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REVIEW

Cellulose and its derivatives for application in 3D printing of pharmaceuticals

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Abstract

Background Three-dimensional printing (3DP) has emerged as an advanced manufacturing technology capable of producing complex yet precise medicines intended for patient-centric drug therapy. However, printable materials currently available for 3DP are far too limited.

Area covered The current article covers various cellulose-based polymers as well as their applications, especially in 3DP of oral solid dosage forms. The review focuses on their physicochemical properties, roles, and functions in conventional as well as 3DP dosage forms, and the characteristics of the obtained printed products are discussed. In addition, the challenges and considerations for processing cellulose-based feedstock materials are briefly presented.

Expert opinion Cellulose and its derivatives are regarded as suitable polymers with a huge potential for applications in 3DP drug delivery systems. It is therefore essential to better understand cellulose-based printable polymers and their applications in 3DP.

Keywords Cellulose · 3D printing · Hydroxypropyl methylcellulose · Hydroxypropyl cellulose · Ethylcellulose · Hydroxypropyl methylcellulose acetate succinate

Introduction

The manufacturing of patient-specific pharmaceuticals and biopharmaceuticals exploiting three-dimensional printing (3DP) technology has gained a large boost and has been increasingly investigated over the past few years (Sandler and Preis 2016; Lim et al. 2018). Though conventional pharmaceutical manufacturing processes (e.g. direct powder compaction, encapsulation) have a long history and are cost-effective due to large-scale (mass-oriented) production, they are based on a "one-size-fits-all" principle, and thus are inefficient for the production of complex, dose flexible, and tunable-release preparations (Rantanen and Khinast 2015). It is obvious that dose requirements can vary according to the characteristics of individual patients such as, gender (Freire et al. 2011), genetics (Elens et al. 2010; Hulot et al. 2011), age (Merchant et al. 2016), body mass (Hamburg and Collins 2010; Taherali et al. 2018), height (Houghton et al. 1975), disease conditions (Breitkreutz and Boos 2007), and metabolic rate (Sandler and Preis 2016). Thus, to overcome the limitations of traditional manufacturing processes and emphasize patient-centric healthcare, customized drug therapy based on the profile of individual patients is essential (Tutton 2012). Advancements in healthcare industries and the introductions of new manufacturing technologies, specifically 3DP has paved the way to a better health care system by enabling the fabrication of precise and personalized medicines, resulting in enhanced therapeutic outcomes.

Three-dimensional printing (3DP), also referred to as "additive manufacturing" (AM) or "rapid prototyping", is a process of fabricating 3D objects by the deposition of material(s) in a layer-over-layer pattern using a printer head, nozzle(s), or other printing methods. A Japanese scientist (Dr. Hideo Kodama) reported the first use of 3DP technology in 1981 (Kodama 1981). Later, in the mid-1980s, another 3DP technology (stereolithography) was first patented by Charles ("Chuck") Hull, co-founder of the first 3DP

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company "3D Systems Corporation", also recognized as "the father of 3DP" (Hull and Arcadia 1986). Further, in 1987, Dr. Carl Deckard first developed and patented selective laser sintering (SLS) 3DP technology. To date, several 3DP technologies have been developed and investigated (Table 1). Amongst them, fused filament deposition (FDM), first developed by Stratasys founder and CEO Scott Crump in 1988, is the most widely used 3DP technology (Crump 1989). All of these 3DP technologies follow a common pathway (Fig. 1): first a 3D model of the object is created using computer-aided design (CAD) for example, digital scanning, computerized tomography, magnetic resonance imaging or optical scanner, and exported to a standard tessellation language (STL) format file. Afterward, the model is constructed into the final 3D object by the deposition of material(s) in a layer-by-layer fashion (commencing from the base to the top layer) through the use of the 3D printer.

During its early days, 3DP was primarily used to design and test object prototypes. However, with recent innovation in the printing tools, easy accessibility of free online design software, availability of low-price 3D printers, improvements in printer resolution, and the simplicity of developing complex products, 3DP technology is currently in the limelight. It is being exploited in myriad fields including the automotive and aerospace (Liu et al. 2017), architecture (Gibson et al. 2002), construction (Tay et al. 2016), fashion (Vanderploeg et al. 2017), food (Godoi et al. 2016), jewelry (Ferreira et al. 2012), healthcare and medical (pharmaceutical, dentistry, tissue engineering) (Lee Ventola 2014) industries and many more. Wu et al. (1996) were the first to exploit 3DP technology (solid free form) to prepare controlled drug delivery devices. Later, with the approval of the first 3D printed pharmaceutical, Spritam® (levetiracetam 1000 mg tablets by Aprecia Pharmaceuticals) by the U.S. Food and Drug Administration (FDA) in 2015 (Aprecia Pharmaceuticals 2015), this technology has opened a new avenue in the manufacturing of pharmaceutical dosage forms. This is evidenced by the trend in recent scientific publications related to 3DP, which have skyrocketed (Lim et al. 2018). However, most of these studies are confined to the development of 3DP prototypes/models or products based on proof-of-concept approaches. The first 3DP medicine was commercialized approximately five years ago and remains the only 3DP pharmaceutical licensed for the human use to date.

