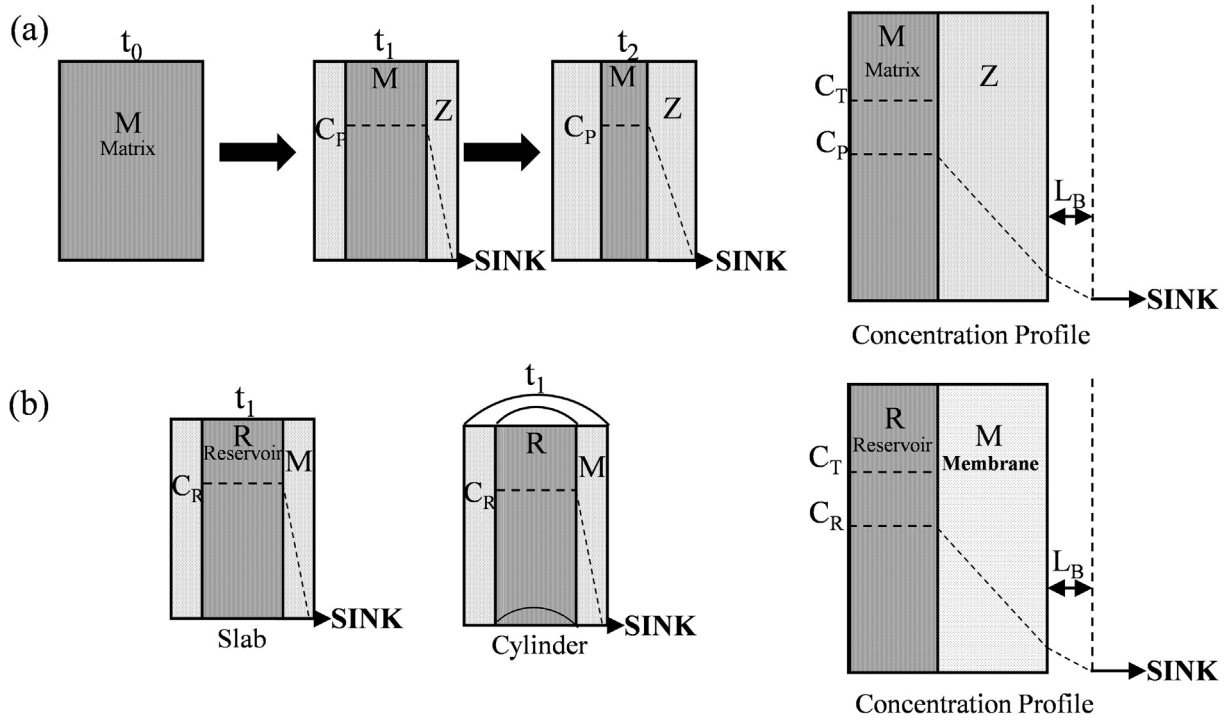

Fig. 2. Monolithic and reservoir release systems. (a) Schematic representing development of concentration profile with time in a monolithic system. M = drug containing matrix; C_P = drug solubility in matrix; C_T = total loaded drug concentration; Z = zone of depletion containing dissolved drug; L_B = boundary layer. (b) Schematic representing development of concentration profile with time in a membrane enclosed reservoir device. R = drug containing reservoir matrix; C_R = drug solubility in reservoir matrix; C_T = total loaded drug concentration; M = diffusion membrane; L_B = boundary layer. adapted from [40]

acidic degradation products themselves catalyze hydrolysis, leading to an autocatalytic degradation.

Controlled release kinetics from an erosion-based system can be achieved using suitable geometric design. A slab-based design surface eroding matrix demonstrated approximately zero order release. In contrast, a cylindrical or spherical construct demonstrated a decrease in release due to reduction in surface area. Bulk eroding matrices demonstrate rapid release of drugs in later phases due to bulk disintegration. PLGA based eroding matrices have been developing for controlled release of macromolecules from 3D printed implants [54].

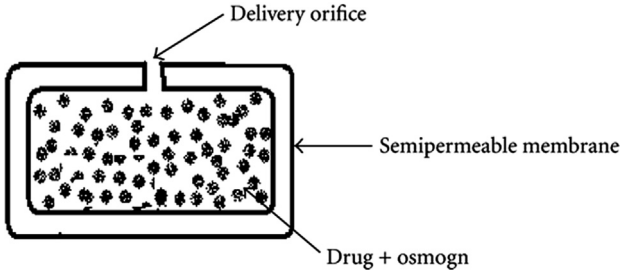

Fig. 3. Schematic representing a simple osmotic pump system [55].

2.2.4. Osmosis

Osmosis mediated controlled release systems are also used for drug delivery applications. Several different prototypes for osmotic pumps based system are developed [55].

However, basically in all osmotic pump based controlled release system, a drug and an osmogen are compacted to form core compartment, which is enveloped by a semi-permeable membrane (Fig. 3). The membrane selectively allows only inward flow of the solvent under osmotic gradient. This inward flow of the solvent leads to dissolution of the drug molecules, which gets released out of the system under the hydrostatic pressure at a constant rate through an orifice present in the system. However, these systems are highly complicated to fabricate, where membrane rupture can lead to dose dumping and are mostly manufactured using conventional approaches. Recently an AM prototype for osmosis mediated delivery of diltiazem was reported [56].

2.2.5. Polymer-drug conjugates

A polymer-drug conjugate can contain one or more drugs covalently conjugated to a polymer chain. Drug PEGylation is widely known, where a drug is conjugated with PEG to prolong the residence time of the drug in the body [57]. This has enabled reduction in dose as well as the frequency of administration [27]. Polymer conjugation also provides protection from enzymatic degradation to the sensitive drugs [57]. In addition to PEG, dextran, N-(2-hydroxypropyl)methacrylamide (HPMAM)-, poly(glutamic acid)-, and polysarcosine- are also employed to deliver highly potent cytotoxic molecules [27,28].

Drugs can be conjugated to linear, branched or hyper branched (dendrimers) polymer structures (Fig. 4). Depending on the type of crosslinker between drug and polymer a pH, enzymatic or reduction sensitive target site specific drug release can be achieved. However, the conjugation/sequestration of drugs with polymers self-assembling in micellar or nanoparticle architectures (e.g. cyclodextrins, block copolymers) provides specific advantages for controlled delivery [27,29,58]. These enable intracellular drug delivery, overcoming various biological barriers. The drug conjugation to polymeric nanocarriers enables a predefined and high drug loading into self-assembled 3D architectures. Additionally, the release of entrapped/sequestered drug via diffusion or degradation of the polymeric nanoparticle provides a more precise controlled release than achieved from a physically entrapping system [59].

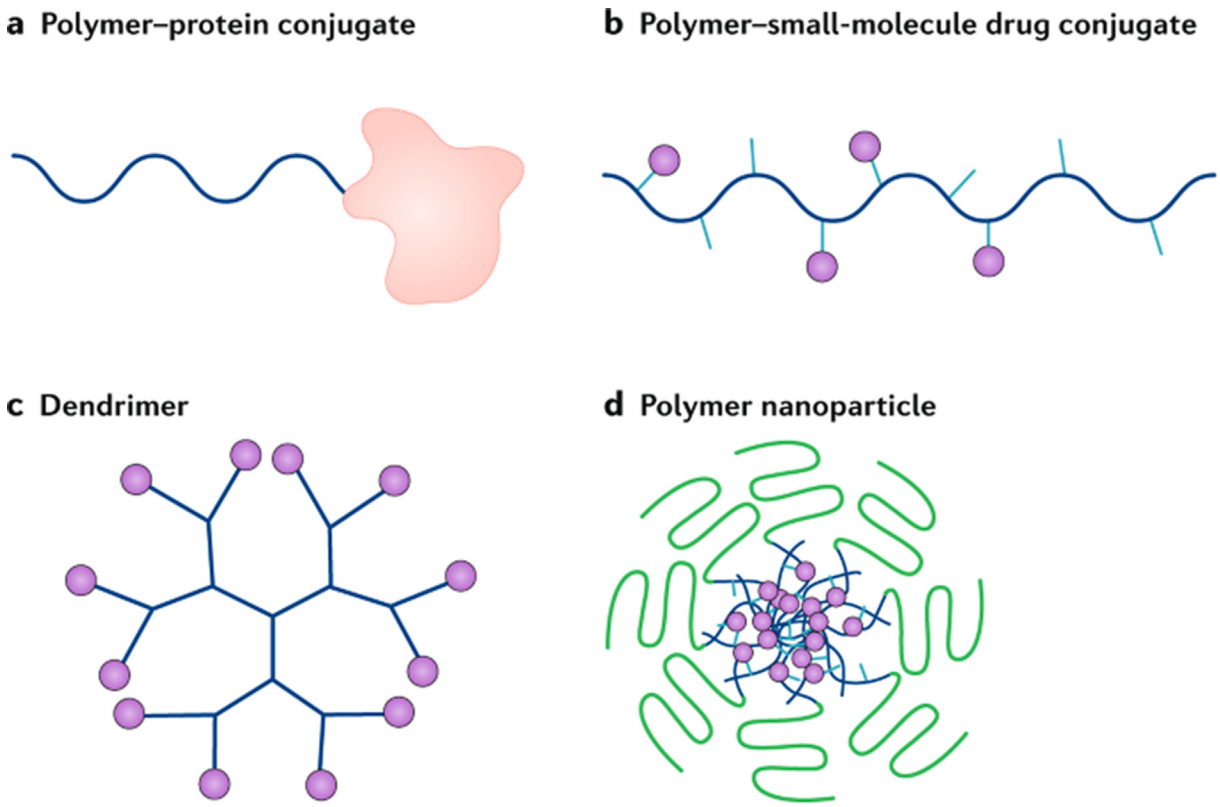

Fig. 4. Schematic representing different polymer-drug conjugate systems. a. polymer-protein conjugate; b. polymer-small-molecule conjugate; c. hyperbranched dendrimer-drug conjugate system; and d. Polymeric nanoparticles are colloidal carriers. The depicted polymeric micelle, polymeric nanoparticles typically possess a core–shell architecture, with a hydrophobic core sequestered by a hydrophilic corona [27].

3. Additive manufacturing

AM is defined as a 'process of joining materials to make parts from 3D model data, usually layer upon layer, as opposed to subtractive manufacturing and formative manufacturing methodologies' by the International Organization for Standardization (ISO) and American Society for Testing and Materials (ASTM) standard (ISO/ASTM 52900:2016) [60]. In AM, 3D computer models are designed directly via computer-aided design (CAD) or mathematical software [61]. Furthermore, for medical related AM 3D models can be based on medical imaging techniques such as computer tomography (CT) and magnetic resonance imaging (MRI). The 3D model is then converted into an stl-file and expressed as a series of cross-sectional slices with a predetermined thickness. These slices are then sent to the AM device to fabricate the final products which closely resemble the original model in geometry and size. This allows for the fabrication of patient specific [62] and 'on-demand' [63] complex structures, which provides promising prospects for improvements in biomedical strategies, including drug delivery.

In this section, we discuss the AM techniques that have been used recently in scientific research for drug delivery devices. We discuss how the techniques work, what requirements the techniques put on the polymers, how the drugs can be incorporated, and the potential of the techniques for the preparation of drug delivery devices. In our literature research, it was clear that the printing techniques could generally be divided into light-based and extrusion-based AM. FDM, also known as fused filament fabrication (FFF), was by far the technique mostly used for the AM of drug delivery devices. Another common technique was vat photopolymerization. Other techniques such as inkjet printing and SLS were sporadically investigated as well. Fig. 5 gives a schematic overview of the AM techniques used in the AM of drug delivery devices described in this review. In the scheme, and this section, we have divided the methods based upon layer formation/deposition methods, this however does not exclude for example material curing being used in extrusion-based AM.

3.1. Extrusion-based additive manufacturing

In this section we discuss AM methods that are based on the selective deposition of materials onto a substrate: fused deposition modeling, direct powder extrusion, pressure assisted microsyringe and 3D inkjet printing.

3.1.1. Fused deposition modeling (FDM)

Fused deposition modeling is an AM technique from the material extrusion category: a 'material is selectively dispensed through a nozzle or orifice' [60]. In FDM, a thermoplastic polymeric filament is melt-extruded through a heated nozzle forming a 2D pattern on a building platform by XY-movements of the nozzle [64]. By adjusting the height of the platform or nozzle in the Z direction, subsequent deposition of the next layer can be facilitated. Originally, two materials were utilized, with one of the materials functioning as a support material. More recent developments allow for the use of multiple materials as actual construct materials [65]. In Fig. 6, a schematic representation of an FDM setup is shown.

The processing parameters will determine the resolution, porosity, mechanical properties of the obtained constructs. The parameters include nozzle temperature and diameter, movement speed of the nozzle, extrusion speed and build direction [66,67]. FDM is an interesting technique for the preparation of AM constructs as it doesn't necessarily require treatment of the constructs post fabrication such as solvent extraction or impregnation [64].