Despite considerable innovations, 3DP in still in its infancy with regards to pharmaceutical formulations. One of the major obstacles limiting its success is the lack of suitable pharmaceutical-grade feedstock materials available for printing. Polymers have always been the key constituents of conventional as well as 3DP pharmaceutical solid dosage forms. In general, polymers are used as binders, diluents or fillers, disintegrants, lubricants, coating agents, solubilizers, release modifiers, etc. in tablets or capsules, and as rheology controlling agents, emulsifying agents, etc. in liquid preparations (Liechty et al. 2010; Siepmann et al. 2019). In 3DP, the feed material influences the choice of printing method as well as the processing conditions such as extrusion temperature, printer settings, dosage structure (shape and size). It also plays a crucial role in the characteristics (e.g. drug loading, drug release profile) of the dosage forms (Ortiz-Acosta and Moore 2019; Azad et al. 2020). However, the range of printable polymers available for 3DP is narrow, possibly due to a lack of understanding regarding the properties, selection criteria, and processing techniques for these feed materials. It is therefore crucial to have a concise understanding of the polymers, their properties, and their impact on product preparation such as their thermal nature (glass transition temperature (T_g), melting temperature (T_m), degradation temperature (T_d)), viscosity, bulk property (particle size, powder flowability), solubility, and processing temperature range. There are several studies and review literatures available that provide comprehensive information on the various types of 3DP as well as their working principles, process considerations, pharmaceutical applications, technical challenges, and key limitations (Lim et al. 2018; Norman et al. 2017; Liang et al. 2018; Alhijjaj et al. 2019; Palo et al. 2017). Thermoplastic materials, specifically polylactic acid (PLA), polyvinyl alcohol (PVA), and poly(caprolactone) (PCL) have been mostly investigated for 3DP and information about their applications, characterization, and considerations for 3D-printed drug delivery is available in recently published literature (Azad et al. 2020; Jain et al. 2018; Konta et al. 2017; Long et al. 2016). Consequently, these areas will not be covered in this review.

Cellulose is an "eco-friendly", pharmaceutical-grade polymeric material that has long been used as an excipient for different types of drug products such as extended or controlled release formulations, osmotic drug delivery, amorphous solid dispersions, and bio-adhesive and mucoadhesive preparations (Kamel et al. 2008; Shokri and Adibki 2013). Unlike synthetic thermoplastic polymers (e.g. PVA, PCL, PLA), which are generally commercially available for ready-made printing, cellulosic filaments with/without drugs need to be produced in-house to be used as feedstock material for FDM 3DP (Zhang et al. 2017b; Giri et al. 2020). It has therefore become crucial to understand the physicochemical and mechanical properties of cellulose and cellulose-based polymers. Unfortunately, details about the physicochemical properties of cellulose polymers, their roles, and functions in 3DP are lacking. Therefore, in this review, we attempt to have a closer look at the cellulosic polymers, especially their physicochemical properties, roles, and applications in conventional as well as 3DP pharmaceuticals. In addition, we have concisely presented and tabulated the recently published literature on cellulose-based 3DP drug delivery,

Table 1 Overview of the main types of 3DP technologies

Types of AM	Working principle	Feed materials	Advantages	Limitations
Selective laser sintering (SLS)	High power laser beam is used to fuses the layers of a powder material	Polymers; PCL, PLA, nylon, polyamide, polystyrene, or metals (steel, titanium, and composites)	Ability to fabricate complex structures with high resolution (~ 100 µm) Fully automated and has high productivity	Slightly rough surfaces (10–100 µm) Limited speed for sintering High energy might degrade feed material(s)
Stereolithography (SLA)	Liquid resin is cured and solidified using UV light to form an object	Photosensitive resin; a curable laser photopolymer or other plastic-like products (ABS)	High-resolution (~ 10–300 µm) and high accuracy Produces products with good surface finishing (~ 2 µm)	Requires additional post-printing curing Slow build process and low throughput Expensive feed materials and equipment
Fused deposition modeling (FDM)	Feed material is melted (solid extrusion) or paste is made (semi-solid extrusion) and then dispensed through nozzle(s) which gets hardens afterward	Filament made of thermoplastic polymers (PLA, PVA, PCL, HPMC, HPC)	Simple and versatile method and easy for home applications Higher drug loading and drug uniformity Low-cost of FDM 3D printers	Requires adequate quality filaments as feedstock material Poor surface texture (3–43 µm) and requires post-printing processes (polishing) High temperature may degrade the feed material(s)
Directed energy deposition (DED)	Focused thermal energy is projected to fuse and deposit molten materials	Stainless steel, copper, cobalt, titanium, nickel, aluminium	Good resolution Fast processing speed	Requires post processing to remove support structures
Inkjet printing	Spraying liquid or droplets of photopolymer depending on the type of binder used (binder or material)	Photocurable polymers; ABS, PLA, PCL, or plastic, metal, and ceramics	Wide range of material choice Rapid printing with high precision and high resolution (20–100 µm)	Require post-curing Tedious to remove supports
Sheet lamination	Sheets of material are layered together, and cut in required shapes by a laser	Sheets of paper or plastic or metals	Ideal for non-functional prototypes	Slightly less dimensional accuracy
Bio-printing	Biological materials (bioink) are dispensed through nozzle(s) or an orifice	Cell-laden hydrogels (chitosan, gelatin, alginate, collagen)	Large choice of starting materials Low printing temperature	Low build time, low accuracy, rough surfaces (10–330 µm)

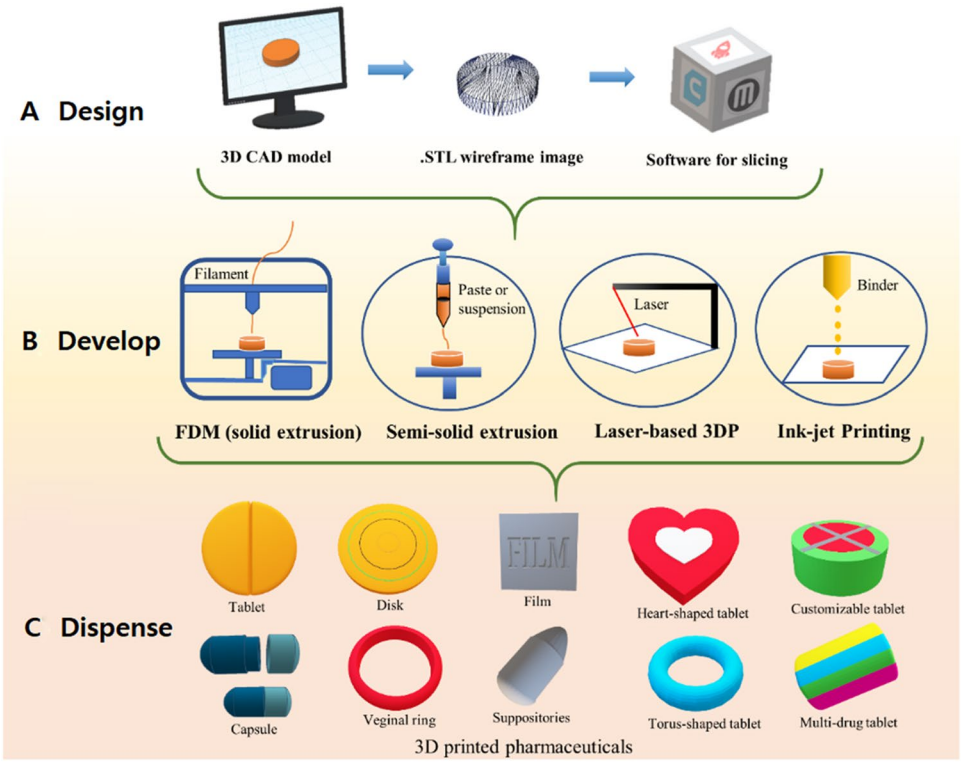

Fig. 1 Schematic illustrations of 3-dimensional printing process: **a** Design of solid dosage forms via computer-aided design (CAD); **b** Develop 3D objects using 3D printers; **c** Post-processing and dispense of the final printed devices

highlighting key information about the processing conditions, rheological and thermal properties, and characteristics of the final product. The closing section delves into the challenges and considerations of cellulose-based 3DP pharmaceuticals.

Cellulose

Cellulose is the most ubiquitous, renewable, and biodegradable organic polymer derived from plant and plant products. It is a nature maven that has shown great potential for use in automotive, plastic, and the medical industries. Cellulose is a chemically linear unbranched polysaccharide composed of substituted glucopyranose monosaccharides linked together at the 1, 4 position with a β-anomeric configuration (Fig. 2). The ribbon-like cellulose chain supports the closely packed arrangement, which enables inter-molecular hydrogen bonding to form structures with high crystallinity. The loosely packed molecules remain amorphous and the hydroxyl groups in the amorphous region are open for chemical reactions. The strong inter and intra-molecular hydrogen bonding makes cellulose insoluble in water and most common solvents (Hinterstoisser and Salmén 2000; Bochek 2003). Cellulose shows high reactivity at an elevated temperature, with an estimated T_g of 230 °C and T_m around 450 °C (Tegge 1985). The reactivity of the C–2, C–3, and C–6 hydroxyl groups imbues cellulose-based polymers with useful properties. Properties such as, plasticity and solubility are greatly affected by the degree of substitution (DS; average number of –OH groups replaced by substituents) and molar substitution (MS; length of side chains). Derivatives with higher DS tend to have lower aqueous solubility whereas the solubility in organic solvents is increased. In contrast, lower DS derivatives are sensitive and dispersive in water (Raymond C Rowe 2013). Further, an increase in MS or DS by nonpolar groups increases cellulose plasticity.