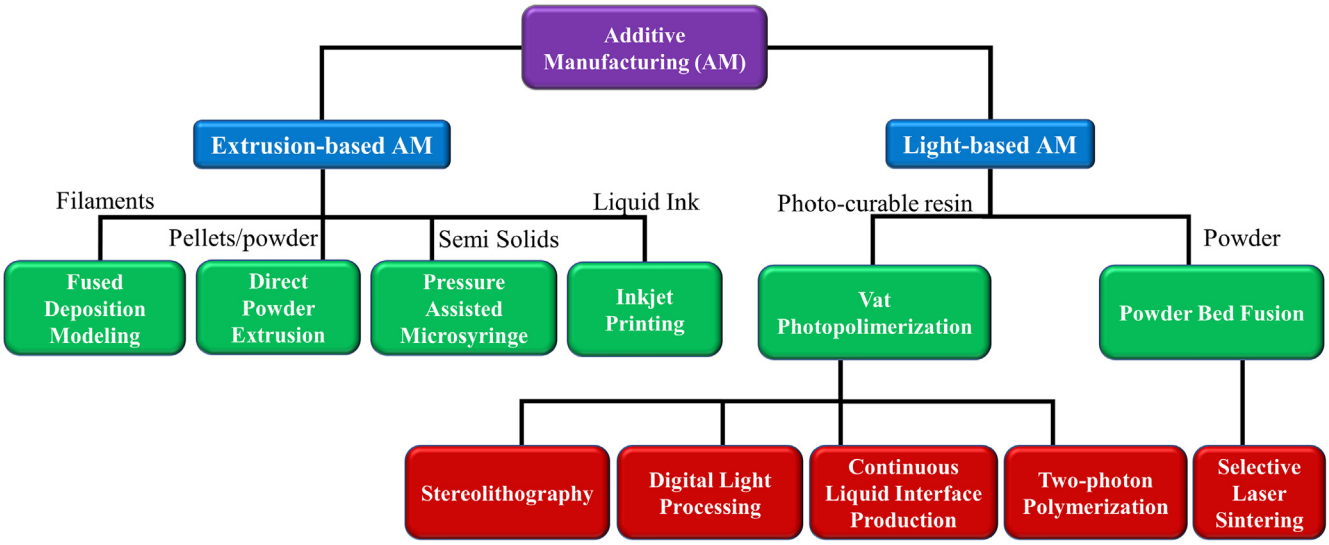

Fig. 5. Schematic showing the AM techniques used in recent studies for the preparation of AM drug delivery devices.

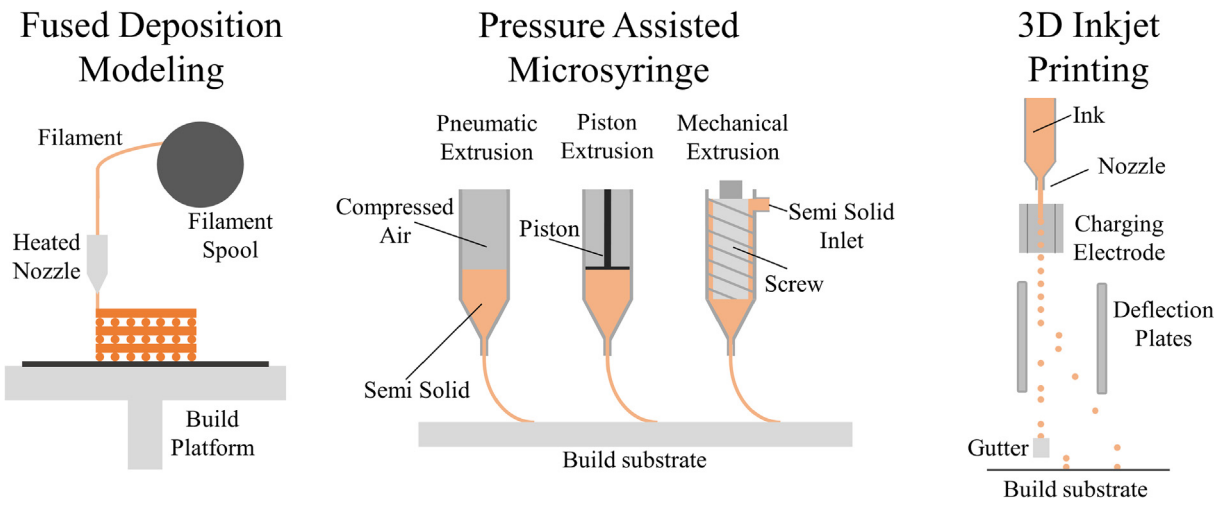

Fig. 6. Schematic overview of Extrusion-based additive manufacturing techniques: fused deposition modeling, the three methods of pressure assisted microsyringe and CIJ 3D inkjet printing.

A critical aspect of FDM is material decomposition during processing [64]. Upon prolonged exposure to heat, polymers tend to thermally decompose. Polymer melts are often highly viscous and require application of considerable pressure to feed them through the nozzle. To reduce viscosity, the temperatures are often increased. The effect of the thermal decomposition of the polymers on the properties of the obtained structures needs to be considered prior to fabrication.

The standard process for producing a drug releasing device by FDM requires the preparation of a filament consisting of a thermoplastic polymer loaded with drug(s) [68]. The drug loaded filament is then used in the FDM device to produce a drug releasing construct. The production of the drug loaded filaments is divided in two general steps: (i) the mixing of the polymer(s) and the drugs (s) and (ii) the subsequent production of the filaments. For step one, an additional pre-step may be required if the form of the polymer is not compatible with the form of the drugs, i.e. polymers are often supplied as pellets while drugs come as powders. A large difference in size of the polymers and drugs is one of the main reasons of inhomogeneous drug distribution in the produced filament [69]. Processes such as melt-blending, physical mixing and homogenizing in the extruder prior to extrusion may therefore require milling and sieving of the polymer(s) as a pre-step. Mixing techniques such as solvent casting do not require this pre-step due to the polymer(s) and drug(s) being dissolved in an organic solvent. In these cases, a stirring step is performed allowing the homogenization of the mixture. The polymer/drug solution is then casted, and the solvent evaporated [70,71].

There are several approaches to produce drug loaded filaments: (i) filament soaking, in which the filament is soaked for a sufficient time period in an appropriate solvent containing the drugs so that the drugs can diffuse into the filament [72,73]; (ii) hot melt extrusion (HME). Single screw extrusion, in which the polymer/drug mixture is fed into an extruder with a single screw. The polymer melts due to shear stress and temperature and finally flows out of the nozzle [68]. Double screw extrusion, which can be co-rotating and counter-rotating. Mixing in this system is generally better as compared to single crew extrusion and has lower shear stresses which is beneficial for sensitive drugs [68]; (iii) melt blending [74] and (iv) piston extrusion [75,76].

In order to develop a well-functioning drug delivery system, it is important to consider loading efficiency, homogeneity of the drug

dispersion in the polymer matrix and efficacy of the drugs after processing. High temperatures, shear stresses and pressures in extrusion systems, and potentially harmful solvents in filament soaking and solvent casting, may harm the efficacy of the drugs and residual solvents may affect the safety of the drug delivery device. The lowest loading can generally be achieved by the solvent soaking approach with amounts to 5% w/w. The efficiency is affected by the amount of solvent and swelling of the filament [77]. Higher amounts are achieved by both the single and double screw extrusion with drug loading up to 60% w/w with loading efficiencies ranging between 70 and 100% as some of the drug may stay stuck on the extruder wall [68,78]. Single screw extrusion results in lower homogeneity as compared to double screw extrusion, as the polymer-drug mixture is mixed more efficiently in the double screw extruder [79]. In the case of piston extrusion, the homogeneity and loading efficiency is limited by pre-mixing.

Compared to conventional techniques used in the preparation of drug delivery devices, FDM poses several advantages. FDM allows for the preparation of individualized, designed dosage forms [80], making it an important technique in the development of personalized medicine [81]. This for example achieved by the inclusion of multiple drugs, for example by multilayer printing [80,82], which allows for treatment of patients that have multiple and very complex drug regimens [83]. In addition, with FDM there is geometric freedom [84], which allows for the preparation of complex structures including compartmentalized capsular devices [83–85]. Such devices can either be manufactured as empty compartments to be filled with the drug later, or as outer shell and inner core in a single process [84] and allow for combinations of drugs, doses and release kinetics [86].

Drug delivery devices prepared by FDM are investigated mainly for oral devices such as tablets [80,82,83,87], capsules [84,86] and innovative radiator designs [81]. Several types of release have been investigated with these devices. Controlled release was reported for drug loaded tablets [8,69,88]. Tablets with extended release were also developed [89]. Melocchi et al. developed capsular devices with the aim of pulsatile release [86,90]. Immediate release was reported from tablets without disintegrant [91] and bi-layered tablets [80]. Multi-layered tablets were prepared with release depending on the position in the tablet [82], and this allows to co-ordinate the drug release and achieve optimized release profiles. Control over drug release was also achieved by preparing capsular devices where the difference in release was achieved by adjusting the design [83]. Devices with both early and delayed release, and devices with both immediate and extended release were prepared in this way.

3.1.2. Direct powder extrusion (DPE)

Due to the aforementioned disadvantages of HME, it would be an advantage to be able to skip that step [92]. Recent developments in AM have introduced an alternative for FDM printing: Direct Powder Extrusion (DPE) [93]. In this technique, pellets or powders are directly printed via extrusion through a nozzle by a single screw extruder. As HME is not required to prepare filaments, disadvantages of the use of filaments such as limitations in the amount of excipient inclusion to obtain printable filaments can be circumvented [94]. In addition, polymers that would otherwise make too brittle or soft filaments can potentially be used in DPE [92].

In a first demonstration of the use of the technique for drug delivery devices, Goyanes et al. showed that it was possible to prepare amorphous solid dispersions of drug in polymer [92]. The obtained manufactured tablets showed good mechanical properties and no drug degradation in the process. A sustained drug release was observed. Ong et al. prepared tablets that showed alcohol resistance and abuse-deterrent properties for dose personalization of opioids [95]. Fanous et al. demonstrated the capability of DPE to prepared honeycomb devises with different infill densities for immediate release dosage forms [94].

3.1.3. Pressure assisted microsyringe (PAM)

Like FDM, pressure assisted microsyringe (PAM, also known as semi-solid extrusion, SSE) relies on the computer-controlled preparation of a 3D structure with designed composition and architecture via the deposition of the materials in a layer-by-layer manner [96]. While having been used extensively in tissue engineering approaches for the preparation of soft tissue implants [97], the use of PAM for drug delivery devices has been relatively recent [96]. The extrusion process is based on pressure: either pneumatic, mechanical of via a solenoid piston [98]. In Fig. 6, a schematic representation of the PAM setups is shown.

The polymer drug mixture is processed as a semi solid: a gel or paste. Semi solids contain an ideal mixture of polymer, solvent and other components (i.e. drugs). The advantage of PAM is that high temperatures are not required [99]. Additionally, high drug loading is achieved with the drug being mixed in the solvent that is used to make the paste, and PAM can be used for multi-drug tablet printing. Furthermore, even poorly soluble drugs can be mixed and incorporated [100]. However, drying as post-print processing is necessary, which may result in shrinking or deformation of the built structure. In addition, due to the use of solvents, drug instability and toxicity may occur. Furthermore, the rheological properties of the semi solid also impact the printing process and structure formation. If the deposited layer is not strengthened enough it cannot withstand subsequent layer and the structure may collapse [101]. This can be prevented by crosslinking of the deposited layer [102].

It is expected that PAM will be used in the preparation of low cost, small batches of tailored, drug releasing tablets [99]. Indeed, PAM has been extensively used for the preparation of tablets [98–100,103,104] and chewable oral dosage forms [105]. In addition, drug releasing composite scaffolds for localized delivery [106], and a drug delivery patch [107] were developed as well. The developed tablets showed several types of release. Khaled et al. [98] printed tablets that showed controlled release. They similarly printed tablets containing three different drugs which showed sustained release [104]. Tablets that showed immediate release (i.e. by disintegration) were prepared as well [100,103]. Drug dissolution appeared to depend on the amount of layers printed and by adjusting the surface area/volume ratio the drug release could be adjusted. Zhu et al. [106] printed drug releasing composite scaffolds, which showed promise as both bone regeneration scaffolds and drug delivery systems. Sustained release of the drugs is achieved with these structures. Yi et al. [107] printed a flexible delivery patch which due to AM can be manipulated in geometry and drug release kinetics. These patches achieve drug release in a prolonged and controlled manner for over four weeks.

3.1.4. 3D inkjet printing

3D inkjet printing involves the preparation of 3D structures through the formation and subsequent deposition of small droplets onto a substrate [108]. The droplets can be either a molten polymer/oligomer, polymer solution, or an ink-binder [109]. Droplet solidification can then take place via cooling, curing, solvent evaporation or polymer growth from gas or liquid respectively.

Droplet generation is either done in a continuous (Continuous Inkjet, CIJ) or in a drop-on-demand (DoD) manner [108]. In CIJ, a continuous stream of ink is ejected from the nozzle as it travels to the substrate. A piezoelectric element in the nozzle breaks the stream into droplets. The positioning of the droplets onto the substrate is precisely controlled by applying a potential to the electrodes present at the nozzle and along the droplets path.

Multiple-jet CIJ systems in which there are multiple nozzles and streams have been developed as well. In Fig. 6, a schematic representation of a CIJ 3D inkjet printing setup is shown.

Alternatively, DoD inkjet printers generate droplets only when required. DoD can generate droplets much closer to the substrate and thus also smaller droplets can be prepared. Droplet generation is achieved by, among others, thermal, piezoelectric, acoustic, and electrohydrodynamic methods [109] of which thermal and piezoelectric are most common. In thermal DoD inkjet printers, there is a heating element present at the nozzle. When a droplet is needed, the element heats the ink inducing vaporization of the ink in the nozzle which in turn creates a pressure pulse forcing the ink out of the nozzle. The inks need to be able to withstand high temperatures in this type of printing [109]. In piezoelectric DoD, an electric pulse is applied to the piezoelectric element at the nozzle which generates a pressure pulse that forces a droplet to be ejected from the nozzle.

3D inkjet Printing is a flexible, high resolution technique with selective deposition at a spatial resolution of up to 50 μm, due to the very low volumes used (picolitres) [108,110,111]. This allows for the preparation of drug delivery devices with personalized dosages and complex drug release profiles [108]. Additionally, the technique has the potential to be considerably scaled up or scaled out [110]. Inkjet printed drug delivery devices have been prepared from solutions, nanosuspensions and melts. Such devices include transdermal microneedles [108], drug containing implants [112], tablets [110] and complex 3D geometries [111]. Additionally, 3D inkjet printing has been utilized to investigate the potential of the technique to fill reservoirs or coat microneedles prepared by other 3D printing methods [113,114]. It has been shown that coating of microneedles with inkjet printing is a very versatile technique with various agents being included in the same microneedle array [108]. These coatings were uniform, and the process did not produce any alterations. For the tablets and 3D geometries, drug loading was between approximately 3 and 25 wt% [110,111]. Kyobula et al. found however, that with loadings between 10 and 25 wt% the relative release rate of the drug slowed down, most likely due to the drug being in its crystalline state at such amounts [111]. With lower percentages, controlled release was observed, while the geometry of the structures was able to affect the release, although the geometry must be chosen very carefully.

3.2. Light-based additive manufacturing

In this section we discuss AM methods that are based on the fusion or curing of a polymeric material by light: selective laser sintering and vat polymerization, which includes stereolithography, digital light processing, and two-photon polymerization.

3.2.1. Vat photopolymerization

In vat photopolymerization a 'liquid photopolymer in a vat is selectively cured by light-activated polymerization' [60]. AM techniques that use a vat and are used in the preparation of drug delivery devices include stereolithography, digital light processing, continuous liquid interface production, and two-photon polymerization [115].

The light source in stereolithography is often a laser, which selectively illuminates the liquid photopolymer, also called a resin, from above. After a layer is completed the build platform moves down into the vat with resin [116]. This continuously supports the structure but requires a relatively large amount of resin.

The laser can also illuminate the resin from below through a transparent bottom in the vat. Alternatively, a UV or blue light projector can utilize a digital mirror device to also illuminate the resin from below. This is called Digital Light Processing (DLP) [116–118]. In this process, the build platform moves up out of the vat after a layer is cured. Fig. 7 provides a schematic overview of DLP. The top-down approach has a few advantages over the bottom-up approach [119]: (i) only small amounts of resin are needed, (ii) no recoating of crosslinked layers is required, (iii) the illuminated surface is always smooth, and (iv) oxygen inhibition is limited due to the illuminated resin not being exposed.

The only drawback is that after a layer has been fabricated, it needs to be separated from the vat. The mechanical forces acting on the (fragile) structures during this process can result in failure [116].

After a newly formed layer is separated from the vat, the resin needs to flow underneath or over the build platform to fill the space left by the newly cured layers[64]. Therefore, the viscosity of the resin cannot be too high. While resins ideally have viscosities of up to 5–10 Pa·s [64,120,121], resins with viscosities of up to 133 Pa·s have been reported [116]. The viscosity can be controlled by including a non-reactive diluent, but the addition of too much diluent will result in extremely fragile network structures which may fail during the separation of build structure and vat [116,121]. In addition, the resin should include a photo-initiator which upon irradiation with UV/blue light breaks up in two radial species [122] that can react with the double bonds of the meth (acrylate) or vinyl groups or with the epoxy-groups of the photo-crosslinkable polymer to form a network. It has to be noted that the toxicity of many photo-initiator used in AM resins remains a concern for drug delivery systems [123]. Natural photo-initiators, such as Riboflavin, have been proposed to be used as a safe alternative [118,123]. In order to obtain the designed structure and not have over-curing of the resin, the light penetration depth of the light needs be controlled [116]. This can be done by the addition of a dye, but other additives that can be included in the resin can decrease the light penetration by light scattering as well [119].

More recently, a novel form of stereolithography has been developed that prints layer-less by moving the build platform up in a continuous manner and having a printing 'deadzone' at the bottom of the vat created by oxygen inhibition [124]. This is called Continuous Liquid Interface Production (CLIP).

Photo-crosslinked networks are a promising group of materials for use in drug delivery devices [125]. By dissolving and/or dispersing the drugs into the macromer solution prior to crosslinking, large amounts of drugs can easily be entrapped in the networks at high efficiencies and excellent dispersity [126,127]. Additionally, photo-crosslinking is fast and usually has only minimal heat generation making it a suitable method for the incorporation of heat sensitive drug molecules. The photo-crosslinkable polymers act as free radical scavengers, avoiding detrimental reactions of the drugs with those radicals [128,129]. The crosslinking density influences the swelling of the networks [130,131], which can be used to control drug release behavior from the networks. However, great care in the selection of the polymer/drug combination is of the highest importance. Xu et al. have reported a Michael addition reaction between the diacrylate group of the photoreactive monomer and the primary amine group of the drugs during the fabrication of a 3D printed oral dosage from by SLA [132].

There are two methods mentioned for loading drug in SLA, DLP and CLIP manufactured drug delivery devices: (i) disperse/dissolve the drugs in the liquid polymer resin prior to printing [70,133,134], and (ii) preparation of a delivery system for the drugs by SLA and subsequent coating of the system or filling a reservoir with the drugs by inkjet printing [113,114]. In the former case, these techniques offer the advantage of high surface finish and resolution, short print times, heat-free printing and the capability to print elaborate geometries which can control the release properties [123]. In this way, drug releasing tablets [118,123,132,134], implants [133,135], topical drug delivery devices [70] and hearing

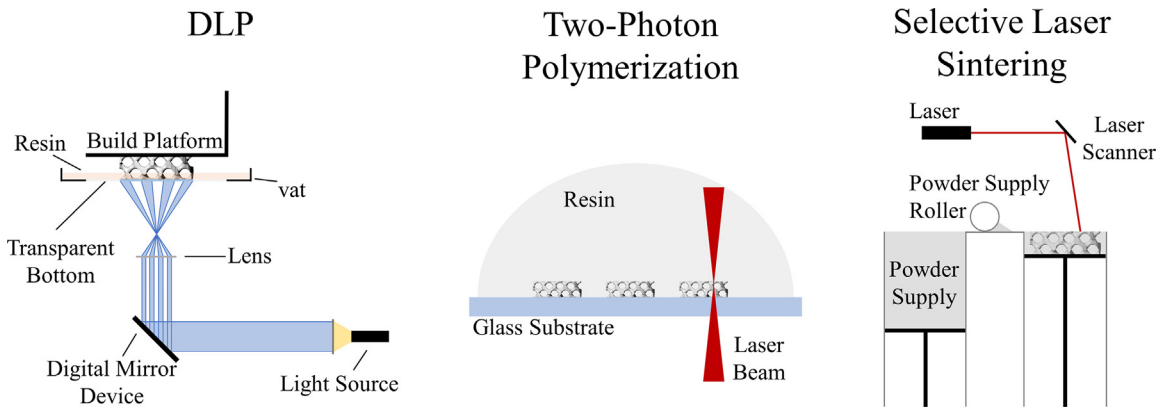

Fig. 7. 2D schematic overview of three types of light-based AM: DLP, two-photon polymerization and selective laser sintering.

aids [136] have been prepared. When the drugs were dispersed/dissolved in the resin prior to crosslinking, amounts between 2 and 10% w/w were incorporated in the resin achieving high loading efficiencies of 94–98% [70,133,134]. Generally, SLA prepared structures show a controlled release of the incorporated drug [70,134], which may be prolonged as the network structure affects diffusion [134,136].

In the latter case, when SLA is used to prepare a delivery system that gets coated with drugs or acts a reservoir, the SLA prepared structures are often drug releasing microneedles. Using vat photopolymerization techniques for the preparation of microneedles is advantageous due to the high resolution, reproducibility, cost efficiency, and fast production [137]. The loading efficiency of these devices depends on the method used to load the drugs. Utilizing CLIP, microneedles with initial burst release and subsequent sustained release [138].

In two-photon polymerization (2PP) a femtosecond laser beam with a wavelength of 780–800 nm is usually used [139]. The beam is tightly focused on the photo-crosslinkable resin that is placed on a glass cover slip. The laser moves along the resin in a computer-controlled manner. After fabrication, the liquid resin is removed by washing with a solvent to reveal the designed 3D structure. Fig. 7 provides a schematic overview of a 2PP setup.

In general, 2PP can have two types of resin [139]. The first is a negative photoresist, where the laser beam results in the crosslinking of polymer chains via radical photo-polymerization meaning that the irradiated regions solidify into the desired structure and the non-solidified material can be washed away. Alternatively, there are positive photoresists where the laser beam results in cleavage of polymer chains resulting in degradation. Here, the reverse structure is irradiated and washed away post-production. Negative photoresists are most popular. The negative photoresists contain the prepolymers, photo initiators and crosslinkers.

A large advantage of 2PP is that it allows for the preparation of structures with much higher resolutions than previously discussed methods [140]. FDM has typical resolutions of 50–200 μm and SLA has typical resolutions of 20 μm. 2PP however, can be utilized to prepare structures in the order of 100 nm.

Do et al. prepared cubical structures which had a solid or woodpile structure [140]. The resins contained 10 wt% drugs and released up to 60% of the drug in 6 days. By varying the cylinder diameter and spacing and de slicing of the model the kinetics of the drug release could be affected. These parameters can be controlled independently of material chemistry, giving release from 2PP constructs cost and time advantages over conventional release methods. Ceylan et al. prepared enzymatically degradable miscroswimmers, which degrade in approximately 120 h and allow for remote magnetic powering and steering [141]. This results in navigation and precise localization allowing for local targeted delivery of drugs and other cargo types. In this way, systemic toxicity effects can be minimized, and the efficacy of single dose administration increased.

3.2.2. Selective laser sintering (SLS)

Selective laser sintering is part of the powder bed fusion (PBF) family of AM techniques. While another PBF technique, multi jet fusion (MJF), uses polymers as well, it has not yet been used for the preparation of polymeric drug delivery devices. In SLS, a powder is irradiated by a laser beam that results in the fusion of the powder at the irradiated parts [28,142]. Subsequently, the build platform is lowered, and a roller deposits a thin, fresh powder layer on top of the previous material. The following irradiation results in the next layer being generated. Fig. 7 provides a schematic overview of the SLS process. When using polymer powders, powder fusion is achieved by heating the polymer to above its melting temperature for semi-crystalline polymers or above the T_g for amorphous polymers followed by cooling [64]. The use of polymers can only result in well-defined structures if the polymers can readily be processed into a powder and have a high melting enthalpy and low thermal conduction [143]. As is the case for FDM, thermal degradation of the polymer during printing needs to be taken into account [143,144].

SLS has been studied for preparing drug delivery devices for the last few decades [145,146] and mainly orally disintegrating tablets are prepared [147]. SLS offers several advantages over other techniques. As no solvent is needed, no drying step or other significant processing post manufacturing is required and printed tablets can immediately be used [148,149]. In addition, SLS has a high turnover rate, does not require filaments or polymerizable components and no liquid binder [148]. The particle size is a very important factor in SLS [150]. Larger particles have better flow properties than smaller particles but reduce the packing density and require more energy for sintering. Smaller particles on the other hand, improve the content uniformity but they tend to aggregate which poses a challenge during the deposition of the new layer. In addition, blend segregation may occur if there is a size difference between components in the formulation. Polymer powders for SLS that are commercially available have a preferred size of 20–60 μm. The high precision of the laser allows for detailed structures and controllable internal architectures [36]. These details can be used to prepare tablets with braille patterns for visually impaired patients, improving patient independence and medicine adherence, and reducing the chance of medicine errors [151]. Personalized medicine can indeed be further improved by SLS prepared tablets, as the drug performance can be tailored to the patient by tailoring the design. By varying the polymers, the effect of drugs, structure

geometry and polymer used was shown [147,152,153]. Depending on the drugs, both pH dependent and pH independent structures were fabricated [152]. By adjusting the dimensions and geometry the release rate could be tailored [153]. In recent studies, drugs were loaded in a range of 5–35 wt%. In all studies, around 100% drug loading was observed meaning the drugs did not degrade during the sintering process [147,152,153].

4. Polymers and polymer properties in drug delivery systems prepared by additive manufacturing

4.1. Essential polymer properties for drug delivery systems prepared by AM

For designing drug delivery systems based on polymers using AM, some general characteristic features are needed that makes them a potential candidate. Fig. 8 presents essential properties of polymers used for drug delivery systems through AM. Mechanical strength, adhesion, rheology, printability, biodegradation, biocompatibility, efficacy, hydrophilicity, particle size, absence of immunogenicity, biological inactivity, release rate, and the presence of functional groups for covalent conjugation of drugs, targeting moieties, or formation of copolymer are the most important properties. In the following sections, we will provide a more detailed description of the most important ones.

4.1.1. Biodegradable and non-degradable polymers

Polymer biodegradation is a phenomenon, which involves the cleavage of hydrolytically or enzymatically sensitive bonds leading to polymer erosion. Polymers used in drug delivery systems can be divided into two main groups, depending on the degradation behavior: (i) biodegradable and (ii) non-degradable polymers.