Cellulose consists of two major derivatives: cellulose ether and cellulose ester. These two derivatives vary in their physicochemical and mechanical properties, but both are used in the pharmaceutical and food industries. Cellulose ethers are derived by replacing H atoms of –OH groups in the anhydro-glucose units of cellulose with alkyl or substituted alkyl groups, whereas cellulose esters are obtained through esterification reactions with organic and inorganic acids in the presence of dehydrating agent or reaction with acid chloride (Cumpstey 2013). Cellulose and its derivatives are utilized as suspending agents in oral liquids (Glass and Haywood 2006), thickening agents in topical formulations (Nahata and Allen 2008), and characteristic drug delivery systems with immediate, controlled/sustained, or delayed release in tablet formulations (Edgar 2006; Kamel et al. 2008).

Cellulose ethers are polysaccharides that are found naturally and consist of methyl cellulose, ethyl cellulose (EC), hydroxypropyl cellulose (HPC), and their derivatives.

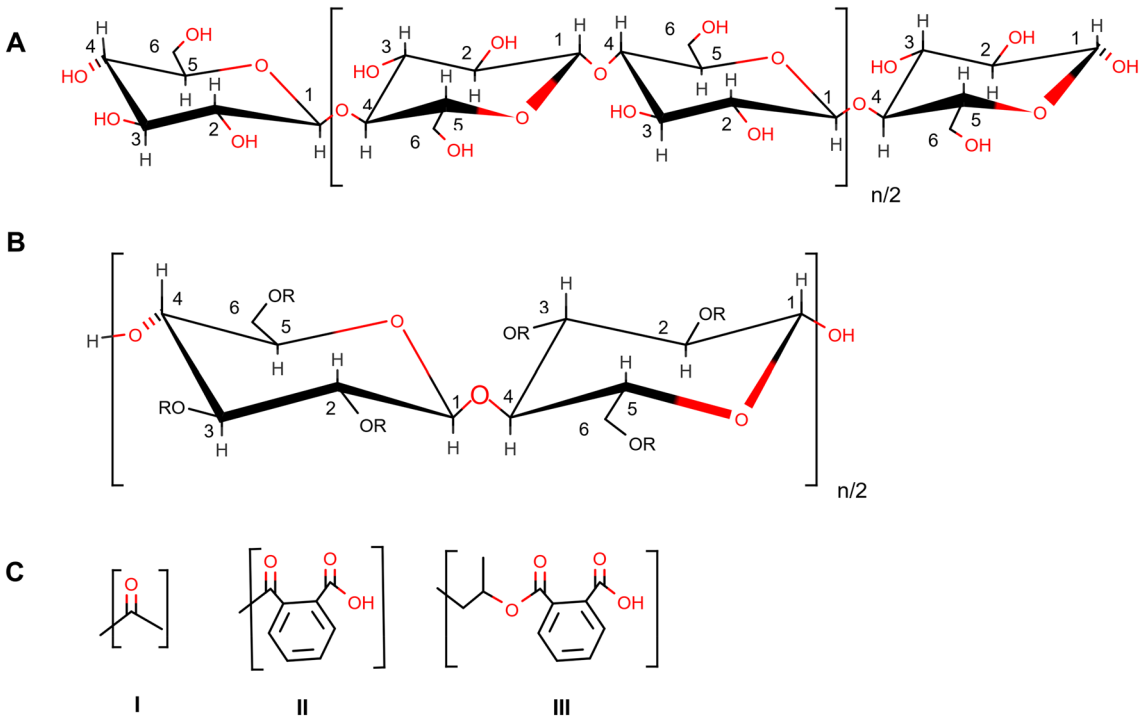

Fig. 2 **a** The chemical structure of cellulose with two β-1,4 linked anhydroglucose units; **b** a general chemical structure of cellulose derivatives; **c** chemical structure of different R groups in cellulose ester derivatives

Substitution with a methyl group on the cellulose structure yields methyl cellulose and further substitution with a hydroxypropyl group produces hydroxypropyl methylcellulose (HPMC). The solubility of cellulose ethers is affected by the DS. With an increase in DS, the solubility gradually shifts from dilute alkali to water and finally to an organic-solvent-soluble stage (de Freitas et al. 2017). Cellulose ethers with moderate and high molecular weights (MWs) are insoluble in water (Kirk Othmer 2004). They also exhibit gelation under influence of thermal energy, which is a desired feature for 3DP (Sarkar 1979). Apart from the gelation, their other thermal characters (T_g, T_m, and T_d), rheological characteristics (viscosity, yield stress, rigidity), and the influence of drug release mechanisms (immediate release, sustained release, controlled release) have broadened the scope of cellulose ethers in 3DP technology (Jamróz et al. 2018). Some of the commonly used cellulose ethers and ester derivatives, and their application in 3D-printed pharmaceuticals are discussed below: (Table 2)

Hydroxypropyl methylcellulose (HPMC)

HPMC or hypromellose is a hydrophilic polymer with partly O-methylated and O-(2-hydroxypropylated) cellulose (Fig. 2). HPMC is an odorless and tasteless, white or creamy-white fibrous or granular powder. The MW of HPMC ranges from approximately 10 to 1500 kDa. It is available in several grades with different viscosities and DS (Table 3). In general, HPMC is soluble and forms a viscous colloidal solution in cold water, but is practically insoluble in hot water, ethanol (95%), chloroform, and ether. HPMC powder is stable in nature (pH 3.1–11) (Lee et al. 2005) but becomes slightly hygroscopic after drying. HPMC undergoes reversible sol–gel conversion, upon application of thermal stress (heating and cooling). Based on the grade and concentration of the material, gelation temperature ranges from 50–90 °C. The viscosity of the solution decreases with an increase in temperature below the gelation temperature and increases with an increase in temperature above the gelation temperature (Sarkar 1979).