Biodegradable polymers play an important role in the pharmaceutical field since there is no requirement for surgical removal as they get degraded over time. Hydrolysis is the most common way of degradation of biodegradable polymers in drug delivery systems. During the hydrolysis, the bonds between the monomers and oligomers start cleaving, leading to weight reduction known as erosion. Crystallinity, T_g, water uptake, and the molecular weight are the factors that affect the rate of polymers' degradation [154]. The most important biodegradable polymers or copolymers used for drug delivery systems are PLA, PLGA and polycaprolactone (PCL) [155]. The degradation of polymers can be divided into three modes, including surface erosion, bulk degradation and bulk degradation with autocatalysis (Fig. 9) [156]. As is shown in Fig. 9, surface erosion includes the hydrolytic cleavage of the polymer backbone only at the surface, while bulk degradation leads to hydrolysis through the entire polymer matrix. The degradation behavior of the polymer in combination with the degree of polymer's crystallinity, water penetration into the system and its porosity, as well as drug diffusion in the polymer matrix can affect drug release from drug delivery systems based on biodegradable polymers.

Non-degradable polymers have also been used in drug delivery systems; however, their drug release mechanism is not as complex as that of biodegradable polymers. For non-degradable polymers, the drug is released by diffusion. Pore size, pore interconnectivity and tortuosity within the polymer matrix, the distribution of the drug throughout the implant and the affinity for the drug to the polymer are the important factors that influence on the drug release rate from non-degradable polymeric systems. The most common non-degradable polymers used in the pharmaceutical applications are polydimethylsiloxane (PDMS), ethylene vinyl acetate (EVA), and polyurethane (PU) [157].

4.1.2. Biocompatibility and non-toxicity

Biocompatibility and non-toxicity are not the same. However, they are the most important features that a polymer-based drug delivery system should have. Toxicity is assigned to cell death mostly produced by soluble products released by a polymer, whereas biocompatibility is related more to the interaction of the polymer with living tissues. Some unwanted soluble products, such as degradation products, monomer residues, solvent, and additives, released from polymeric materials, may lead to toxicity [158]. Cytotoxicity of polymers can be evaluated using three different tests, including primary (level I), secondary (level II), and preclinical (level III) tests. *In vitro* and *in vivo* assessments can be done in level I tests. For cytotoxicity tests *in vitro*, the effects of the polymers directly on the cultured cells will be evaluated using different cell lines. To assess the tissue response, the polymeric materials can be implanted subcutaneously or intramuscularly *in vivo,* for example in mice, rats or rabbits [159]. Contact of a non-toxic polymer with living tissues may lead to non-specific and/or specific tissue reactions. A schematic presentation of possible reactions to contact between polymers and proteins and cells involved in the reactions is shown in Fig. 10. As can be seen in the figure, there are two cases that have been considered: (i) tissue compatibility, which means no permanent contact with blood and (ii) blood compatibility, which shows the permanent contact with blood [158]. To evaluate the polymers' biocompatibility, macrophages that are present in the whole body, including the oral tissues, play a key role in the pathogenesis of the inflammatory response [160]. In the next step, the animals' tissue that received drug containing systems through oral, injection or implants, should be assessed during level II tests. If the polymeric system has successfully passed the levels I and II tests, level III test should be done, and the systems should be tested in humans to assess its performance [159].

4.1.3. Mechanical properties

Since polymers are widely used in pharmaceutical applications, their mechanical properties should be determined and evaluated. Deformation of a drug delivery systems' structure when subjected to an external force, can influence their performance and stability [161]. If a drug-loaded polymeric carrier decomposes during application due to mechanical damage before reaching the final target, premature drug release will be the result, which leads to using high doses for the patient. Therefore, determination of a polymers' mechanical properties, including deformation mechanisms and the elastic modulus can be beneficial to optimize the properties of these materials with respect to the final product or location of use [162,163]. Küçükoflaz et al. developed a series of poly (vinyl acetate-co-divinyl benzene) microspheres with various monomer/cross-linker contents for oral/topical sustained drug release applications and investigated the elastic compression behavior of the prepared systems. The addition of divinyl benzene to the polymer structure caused the mechanical properties to change, with an increase in elastic modulus from 600 MPa to 1.6 GPa. In terms of drug release practices, the microspheres with a high content of divinyl benzene were found to carry drugs with high organic solubility and under mechanical stresses of less than 1.0 GPa [163].

4.1.4. Rheology and printability

Rheology is a critically important factor for predicting polymer's printability and the properties of the final pharmaceutical products as well as controlling the reproducibility of the printed structure. In addition, for bulk hydrogels the rheological properties are essential since the strength depends partially on these properties to obtain rheological synergies favorable to adhesion. For extrusion-based AM techniques, such as FDM and PAM, nozzle diameter, pressure drop and feed rate, as well as the thermal properties of

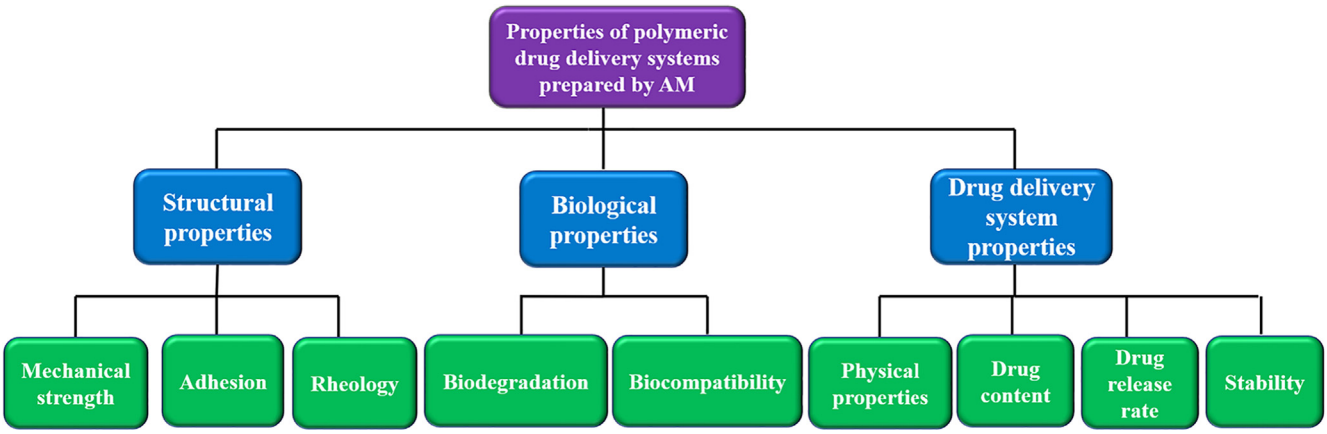

Fig. 8. Essential properties of polymers used for drug delivery systems prepared by AM.

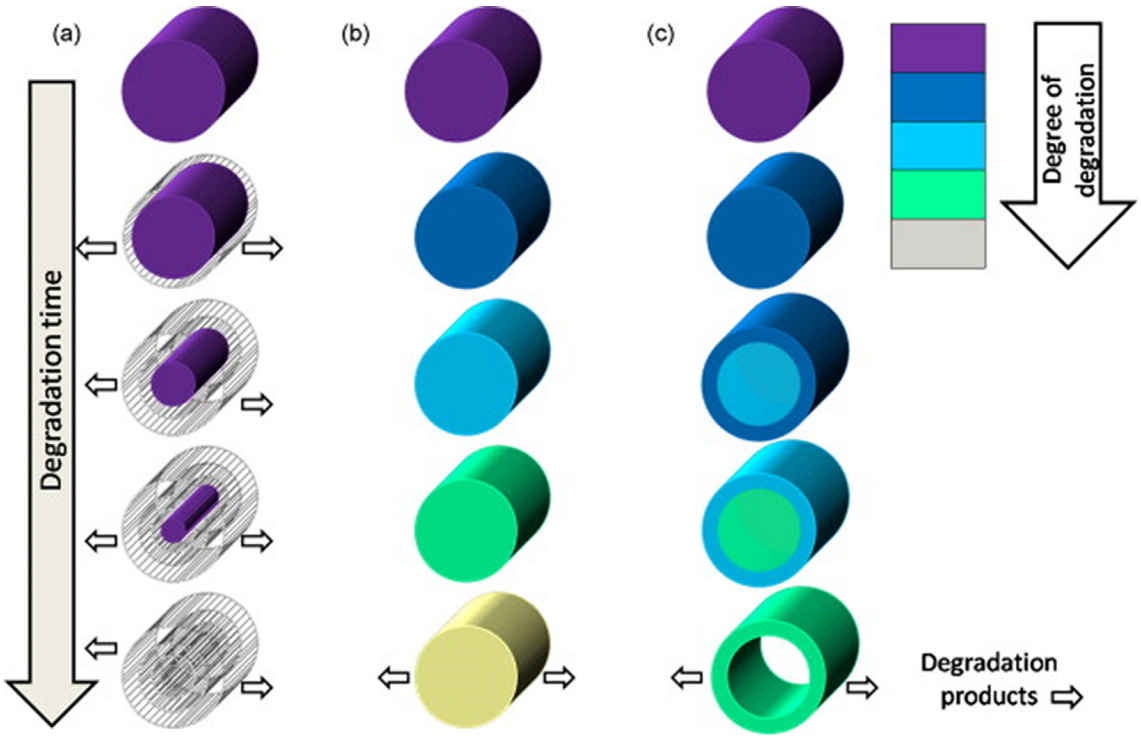

Fig. 9. Degradation behavior for degradable polymers: (a) surface erosion, (b) bulk degradation and (c) bulk degradation with autocatalysis [156].

the feed can influence on the rheological properties of polymers, excipients and formulation compositions [164,165]. For these techniques, understanding of how the flow behavior of the feed materials changes as a function of time, shear and/or extensional deformation, and deformation rate, is helpful to optimize the process conditions and select suitable polymeric materials.

Moreover, polymer viscosity, which is used for determining the stress and deformation rate relationship and to express the resistance to flow, is a very effective parameter for deriving the optimum conditions for extrusion-based AM techniques. Polymer viscosity can be affected by the shear rate used during printing process. Shear thinning behavior can be seen at high shear rates in the printing stage, leading to a decreased polymer viscosity [96].

4.2. Polymers in AM technologies for drug delivery

In the pharmaceutical industry, AM technologies are progressing to overcome the traditional manufacturing of drug delivery systems. However, only some polymers with mentioned properties can be used for the manufacturing of AM drug delivery systems for patient-customized medication with miniaturized dosage forms. In the following sections, we will review the most commonly used polymers and their properties and applications in AM technology for drug delivery systems.

4.2.1. Poly (ε-caprolactone) (PCL)

One of the suitable biodegradable polymers used for development of long-term drug delivery systems is PCL, owing to its flexibility, ease of processing and biocompatibility with a very low degradation rate. PCL has been approved by the FDA for specific applications used in the human body, such as drug delivery systems, sutures or adhesion barriers. PCL is a semi-crystalline polyester, which has a melting point of 55–60 °C and T_g of −54 °C with great organic solvent solubility [166]. Since PCL shows a high permeability to many drugs, is biocompatible, and can be fully excreted from the body once resorbed, it can be used for controlled

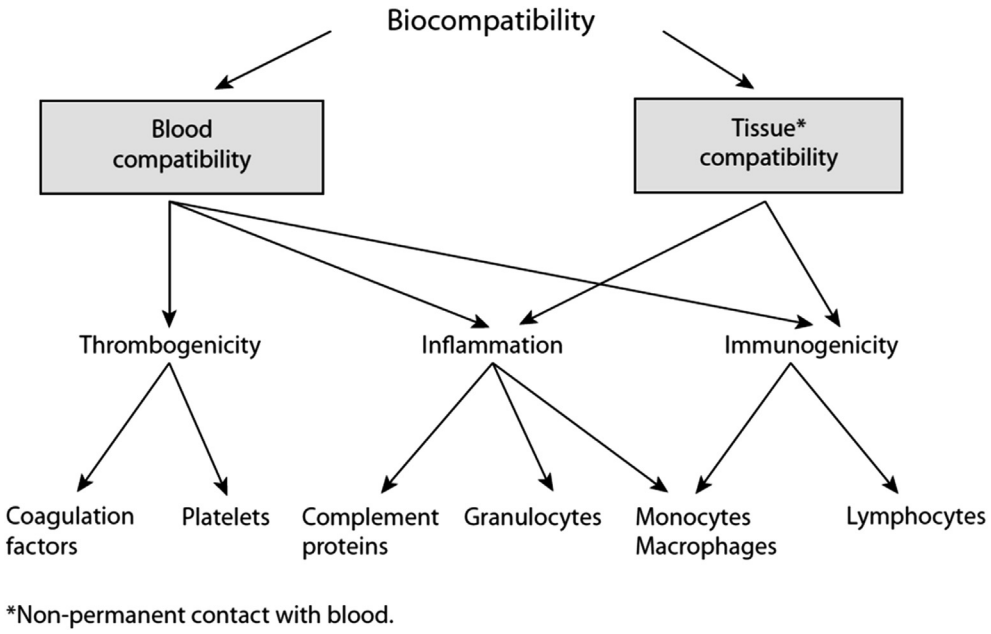

Fig. 10. Schematic representation of possible reactions to contact between polymers and some proteins and cells involved in the reactions [158].

drug delivery applications [154,156]. PCL biodegradation is slow compared with other polymers, which can be used for implantable drug delivery systems to deliver the drugs at a prolonged rate (up to months or years). Capronor™ is a commercial PCL-based contraceptive implantable capsule for prolonged release of levonorgestrel for over a year, which will be eliminated from the body by bioerosion after 2–3 years [167]. Asikainen et al. [133], prepared PCL-based scaffolds using SLA for controlled release of lidocaine. The model drug was dissolved in the polymer matrix and was released through a diffusion-controlled mechanism. The influence of scaffolds' porosity and surface to volume ratio to the lidocaine release was studied and the results revealed that the scaffold porosity clearly affected the lidocaine release, which was faster from porous samples compared to the solid ones. However, the drug release profiles were not affected by the degree of porosity and surface to volume ratio of scaffolds (Fig. 11).

Drug-containing PCL-based implantable prototypes of intrauterine system (IUS) were developed using FDM [168]. The T-shaped prototypes were filled within the entire length of their backbone with 3 different indomethacin contents (5%, 15%, and 30%) (Fig. 12). The amount of loaded drug can affect the filaments' morphology and drug solid-state properties. A poorer quality of the device was obtained at higher drug loading. The degree of crystallinity, geometry and internal/external structure of the products influenced the rate of drug release from both filaments and prototypes. Because of the lower degree of the drug crystallinity in printed IUS, the drug release profiles from the printed devices were faster than from the corresponding filaments. Diffusion was the main mechanism of the drug release according to the *in vitro* studies and PCL biodegradation had insignificant influence.

Desired release profiles can be achieved by blending PCL with other polymers, leading to changes in degradation kinetics. Govender et al. [169], developed AM scaffolds with PAM using PCL, polyvinyl alcohol (PVA) and polyacrylic acid (PAA) blend. They prepared PCL-based scaffolds using different molecular weights of PCL and filled the free areas of scaffold by printing PVA–PAA hydrogel layers containing sodium indomethacin. Adding the PVA–PAA hydrogel to the PCL scaffold caused increasing the structural strength of the scaffold. The porosity evaluation revealed that the printed PCL blend had the lowest size and pore volume owing to the applied pressure during the printing process; however, they were in the acceptable range for application as a drug delivery-structural support system. The PCL–PVA–PAA scaffolds were used as a support system for load-bearing tissue damage where inflammation was high and showed controlled release of indomethacin.

4.2.2. Poly(lactide) (PLA)

PLA is a synthetic biodegradable aliphatic polyester, with considerable applications in drug delivery systems prepared by AM. PLA is a non-toxic, thermoplastic, high-strength, and high modulus polymer, which is mostly considered as an appropriate polymer for processing by FDM [170]. The degree of crystallinity and mechanical stability of PLA can affect the drug release of encapsulated medicines. PLA is obtained through direct polycondensation of renewable lactic acid, or through ring-opening polymerization of lactide, which is degradable through hydrolysis. Since there are two optical isomers of lactic acid, L- and D-lactic acid, there are four forms of PLA: poly(L-lactic acid) (PLLA), poly(D-lactic acid) (PDLA), poly(D,L-lactic acid) (PDLLA), and *meso*-poly(lactic acid). Among them, PLLA and PDLLA are the most studied and used forms in pharmaceutical applications owing to their intrinsic properties. PLLA has melting point of 175 °C, T_g of 60–65 °C, and mechanical strength of 4.8 GPa; whereas, PDLLA has lower T_g and mechanical strength (55–60 °C and 1.9 GPa) [171].

Luzuriaga et al. [172], developed biodegradable PLA-based microneedles (MNs) for transdermal drug delivery using FDM. Several MN shapes were designed and printed with custom needle density, length, and shape. The Scanning electron microscopy images showed the needle tip sizes were in the range of 1–55 μm, which could successfully penetrate and break off into porcine skin. The biocompatible MNs were able to penetrate the outer layers of skin and deliver a model therapeutic agent as shown in Fig. 13.

In another study, Fu et al. [173], applied FDM for preparation of progesterone-loaded vaginal rings with different shapes (O, Y, and M shaped) and a controlled release profile using a PLA/PCL blend (ratio 8:2) and tween 80. To overcome the solubility limitation of progesterone in water, PEG 4000 was used for preparing proges-

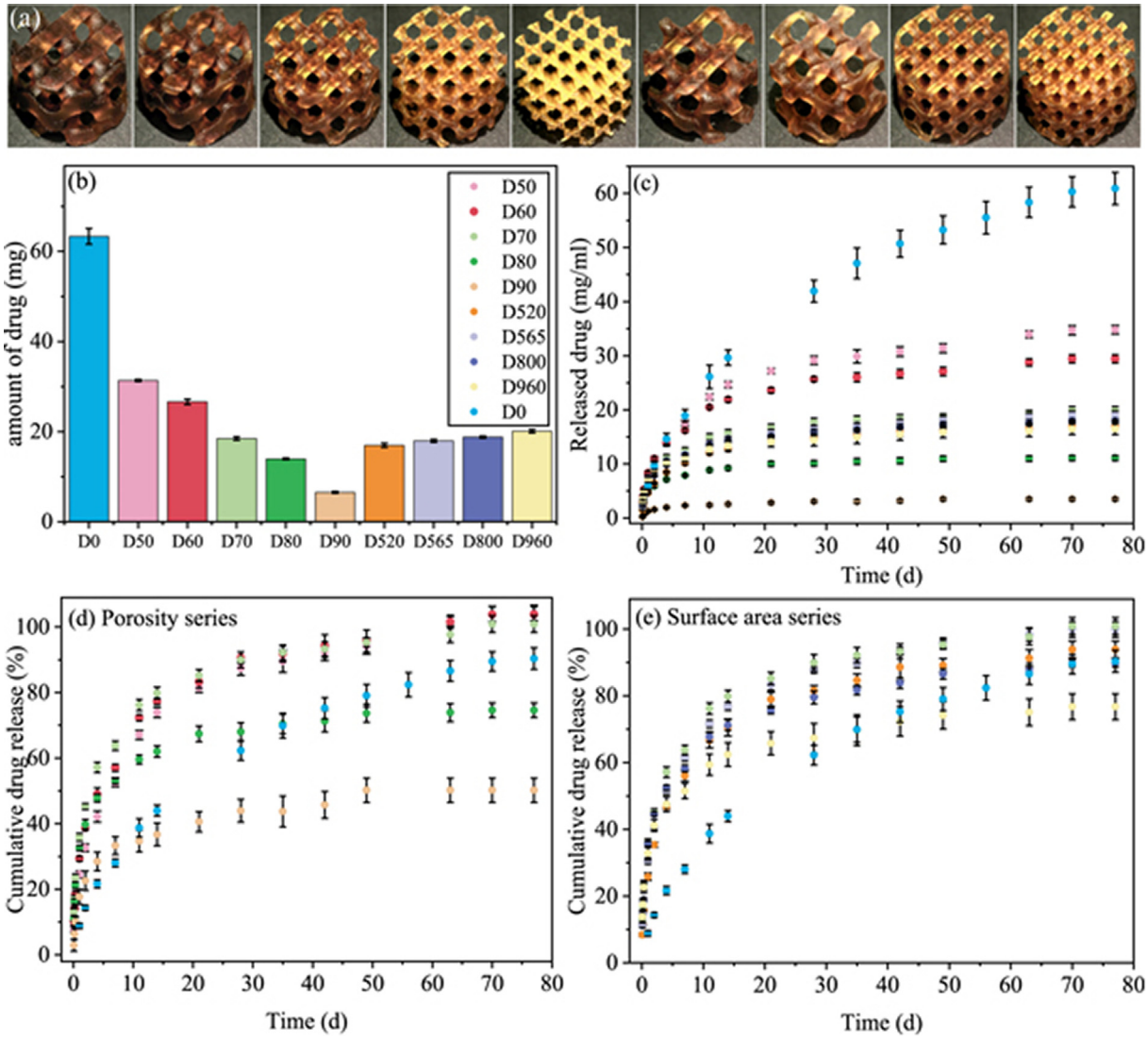

Fig. 11. (a) Dried scaffolds after drug release with different degree of porosities (D0, D50, D60, D70, D80, D90, D520, D565, D800 and D960), (b) amounts of loaded lidocaine in scaffolds, (c) cumulative release of lidocaine, (d) drug release profile by changing porosity (e) drug release profile by changing surface area [133].

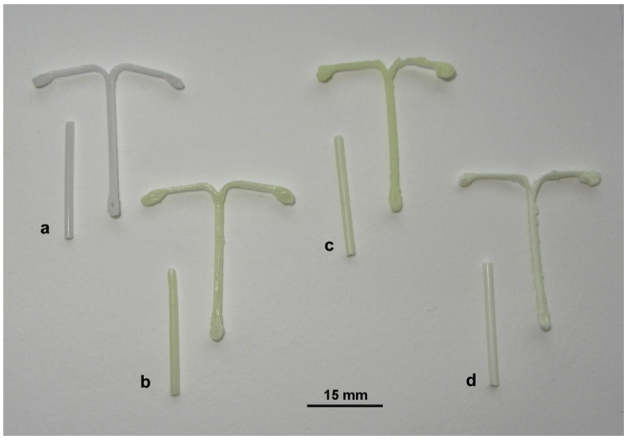

Fig. 12. PCL-based implantable prototypes prepared by FDM containing (a) 0%, (b) 5%, (c) 15%, and (d) 30% of indomethacin loading [168].

terone solid dispersions to improve the release of progesterone in vaginas, as the PLA/PCL rings were hydrophobic, which would restrict the release of progesterone. To increase the hydrophilicity of printed rings, the surfaces of PLA/PCL particles were coated by 2% Tween 80. They showed a sustained release profile, which could find application in the treatment of local gynecological disorders.

4.2.3. Poly (lactide-co-glycolide) (PLGA)

PLGA is the copolymer of lactide and glycolide, which is approved by the FDA for pharmaceutical applications as a biocompatible and biodegradable polymer. It is the most well-known and widely applied polymer in the development of various drug delivery systems. PLGA is an aliphatic polyester that is formed through the copolymerization of lactic and glycolic acid monomers to yield different formulations depending on their copolymer composition [174]. All PLGA compositions have T_g of 40–60 °C, depending on the copolymer composition and are thermoplastic and amorphous below the T_g [175]. If the ratio of lactic acid is higher than glycolic acid, the final copolymer is more hydrophobic due to the higher hydrophobicity of lactic acid leading to a lower degradation rate of PLGA and a slower drug release rate. The hydrophobicity of the drug and copolymer can be matched better by manipulating the copolymer composition, leading to an improved uniform dispersion of drug throughout the polymer matrix or to stabilize encapsulated proteins. Furthermore, the increased lactide ratio in

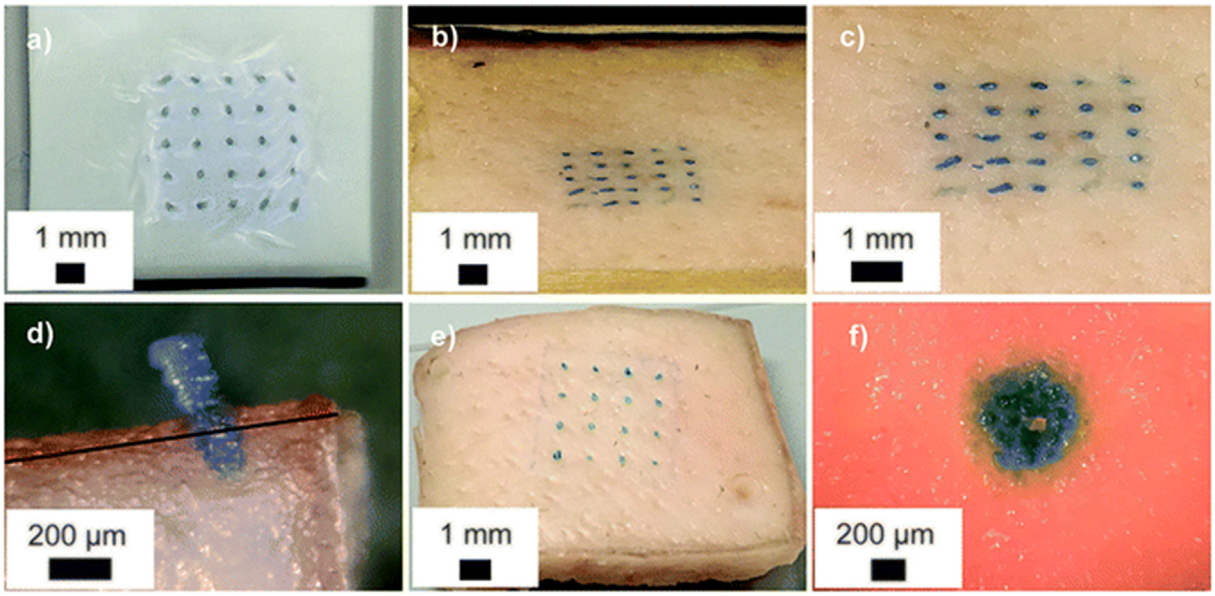

Fig. 13. Fracture test of PLA-based microneedles prepared by FDM a) in parafilm, b) in porcine skin, c) zoomed in image of porcine skin, and d) cross-section image indicating needle penetration depth in porcine skin. The solid line represents the end of the stratum corneum. Penetration test of microneedles e) to demonstrate the diffusion of methylene blue in the porcine skin and f) close up image of a single puncture showing delivery in the surrounding tissue [172]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

a PLGA copolymer, not only prolongs the release and degradation time, but also enhances the rigidity of the material [176].