HPMC is one of the most widely studied polymers for pharmaceutical applications. It is mainly used as a tablet binder, film coating agent, drug solubilizer, delayed/extended release formulation, and suspending or thickening agent in liquid formulations (Chowhan 1980; Banker et al. 1981; Shah et al. 1989; Yokoi et al. 2005; Patere et al. 2015). Drug release from the HPMC matrix involves a complex mechanism (Kwon et al. 2019). Many dynamic processes are involved in the course of gel layer formation, drug dissolution, and diffusion through the gel layer as there is no distinct limitation on swelling, diffusion, and erosion (Peppas et al. 1980; Lee and Peppas 1987). It has been rationalized that primarily soluble drugs are released through diffusion from

Table 2 Cellulose derivatives with their trade names and applications

Cellulose derivatives	R groups	Trade names	Applications
Methylcellulose	H, CH_3	METOLOSE® SM, METHOCEL™ A	Disintegrant, binder, hydrophilic matrix
Hydroxypropyl cellulose (HPC)	H or $[CH_2CH(CH_3)O]_nH$	NISSO-HPC®, Shin-Etsu® L-HPC Klucel™	Binder, disintegrant, osmotic pump, hydrophilic matrix
Hydroxypropyl methylcellulose (HPMC)	H, CH_3, or $CH_3CH(OH)CH_2$	METHOCEL™ E, F, J & K, METOLOSE® SR PHARMACOAT®	Hydrophilic matrix, disintegrant, binder, osmotic pump, protective coating
Ethyl cellulose (EC)	H, CH_2CH_3	Aquacoat ECD®, Ethocel™	Binder, insoluble coating
Cellulose acetate (CA)	H, I	Eastman™ CA–398–10NF/EP	Filler, pressure-controlled membrane
Cellulose acetate phthalate (CAP)	H, I or II	Aquacoat CPD, Cellacephate	Enteric film coating, matrix binder
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	H, CH_3, I, $CH_2CH(OH)CH_3$, $COCH_2CH_2COOH$, $CH_2CH(CH_3)OCOCH_3$ or $CH_2CH(CH_3)OCOCH_2CH_2COOH$	Shin-Etsu AQOAT®	Micronized grade (F) for aqueous coating, Granular grade (G) for solvent-based coating, Solid dispersion
Hydroxypropyl methylcellulose phthalate (HPMCP)	H, CH_3, $CH_2CH(OH)CH_3$, II or III	Shin-Etsu® HPMCP	Enteric coating

Table 3 Overview of commercial grades of HPMC (Ghebremeskel et al. 2007; Patil et al. 2016)

Trade names	Molecular weight (kDa)	Nominal viscosity (mPa·s)	T_g (°C)	T_m (°C)	T_d (°C)	Moisture content (%)
Methocel K3 premium LV (2208 substitution type)	–	3	170–180	–	> 250	–
Methocel K100 premium LVEP (2208 substitution type)	25	100	147	168	259	< 0.5
Methocel K100M premium (2208 substitution type)	150	100,000	96	173	259	< 1.5
Pharmacoat® 606 (2910 substitution type)	10	6	139	–	244	< 2.0
AFFINISOL™ HPMC HME (15 cp, 100 cp, 4 M)	–	15, 100, 4,000	117–128	–	> 250	–

the gel layer while hydrophobic drugs are mainly released through gel erosion (Johnson et al. 1993; Lindner and Lippold 1995). The drug release from HPMC matrices becomes slower as the average MW of the polymer increases. Higher viscosity grades HPMC are used to retard the drug release from the matrixes at a level of 10–80% w/w while, lower viscosity grades are utilized in aqueous film-coating solutions (Nokhodchi et al. 2012). HPMC at 2–5% concentration may be used as a binder in wet granulation process. Apart from tablets, HPMC prevents aggregation of floccules and helps to maintain the deflocculating state (inhibiting sediments) in colloidal systems. Further, HPMC (0.45–1.0%w/w) is used as a vehicle in eye drops (Fernandez-Vigo et al. 1990). HPMC is "generally regarded as safe" (GRAS), nontoxic, and non-irritating polymer and does not pose any hazards to health. However, an excessive oral consumption may have a laxative effect (2017).