Since the drug delivery system based on PLGA alone cannot achieve both a long drug release time and flexibility simultaneously, PLGA was blended with PCL to prepare 3D-printed patches by PAM for the delivery of 5-fluorouracil (5-FU), an anti-cancer drug, in a controlled manner and at therapeutic dose [107]. Patches were prepared by melting PLGA/PCL/5-FU followed by loading of the melt in the printing head of multi-head deposition system (MHDS). The MHDS consists of a nozzle-connected printing head, pneumatic pressure controller, and three-axis linear motion controllers. The PLGA/PCL/5-FU was extruded from the reservoir at 600 kPa and 140 °C and deposited on the stage with various shapes at room temperature (Fig. 14). The fabricated flexible patches showed a controlled drug release profile over four weeks, leading to the growth inhibition of subcutaneous pancreatic cancer xenografts in mice, with minimum side effects. To study the *in vivo* therapeutic effects of 3D-printed patches, two PLGA/PCL patches containing 100 and 150 mg 5-FU (P100 and P150) were attached under the tumor. The tumor size in mice that received P100 or P150 patches significantly decreased compared to the P0 patch group. In addition, the tumor growth was inhibited more significantly in the mice implanted with P100 at 24 and 28 days compared with P150 patch. The tumor size was decreased with P150 in comparison with P100 in the first 5 days, but after that the decrease in size was insignificant, whereas P100 decreased the tumor size constantly.

In another study, Do et al. [177], prepared tubes using PAM, consisting of alginate shell and PLGA core to develop controlled and sequential delivery systems for fluorophores. The prepared tubes showed no cytotoxicity when incubated with the human embryonic kidney (HEK293) cell line or bone marrow stromal stem cells. Alginate tubes were printed using coaxial extrusion printing system and after which PLGA was injected manually. Fluorescein was loaded in the alginate sheath and rhodamine B was loaded in the PLGA core. Fig. 15 displays the fabricated device and the two layers are visualized through light microscopy (Fig. 15B). Fig. 15C shows that rhodamine B was homogenously mixed and dispersed throughout the core of the alginate-PLGA tube. *In vitro* drug delivery studies revealed that alginate-PLGA tubes enable a discrete and sequential release of two distinct molecules. The results showed that the fluorescein diffusion through the alginate sheath had occurred before the release of rhodamine B from the PLGA core. This phenomenon led to an initial release of fluorescein followed by a delayed release of rhodamine B, which was consistent with the nature of the layered system. To highlight the advantage of developed system's structure, it was shown that rhodamine B in combination with PLGA without incorporation into the core of the alginate tube was released very quickly into solution.

4.2.4. Polyvinyl alcohol (PVA)

PVA is a thermoplastic polymer, usually employed for oral dosage forms as a binder, control release agent or polymer carrier for amorphous solid dispersions. PVA has good water solubility, mechanical strength and bio-resorption. The melting point and T_g of PVA are 200 °C and 85 °C, respectively, and it degrades at a temperature range of 350–450 °C. Xu et al. [178], reported PVA-based tablets using FDM, which were injected with paracetamol (APAP)-containing gels (Fig. 16A). Moreover, as shown in Fig. 16B, they prepared three types of tablet models, Cylinder, Horn and Reversed Horn, with controlled structures to evaluate the effect of the inner architecture of scaffolds on the drug release profile. The *in vitro* drug release results revealed that the release profile can be controlled by using different geometries, which can be constant, gradually increasing, and gradually decreasing release profiles. Based on the obtained results, the horn model showed an increasing release profile that can be suitable for the patients who have the drug resistance during medication. On the other hand, the reversed horn model showed a decreasing release profile, which can be suitable for hypertension cure.

PVA-PEG graft copolymer (Kollicoat® IR), was used as a hydrophilic matrix for preparation of printed tablets containing levetiracetam (LEV) using PAM for pediatric subgroups [103]. The drug release studies revealed that by increasing the layer numbers of printed tablets drug release rates were decreased. In addition, a prolonged disintegration time was achieved by increasing the

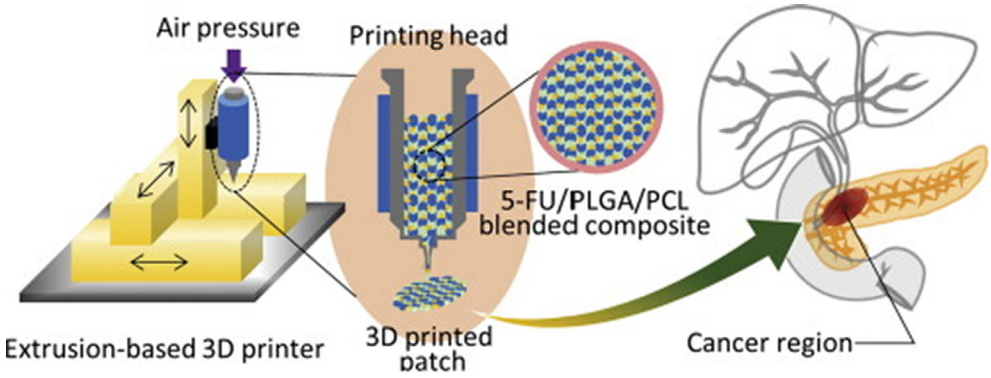

Fig. 14. Preparation of 3D-printed patch containing PLGA/PCL/5-FU using PAM [107].

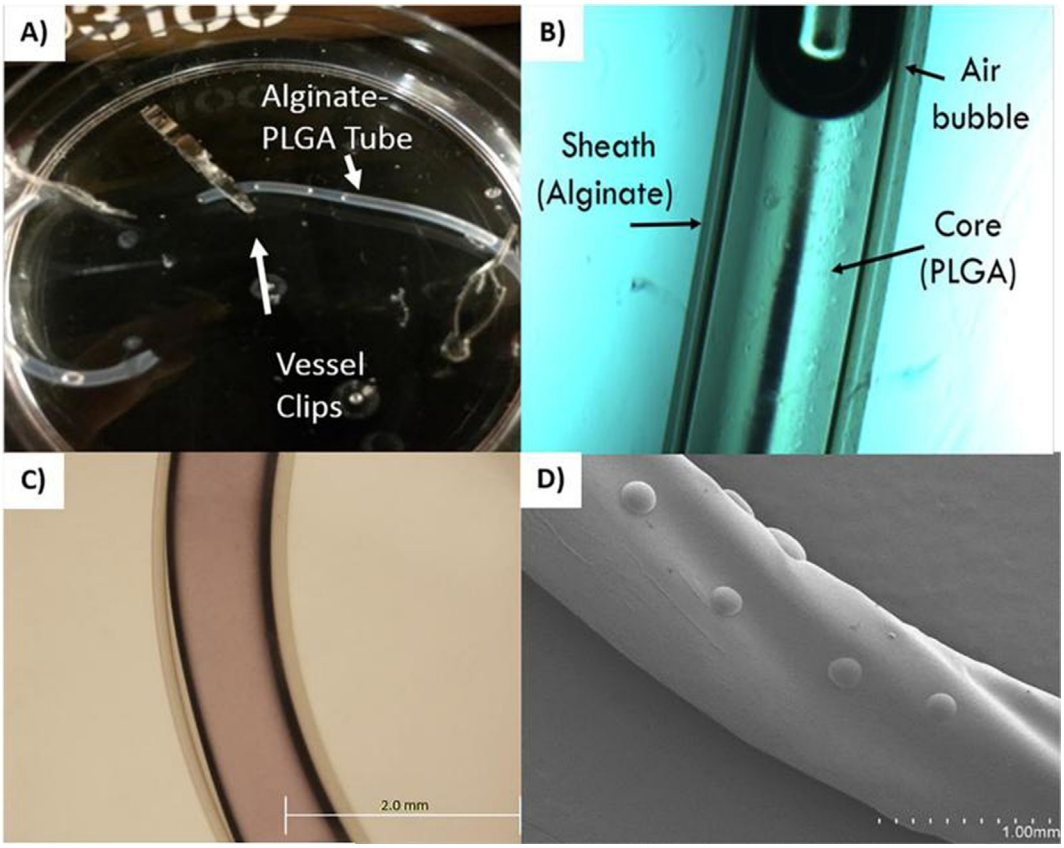

Fig. 15. Images of alginate-PLGA tubes prepared by PAM. A) A photograph of an alginate-PLGA tube. B) A light microscope image of an alginate-PLGA tube with the alginate sheath and PLGA core. C) C) A light microscope image of an alginate-PLGA tube, where the clear shell is alginate and the light-purple core is PLGA containing rhodamine. D) A SEM image of alginate-PLGA tube [177]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

amount of polymer leading to decrease the drug release rate. Moreover, the surface area/volume (SA/V) ratio that is also linked to the dissolution behavior of the printed tablets, was found to be important factor, which can affect the drug release rate. Higher SA/V ratios showed faster drug release.

4.2.5. Ethyl cellulose (EC)

Ethyl cellulose (EC) is a water-insoluble thermoplastic polymer that has been recently found to be used in AM pharmaceuticals. EC is a linear polysaccharide derived from cellulose, in which some of the hydroxyl (–OH) functional groups are replaced by an ethoxy group ($-O-CH_2-CH_3$). It has a T_g of around 130 °C and a melting point of around 180 °C, which are dependent to the polymer molecular weight. EC is highly flexible and transparent and has considerable mechanical strength, toughness and film forming ability. In addition, EC has good compatibility with organic materials that allows it to be used as a rheology modifier in films, binders, adhesives, and hot blends with other polymers [179]. These properties are taken advantage of while using EC in AM in the pharmaceutical industry. EC is usually used for sustained drug delivery systems as a polymer in drug formulations [180]. Yang et al. [181], reported additively manufactured tablets with an internal scaffold structure using EC for the sustained release of ibuprofen. Ibuprofen and EC, together with other excipients, were mixed and extruded into filaments by HME and printed into tablets by FDM (Fig. 17). The drug release behavior was affected by drug con-

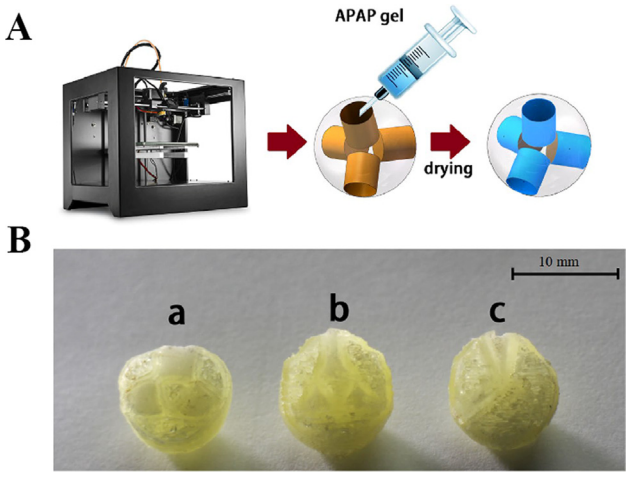

Fig. 16. A: The process of preparing 3D printed PVA-based tablets through FDM method injected with paracetamol (APAP)-containing gels. B: Photos of 3D printed tablets with the three models. (a) Cylinder model, (b) Horn model, (c) R-Horn model [178].

tent, release modifiers, fill density, and shell thickness. In addition, the printing shape and quality were dependent on the drug content, printing temperature, print speed, layer height, fill density and shell thickness. A controllable 24 h sustained ibuprofen release behavior was achieved through a diffusion-erosion mechanism.

Multi-drug and controlled release miniprintlets with different sizes were developed by Awad et al. using SLS [36]. They investigated the suitability of SLS for manufacturing of miniprintlets using EC and Kollicoat IR as polymeric matrices and incorporating two model drugs, paracetamol and ibuprofen. The dual miniprintlets were prepared in two various configurations (Fig. 18); in configuration A (Con A), paracetamol was mixed with Kollicoat IR (Par/KIR region) and ibuprofen was with EC (Ibu/EC region). In configuration B (Con B), the positions of the drugs were exchanged, and paracetamol was mixed with EC (Par/EC region), while ibuprofen was mixed with Kollicoat IR (Ibu/KIR region). The release studies revealed that the release profiles were affected by varying the polymer and were programmed to achieve customized drug release patterns. The results showed that one drug was released immediately from the Kollicoat IR matrix, whereas the second drug mixed with EC was released in a sustained way over an extended time.

4.2.6. Hydroxypropyl cellulose (HPC)

Hydroxypropyl cellulose (HPC) is a flexible and water-soluble polymer, which is a cellulose ether of which the hydroxyl groups on the backbone have been hydroxypropylated. HPC is suitable for formulating drug release systems with different release profiles owing to its availability in different grades of viscosity and average molecular weights (M_W). High molecular weight HPC has high swellability, which is suitable for controlled-release drug delivery systems. HPC has high levels of hydroxypropyl functionalities (~70%) and is more hydrophobic compared to other water-soluble cellulose ethers. HPC has a low T_g in the range of −25 °C to 0 °C as the moisture content varies from 1 to ~10% [182]. It is a highly thermostable polymer that makes it suitable for processes that require melting and extrusion [96].

3D-printed tablets based on an EC and HPC blend using HME and FDM were developed by Borujeni et al. to achieve zero order sustained release profile of carbamazepine (CBZ) [183]. The ratio of EC: HPC: CBZ blend had influence on the extruded filaments' mechanical and printability properties. The filament formulation containing CBZ, EC and HPC (3, 64.7 and 32.3% w/w, respectively) showed optimum printability and mechanical properties with hardness of around 72 N, which is suitable for handling and packing. Both blank and CBZ containing tablets prepared by HME and FDM were cylinder-shaped and their size were about 13 mm in diameter and about 3.5 mm in thickness. The optimum filament showed a first order drug release pattern, while the additively manufactured tablets showed a zero-order drug release and slower drug release rate than the optimum filament.

To overcome one of the major disadvantages of FDM by avoiding the filament preparation by HME, Goyanes et al. [92], used DPE for fabrication of sustained release itraconazole printlets (3D printed tablets) using four HPC grades (UL, SSL, SL and L) and evaluated the characteristics of the printlets. The prepared printlets showed a cylindrical shape and good adhesion between the printed layers with good mechanical and physical characteristics. As shown in Fig. 19, by reducing the molecular weight of HPC, the smoothness of the printlets was increased in the following order:

HPCUL > SSL > SL > L.

The printlets prepared by ultra-low molecular grade HPC (HPCUL) showed faster drug release than the other HPC grades, since itraconazole was found as an amorphous solid dispersion.

4.2.7. Hydroxypropyl methylcellulose (HPMC)

HPMC is a cellulose ether derivative in which the hydroxyl groups present in the cellulose ring have been substituted with one or more hydroxypropyl methyl groups. HPMC is a hydrophilic (water soluble), biodegradable, and biocompatible polymer that is used to increase the potential of active pharmaceutical ingredients (APIs) in the sustained release of drugs. It has high swellability, which affect the release kinetics of pharmaceuticals. HPMC has a T_g of 170–198 °C and by heating above 75–90 °C, it forms a gel [184]. Because of this property, HPMC has been used as capsule shells as a substitute for gelatin [185]. However, the dissolution and disintegration of HPMC capsules will decrease by increasing the temperature above 30 °C. Therefore, it usually advised to take HPMC capsules with cold water. The advantage of these capsules compared with hard gelatin capsules is their wider consumer acceptance because some of their ingredients are attained from vegetable sources [186].

Kadry et al. [35] used HPMC and diltiazem as a model drug, to develop both drug-free and drug-impregnated filaments for preparing tablets using FDM. They studied the thermal, crystalline and cytotoxicity properties of the filaments, and designed and printed tablets with several infill densities and patterns. The *in vitro* drug release profiles and *in vivo* oral absorption of drug in rats were also investigated (Fig. 20). According to the *in vitro* drug release results, the drug release profile was influenced by infill density, as well as infill patterns in which by increasing the infill density to 100%, the percentage of released drug was dramatically declined. By alternating drug-free and drug-loaded layers in some tablets, a delayed and intermittent drug release profile was seen, which depends on when the drug-loaded layers encountered the dissolution media. In addition, the oral absorption patterns also reproduce absorption profiles similar to those of *in vitro* release profiles and exhibited immediate, extended, delayed, and episodic absorption of the drug from the rat gastrointestinal tract (GIT).

4.2.8. Polyvinyl pyrrolidone (PVP)

Polyvinyl pyrrolidone (PVP) is a biodegradable and hydrophilic polymer, derived from N-vinylpyrrolidone monomer. PVP has been employed for a wide range of drug delivery applications, which include oral, topical, transdermal, and ocular administration. It has unique physical and chemical properties, including biocompatibility, nontoxicity, chemically inert, temperature-resistance, and

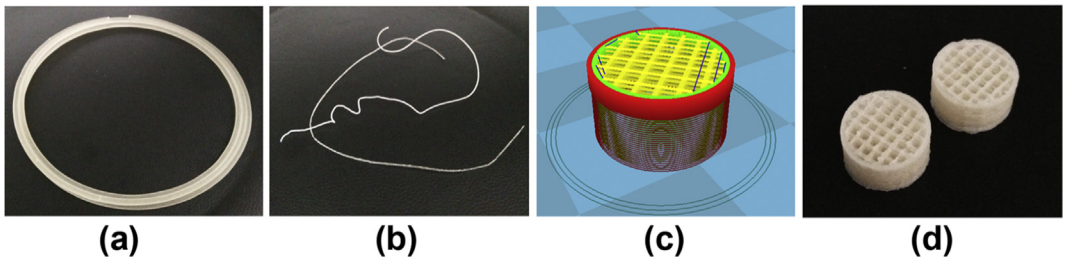

Fig. 17. Typical appearance of a) HME filaments (ibuprofen = 20%, EC:HPMC = 3/1), b) printing filaments (printed at 175 °C, 60 mm/s), c) STL model and d) printed tablets [181].

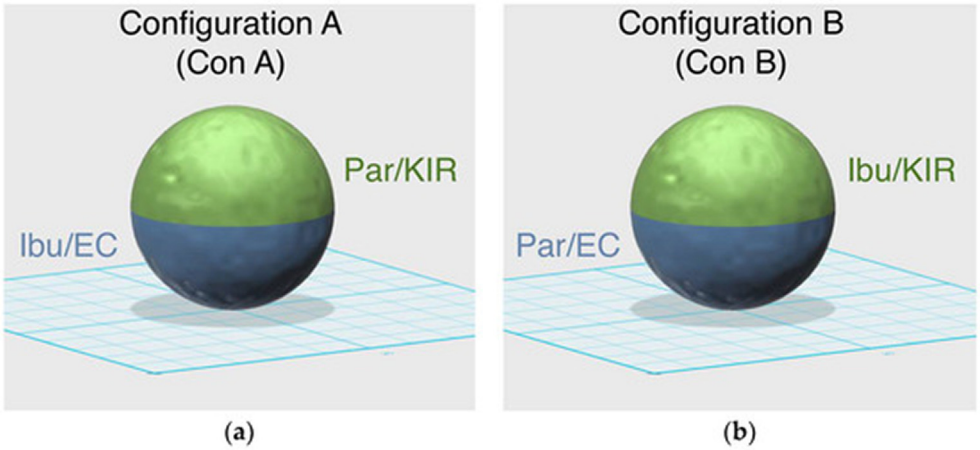

Fig. 18. Schematic representation of dual miniprintlets with different compositions prepared by SLS: (a) configuration A and (b) configuration [36].

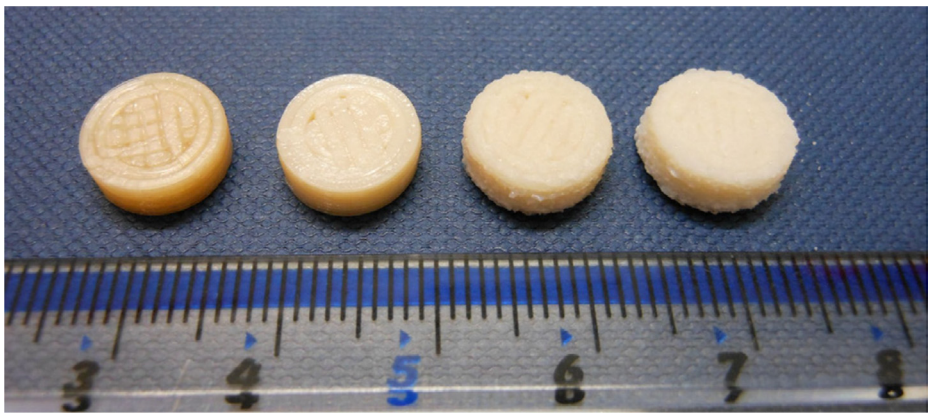

Fig. 19. Pictures of itraconazole printlets prepared by DPE using four HPC grades, from left to right: Formulation UL, SSL, SL and L. Units are cm [92].

pH-stability, solubility in water and numerous organic solvents, which make it suitable polymer for drug delivery systems [187]. Okwuosa et al. [188], developed individualized gastro-resistant tablets, which are associated with major challenges for clinical staff in hospitals and healthcare centers. They are employed in a wide range of shell-core designs using PVP as a core and methacrylic acid co-polymer as a tablet shell. A twin-screw HME was used for preparation of filaments for both core and shell. A powdered blend of PVP, plasticizer (TEC), filler (talc) or tribasic phosphate sodium (TBP) and API (theophylline) was taken in an optimized ratio to create core of tablet. Eudragit L100-55, TEC and talc were mixed at 135 °C for 5 min in HME and the extrusion was performed at 125 °C using a nozzle (1 mm) to prepare tablet shell. FDM was used to prepare shell-core tablets. The prepared tablets showed gastric resistant properties and a pH-responsive drug release profile in both phosphate and bicarbonate buffers.

In another study, SLS was used to develop personalized solid oral dosage forms with different shapes and Braille or Moon patterns on their surface targeted to blind or visually impaired individuals (Fig. 21). Kollidon VA64, a vinylpyrrolidone-vinyl acetate copolymer, was used for SLS printing owing to its good printability and fast disintegration properties and paracetamol was also utilized as a model drug. Fig. 21 shows the printlets fabricated by SLS with intricate and complex patterns, which confirms the

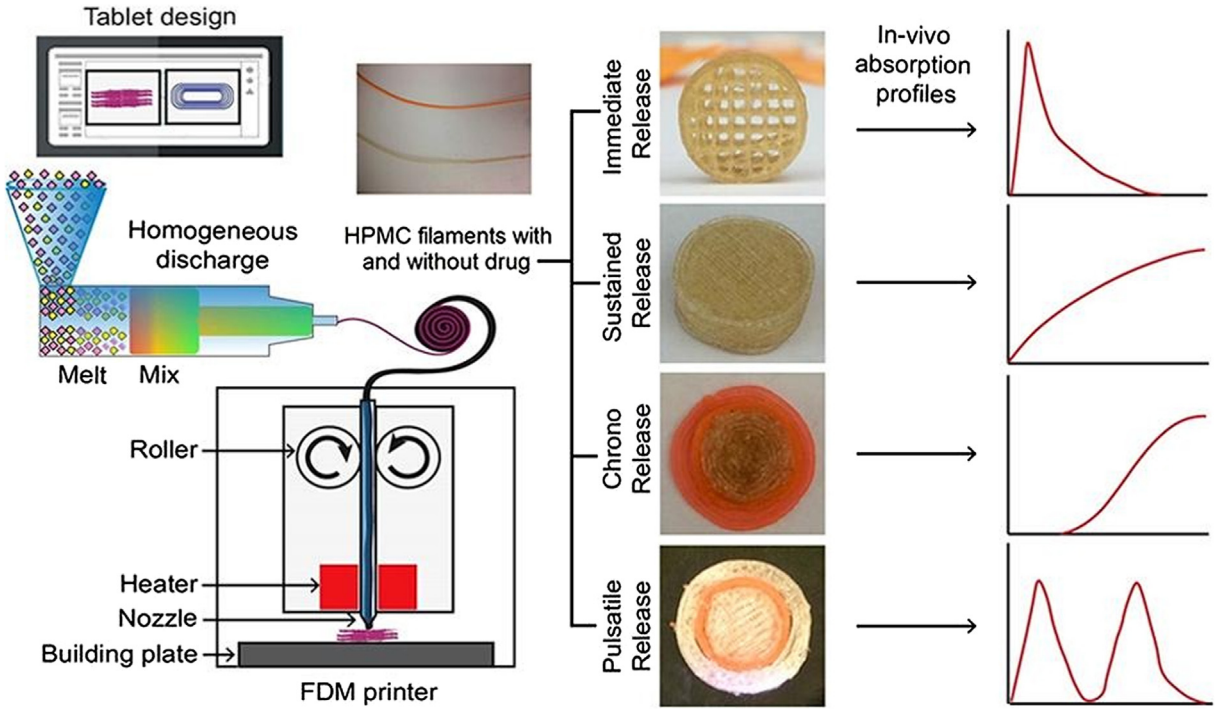

Fig. 20. Multi-purposable filaments of HPMC for AM of medications with tailored drug release and timed-absorption using FDM [35].

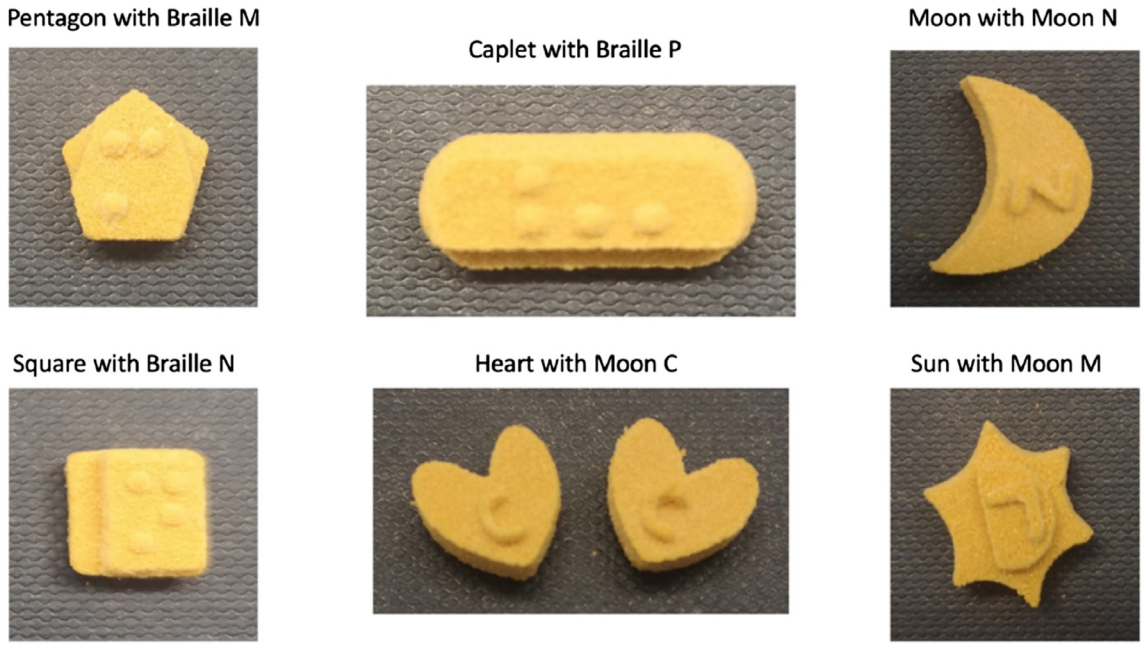

Fig. 21. Printlets with different shapes having Braille or Moon patterns using SLS and vinylpyrrolidone-vinyl acetate copolymer [151].

potential of this technique for providing a revolutionary approach to improve medication adherence and independence amongst visually impaired patients to reduce medicine errors [151].