HPMC has been widely studied for the preparation of oral solid formulations using melt extrusion, inkjet, and laser 3DP technology. HPMC has a broad range of T_g values (160–210 °C), with a high melt viscosity, and a low degradation temperature (T_d), making it difficult to use for hot-melt extrusion (HME) processing (Bennett et al. 2015). Several studies have reported the use of plasticizers such as, polyethylene glycol (PEG), triacetin and triethyl citrate (TEC) to facilitate extrusion of HPMC filaments for 3DP (Goyanes et al. 2016; Kempin et al. 2017; Beck et al. 2017). However, the concentration of the plasticizer added should be considered as a few reports observed that plasticizers can affect gastrointestinal (GI) motility and lead to variations in gastric and intestinal transit times (Basit et al. 2001; Johnson 2002; Oosaka 2014). Khizer et al. (2019) demonstrated the use of hydrophilic polymers (Methocel®K4M, K15M, and K100M) without the aid of plasticizers in drug release (Fig. 3). The authors reported that using a low MW drug helped to plasticize the polymer during extrusion and thermal characterization ensured the operating temperature (170 °C) was below the degradation temperature of both the drug and polymer. The HPMC grade with the highest viscosity and molecular size, K100M, exhibits maximum

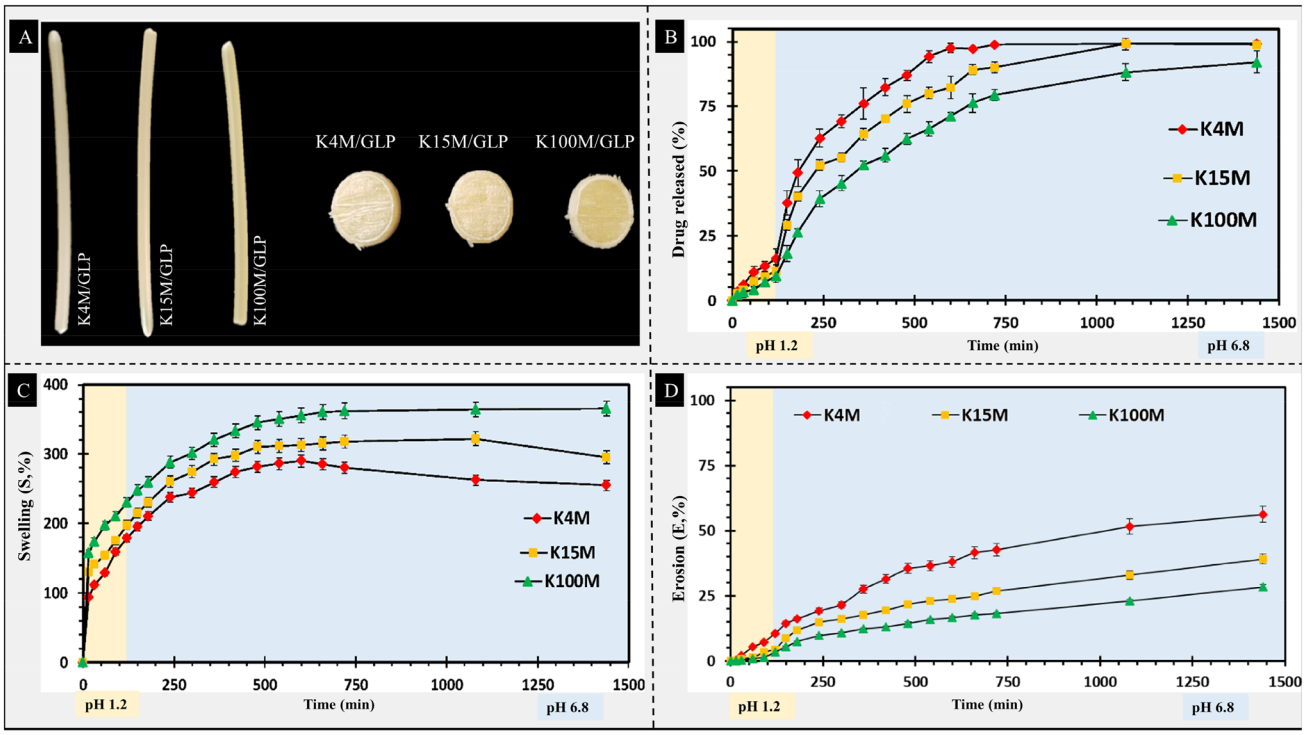

Fig. 3 **a** Different HME extruded filaments and 3D-printed hydrophilic tablets; **b** Drug (glipizide) release vs time profile; **c** Swelling vs time profile of 3D-printed HPMC matrix tablets; **d** Overall matrix erosion vs time profile of 3D-printed HPMC matrix tablets (reproduced with modifications from Khizer et al. (2019))

water uptake, resulting in maximum swelling compared to K15M and K4M grade HPMC. However, the drug release characteristics are contradictory; K4M has the highest drug release (> 90% in 750 min) followed by K15M and K100M, respectively. The study concluded that a higher viscosity for HPMC accounts for a higher swelling rate while reducing the erosion rate, resulting in a sustained drug release rate.

In another study, Kadry et al. (2018) utilized HPMC with no other additives for the manufacture of 3D-printed tablets with a customized drug release behavior. HPMC 15LV-loaded diltiazem filaments were extruded and printed at 135 °C and 170–180 °C, respectively, with different infill percentages, and infill patterns. Drug loading of 98.76 ± 1.52% in all filaments and 95–105% in various tablets corroborated the absence of degradation despite the harsh extrusion temperature. During extrusion, the drug was found to be dispersed within the HPMC matrix, resulting in the loss of drug crystallinity. An in-vitro dissolution study revealed different release patterns (immediate, sustained, chrono, and pulsatile) which were related to the geometry of the fabricated dosage forms (infill densities as well as infill patterns). Similarly, other researchers prepared different 3DP dosage forms with tunable drug-release characteristics utilizing different grades of HPMC polymer (Goyanes et al. 2014, 2015; Zhang et al. 2017c).

In order to address the problems of HPMC thermal degradation and facilitate extrusion process, AFFINISOL™ HPMC HME-grade polymers were specially designed with low T_g and melt viscosity (Gupta et al. 2016). Previous studies showed that AFFINISOL™ has a wide thermal operating window and solubilizing capability for hydrophobic drugs (Amidon et al. 1995, Kaushik and O'donnell 2016). In addition, AFFINISOL™ has a lower moisture uptake property than other HPMC-grades, which might improve the physical and chemical stability of prepared solid dispersions during storage. The solid dispersions of ritonavir (BCS Class II) prepared using AFFINISOL™ showed high drug loading, an improved dissolution profile, and the absence of drug degradation and phase separation upon storage (Bauer et al. 2001; Kaushik and O'donnell 2016).

HPMC was used along with other thermoplastic polymers to simplify extrusion processing and control drug release. Zhang et al. (2017b) had explored the combination of HPMC E5 and Soluplus® with acetaminophen (as a model drug) to prepare zero-order release 3D-printed tablets. The dispersion of the drug into the HPMC matrix during melt extrusion resulted in the formation of solid-dispersion filaments. Complete drug release was observed from all tablets within 24 h with no notable Active Pharmaceutical Ingredient (API) or excipient degradation. The erosion and swelling

mechanisms were found to govern drug release from the 3D-printed tablets.

Other than HME-FDM, Khaled et al. (2014) employed a pressured assisted-deposition system to fabricate guaifenesin bilayer tablets using different HPMC grade polymers (HPMC 2910 & HPMC 2208) for immediate and sustained release. The developed bilayer tablet had high drug loading capacity (up to 600 mg) comparable to that of marketed formulations. Fina et al. (2018b) demonstrated the oral disintegration properties of an HPMC and Kollidon-based formulation of paracetamol using SLS technology. The authors found that changes in the laser scanning speed caused alterations in the drug-release characteristics from the printlets. A higher laser scanning speed led to less sintering impact between the powder particles, resulting in the formation of a porous structure. The drug was transformed into an amorphous form and drug loading analysis conformed that degradation did not occur during the sintering process.

Hydroxypropyl cellulose (HPC)

HPC is a non-ionic cellulose ether in which hydroxyl groups on the cellulose backbone are hyroxypropylated. It is produced from the reaction of alkali cellulose and propylene oxide at high pressure and temperature. HPC powder is a white to slightly yellow-colored odorless and tasteless powder with an average MW of HPC ranges from 20–1500 kDa. HPC is fully soluble in cold water but poorly soluble in organic solvents such as methanol, ethanol, isopropyl alcohol, and acetone. The solubility profile of HPC is temperature dependent as it is not soluble in hot water and precipitates as a highly swollen floc at temperatures between 40–45 °C. Commercially, HPC is available in various grades with different MWs and varying viscosity (Table 4). The viscosity decreases with an increase in temperature until a sudden drop in viscosity is observed when temperature reaches 45 °C due to the limited solubility of HPC. However, original viscosity can be restored as the process is reversible by cooling (Rwei et al. 2009; Raymond C Rowe 2013). The aqueous solution of HPC are stable at pH 6.0–8.0, but increase in pH induces alkali catalyzed oxidation reaction which may degrade polymer and at low pH, acid hydrolysis may occur resulting into decrease in solution viscosity (Koo 2016). In general, HPC is regarded as a safe, non-toxic, and non-irritant pharmaceutical-grade polymer.

Table 4 Overview of commercial grades of Hydroxypropyl Cellulose (Klucel ™ HPC-Ashland)

Trade names	Molecular weight (kDa)	Viscosity (mPa·s) in aqueous solution of stated concentration (wt%) at 25 °C
Klucel HF	1150	1500–3000 (1%)
Klucel MF	850	4000–6500 (2%)
Klucel GF	370	150–400 (2%)
Klucel JF	140	150–400 (5%)
Klucel LF	95	7–150 (5%)
Klucel EF	80	300–600 (10%)
Klucel ELF	40	150–300 (10%)

HPC is a good binding, film coating, thickening and emulsifying agent in pharmaceutical formulations. Higher MW grades are used as controlled-release matrix former while lower MW grades with concentrations of 2–6% are most typically used as binders in wet/dry granulation and direct compressions, and 15–35% may be used to prepare extended drug-release formulations (Delonca et al. 1977; STAFFORD et al. 1978; Johnson et al. 1993; Raymond C Rowe 2013). In addition, low substituted HPC (L-HPC) is used as a tablet disintegrant (Kleinebudde 1993). The release rate of drugs increases with decreasing HPC viscosity; however, the addition of anionic surfactants increases HPC viscosity, thereby decreasing the drug-release rate. (Bercea et al. 2018).