4.2.9. Polyethylene glycol diacrylate (PEGDA)

Recently, PEG-based hydrogels have been widely used in the pharmaceutical field. Among PEG hydrogel-forming polymers, polyethylene glycol diacrylate (PEGDA) is a short chain polymer that has been investigated as a photopolymerizable acrylate to prepare hydrogels via AM technologies. Water solubility and availability of acrylate groups make this polymer a first choice to prepare hydrogels using light-based AM techniques. 3D-printed PEGDA-based scaffolds were developed by Vehse et al. using micro-SLA based on diode laser curing (DLC) for acetylsalicylic acid (ASS) delivery [189]. The mechanical analysis showed that the ASS concentration affected the compressive strength of the 3D-printed scaffolds. According to the reported results, the enriched and DLC-cured PEGDA showed the compressive strength of 7–10 MPa, while the samples without ASS showed the compressive strength of 14 MPa. The drug release characteristics were studied

in a physiological NaCl solution and the results showed an initial burst release phase and the ASS was released within the first 3 h. In another study, PEGDA was used as a crosslinker to prepare pH-sensitive hydrogel-based drug delivery system. The drug release profile was dependent on amount of PEGDA and was delayed by increasing the amount of PEGDA in the reaction mixture [190]. Martinez et al. [191], used SLA to prepare cross-linked ibuprofen-loaded hydrogels. Hydrogels containing up to 30% w/w water, and 10% w/w ibuprofen, were successfully printed. Dissolution profiles exhibited that ibuprofen release rates were dependent on water content and the hydrogels with higher water content showed a faster drug releasing profile (Fig. 22).

4.2.10. Ethylene vinyl acetate (EVA)

One of the most commonly used non-degradable polymers in implantable controlled-released applications is EVA, a copolymer of ethylene and vinyl acetate (VA). EVA is biocompatible and non-toxic, which has FDA approval for pharmaceutical applications. The VA content in an EVA copolymer can range between 0 and 40% with the amount affecting the properties of the copolymers, including polarity, adhesion, impact resistance, flexibility, optical properties, compatibility, stiffness, softening point, melting point, and crystallinity. Various grades of EVA copolymers have good printing potential and have been used in pharmaceutical applications for decades for the development of implantable drug delivery systems, such as custom-made T-shaped IUS and subcutaneous rods by FDM. EVA was used to print 5% and 15% indomethacin-loaded filaments. It was found that the indomethacin in the 3D-printed prototypes was amorphous, while it was crystalline in the corresponding HME filaments. This difference affects the drug release profiles from the filaments and printed prototypes, leading to a faster release from the prototypes prepared by AM [192].

4.2.11. Polyurethane (PU)

PU is a non-degradable thermoplastic polymer, which can be tailored with biocompatible characteristics to biological systems, such as blood, organs and organic tissues and biodegradability depending on its components. It is comprising of a relatively long and flexible oligodiol (soft segment) and a relatively rigid part imparted by a chain extender, diisocyanate (hard segment). The mechanical properties of PU can be easily modified and optimized by altering the hard and soft segment ratio and composition [193].

To improve biocompatibility and toxicity reduction, waterborne PUs and organic solvent-free PU systems have been developed for the controlled release of drugs, especially in the form of nanoparticles [194], hydrogels [195], films [196] and biodegradable implants [197]. Hung et al. [198] developed water-based PU scaffolds with a controlled release function for customized cartilage tissue engineering using low-temperature PAM. The scaffolds were printed from the printing ink containing an aqueous dispersion of PU, high viscosity hyaluronan and bioactive ingredients transforming growth factor beta-3 (TGFβ3) or a small molecule drug Y27632 to replace TGFβ3. The reported scaffolds increased the self-aggregation of mesenchymal stem cells (MSCs) and showed a time-dependent release profile of the bioactive ingredients. They suggested that the chondrogenic differentiation of MSCs and the produced matrix can be used for cartilage repair.

Recently, the use of isocyanate-based monomers in PU synthesis raised severe health concerns. Therefore, in the last decade, researchers have attempted to develop alternatives, to reduce the concerns about the toxicity and the environmental impact of the reagents used in PU synthesis. Isocyanate-free PUs have been recently developed as sustainable, more biocompatible, and environmentally friendly alternatives to traditional isocyanate-based PUs. Isocyanate-free PUs have good potential to be used in biomedical applications [199,200]. However, until now, no work has been done for preparing drug delivery systems based on isocyanate-free PUs using AM.

4.2.12. Polydimethylsiloxane (PDMS)

PDMS is one of the most common non-degradable polymers employed in drug delivery systems. Instead of the hydrocarbon backbone in the other polymers, there are inorganic Si-O-Si units in the PDMS backbone. Through modification of the PDMS structure and changing the degree of cross-linking, desirable mechanical properties that are needed for implantable materials can be achieved [201]. Due to the hydrophobic nature of PDMS, hydrophobic drugs are usually incorporated in the polymer for sustained release [46]. PDMS was used for controlled release of different drugs, such as hormones, digitoxin, histamine and atropine from different drug delivery systems with various shapes [201,202]. Holländer et al. [102], reported UV light cured PDMS devices prepared by SLA for drug delivery application. 3D printed structures with different pore sizes and different drug loadings were prepared using prednisolone as a model drug. It was concluded that the drug release rate was influenced by altering the surface area/volume ratio. In this study, both the extrusion-based AM and the UV-crosslinking was performed at room temperature, which make this method an alternative for development of controlled release systems comprising temperature sensitive drugs.

In this section, a wide variety of polymers that were used for preparing drug delivery systems by different AM techniques were discussed. However, since this field is rapidly developing, there are many published research studies that used several polymers or polymer blends for developing drug delivery systems using AM.

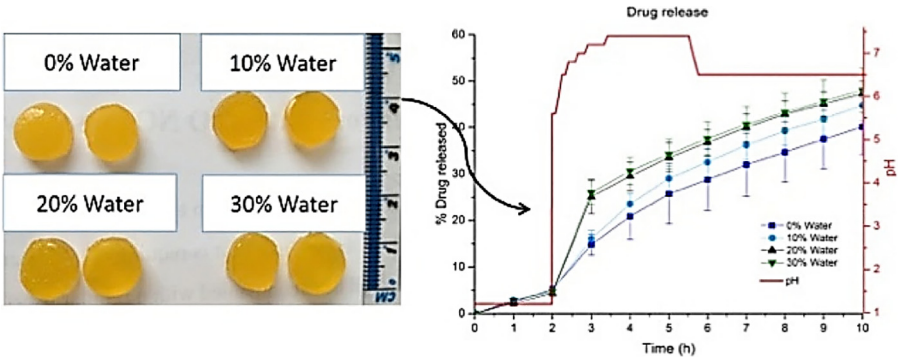

Fig. 22. Printed hydrogels containing photoinitiator with various water contents (the scale is shown in cm) and dissolution profiles of ibuprofen from the four printed hydrogels in the dynamic dissolution system (n = 3). Red line shows the pH values of the media [191]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1 gives a comprehensive overview of materials (polymers and drugs) and several AM techniques used for the development of drug delivery systems.

Table 1
Comparative overview of polymers and drugs used in different AM techniques for development of drug delivery systems.

AM technique	Polymers	Drug model	References
FDM	PVA	Glipizide	[203]
	Eudragit®RS	Quinine	[71]
	PCL		
	PLLA		
	EC		
	PVA	Paracetamol	[8]
	HPC	Acetaminophen	[90]
	PLA	Acetaminophen	[204]
	PVA		
	HPMC		
	PVA-PEG graft copolymer		
	PEG		
	EVA	Indomethacin	[192]
	PVPA, PVA-g-PEG, HPMC	Haloperidol	[205]
	PLA	Fluorescein	[172]
	PVA, PLA, Eudragit (poly (meth)acrylate)	Glimepiride, Metformin, Mannitol	[206]
	PLA, Eudragit	5-Fluorouracil and triethyl citrate	[207]
	EC, HPMC	Ibuprofen	[181]
	PCL/Eudragit®RL100	Deflazacort	[77]
	Commercially produced Flex EcoPLA™ (FPLA)/PCL	Salicylic acid	[70]
	PCL	Lidocaine	[133]
	PLA/PVA	Clobetasol propionate	[208]
DPE	HPC	Itraconazole	[92]
		Caffeine	[94]
		Tramadol	[95]
PAM	HPMC/Sodium starch glycolate (SSG)/ Microcrystalline cellulose (MCC)	Guaifenesin	[98]
	HPMC/PEG	Glipizide	[104]
	2-Hydroxypropyl-β-cyclodextrin (HPβCD)/ HPMC	Carbamazepine	[100]
	PLGA/PCL	5-fluorouracil (5-FU)	[107]
Inkjet printing	PLLA	Levofloxacin	[112]
SLA	PVA		[114]
	PEGDA	Paracetamol	[120]
	Dental SG, Formlabs	Insulin	[113]
	PEGDA/PEG	Salicylic acid	[70]
	PDMS	Prednisolone	[102]
CLIP	PEGDMA	Bovine serum albumin, ovalbumin, and lysozyme	[138]
	PEGDMA, HEMA	Rhodamine B	[135]
SLS	PEO, Eudragit, EC	Paracetamol	[153]
	Kollicoat IR (75% PVA and 25% PEG copolymer) Eudragit L100-55 (50% methacrylic acid and 50% ethyl acrylate copolymer)	Paracetamol	[152]
	Kollidon® VA 64 and microcrystalline cellulos	Clindamycin palmitate hydrochloride	[148]
	Cyclodextrin Cavamax® W7 and Kollidon® VA-64	Ondansetron Hydrochloride	[209]
2PP	PEGDMA	Rhodamine B	[140]
	Gelatin methacryloyl, lithium phenylphosphosphinate, iron oxide, poly(ethylene glycol) amine	Dextran-FITC	[141]

5. Conclusions and future perspectives

Even without the use of AM, the potential of polymer-based drug delivery devices is evident. Polymers allow for drug delivery *in vivo* over an extended period at the exact site of action. Additive manufacturing can add novel dimensions towards truly tailored drug release profiles and targeted delivery as AM allows for personalized medicine and enables the preparation of complex geometries which can influence the drug release. Consequently, the use of AM for the preparation of polymeric drug delivery devices is receiving increasing amounts of interest in scientific research.

The highly regulated pharmaceutical industry is also highly conservative towards changing the established and validated procedures. In addition, AM may still need time to challenge the capacity of current conventional and highly efficient preparation methods of drug delivery systems. One of the first challenges in the field will be to further push the enormous potential of personalized medicine by AM into the pharmaceutical industry.

Future developments in polymeric drug delivery include improvement of the functionality of the polymers, the incorporation of multiple drugs at the same time and programmed release. Improved functionality can be achieved by increased thermal and electrical conductivity, dielectricity, biocompatibility and degradability. These improved functionalities could be utilized to obtain more control over the release. Ultimately, this could result in true programmed release, for example by using the improved functionalities to enable drug release influenced by outside stimuli.

The next level of AM development is to achieve printing of truly multifunctional, multimaterial structures. Multimaterial AM processes usually utilize multiple nozzles for varying the material type, functionality and composition of each layer. Such multimaterial approach can significantly enhance the performance of manufactured structures. This does increase the complexity of the design process, as the effect of polymer-polymer and polymer-additive (composite materials, drugs or bioactive agents) interactions, and localized differences in mechanical and degradation properties need to be taken into account, perhaps even at a voxel-by-voxel level. This process can be revolutionized by using AI to help determine the desired formulation [210].

In addition, a recent development in the AM field and 4D printing [59] may have features that are interesting for the drug delivery systems. As with AM in 3D, structures are prepared in a layer-by-layer manner. However, 4D printing adds a 4th dimension, which was initially defined as 'time'. In other words, these structures can change in shape or function over time depending on their environment or as a response to stimulation. Intelligent drug delivery devices prepared by AM that in response to their surrounding change the type or rate of drug released would be an incredible step forward in personalized medicine. 4D printing could make this possible. Recently, drug delivery devices were prepared by FDM which showed the ability to change shape based on temperature over time and the drug release was influenced by the shape of the device [211,212]. An interesting class of materials for 4D printing is formed by polymer conjugates. These intelligent release systems, along with AM, provide specific opportunities for designing programmable control release systems [59].

Further improvements could be achieved by improving the production methods of the drug/polymer feedstock materials used by the several AM techniques. Currently, the preparation of these materials routinely involves solvents or heat which poses a limiting factor in the use of bioactive agents and drugs where milder conditions are preferred. Additionally, improvements here can be achieved by the (re)design and synthesis of novel monomers and polymers that have specifically tailored thermal and rheological

properties that fit with the AM technology they are intended for. Furthermore, this (re)design may positively affect the potential release mechanisms and kinetics, biocompatibility and toxicity of currently available polymers making them more suitable for drug delivery applications.

The challenge for AM of drug delivery devices is to combine the above-mentioned developments. This challenge should be considered an opportunity as applying the development of each respective field may be accelerated and completed by the other field. Through multimaterial printing for example, multiple drug can be incorporated and their positioning in the structure can be carefully controlled. By choosing the polymers carefully, so can be the type and moment of release.

AM of polymeric drug delivery devices is a rapidly expanding field that profits from developments in both separate fields. With the rapid technological advances in the field of AM and the continuous development of polymeric materials for AM, it seems only a matter of time before personalized, multimaterial, multifunctional drug delivery devices prepared by additive manufacturing find their way into the clinic.

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