The thermoplastic properties of HPC make it blend-able for extrusion processes. It has been reported that HPC has a biphasic T_g. The first T_g appears roughly at − 4.5 °C, while the other above 100 °C due to molecular mobility complexities in the polymer structure (Vasanthavada et al. 2011). The low T_g of HPC results in low melt viscosity and fast melt flow properties depending on its MW. The extrusion process for low MW is possible at low as 120 °C and high MW grade products can be processed at 200 °C without the use of a plasticizer (Michael A. Repka 2013). Currently, HPC is being investigated for the manufacture of various 3D-printed products. For example, Arafat et al. (2018) employed an innovative design approach to fabricate immediate release tablets with unique built-in gaps or "Gaplets" printed using HME-FDM 3DP. Filaments of SSL-grade HPC polymer-loaded with theophylline were used to print capsule-shaped devices with interconnected blocks. Thermal analysis revealed no changes in the drug crystallinity during thermal processing. The unique geometry of the printlets and the presence of the HPC polymer promoted rapid drug release (> 80% in 30 min) from the devices.

Melocchi et al. (2015) successfully prepared a capsule-shaped device for the oral pulsatile release of acetaminophen. In-house filament extrusion was carried out at 50–165 °C based on the concentration of HPC in the formulation. The 3D-printed hollow capsular device made from net HPC filaments exhibited a typical pulsatile–release profile, with a lag phase of approx. 70 min, after which drug release was completed within 10 min. Thus, the obtained results were consistent with those form capsule shells developed using injection molding (IM) technology with the same composition.

In another study, a floating pulsatile drug delivery system was explored by utilizing the HPC polymer. Dumpa et al. (2020) demonstrated that HPC polymers could be used with a thermolabile drug to achieve a floating pulsatile drug delivery in the GI environment. Traditionally manufactured (direct compression) theophylline tablets were enclosed (core) in depositing 3D-printed HPC (Klucel LF) outer layers. The device showed a lag phase of 30 min to 6 h before drug release, depending on the polymer shell thickness and tablet geometry. Similarly, in another study, in-house made theophylline-loaded HPC filaments were used as feedstock to prepare FDM 3D-printed gastro-floating tablets (Giri et al. 2020). The printed tablets showed prompt floatation ability, could remain afloat for > 10 h, and were reported to follow zero-order drug release kinetics. However, thermal processing (HME and FDM 3DP) causes crystalline drugs to transform into a partially crystalline form.

Four different grades of HPC polymer (i.e. SL, SL-FP, SSL, and SSL-SFP) were investigated as solid dry binders for a tablet formulation employing the drop on solid (DoP) 3DP technique. The polymers were studied for flowability, friability, viscosity, and surface tension, which can affect the critical quality attributes of the 3D-printed tablets. Amongst the formulations evaluated, caffeine-loaded HPC (SSL-SFP grade) 3D-printed tablets exhibited high drug loading, and the fastest drug release (within 21 min), which was attributed to their low viscosity. On the other hand, slower disintegration and dissolution behaviour were observed with higher viscosity binders (SL and SL-FP formulations). Overall, the authors endorsed HPC as an appropriate polymer for DoP 3DP of robust solid dosage forms (Infanger et al. 2019). In a general sense, these studies suggest that careful selection and optimization of polymer properties could lead to the successful development of 3D-printed medicines with dose-flexible and distinct drug-release characteristics.

Ethylcellulose (EC)

EC is used in traditional pharmaceutical formulations as a coating agent, tablet binder, filler, flavoring agent, and viscosity increasing agent. Primarily, EC is employed for the hydrophobic coating of tablets and granules in oral formulations, modifying drug release (Porter 1989), masking unpleasant tastes (Sarisuta and Sirithunyalug 1988), or improving the stability of a formulation (Parikh et al. 1993). EC is also used to form water insoluble films and since coated films of higher viscosity grade EC are stronger, they are used for drug microencapsulation. Further, EC is used as a thickening agent in topical formulations such as creams, lotions or gels (Bothiraja et al. 2014; Maiti et al. 2011) (Table 5).

The suitability of EC polymer for 3DP depends on its thermal characteristics, thermoplasticity, and miscibility with incorporated plasticizers. EC is viable for FDM modeling and other applications that require adequate thermoplasticity. Accordingly, plasticizers or softening agents are used along with EC to decrease the softening point, and to improve the thermoplasticity. The thermoplastic property of lower viscosity grades EC is comparatively better than that for higher MW grades, as low MW shows better alignment and less steric hindrance (Michael A. Repka 2013). The T_g of EC is 129–133 °C, and its degradation temperature (T_d) is 280 °C (Aggour 2000). The products developed using EC above its softening temperature (156 °C) might be brittle as oxidation is likely to occur; however, this can be prevented by using antioxidants such as ascorbic acid (Michael A. Repka 2013). The products are less likely to undergo oxidation below their softening point, which opens the possibility for the use of EC in the extrusion process.

Melocchi et al. (2016) successfully demonstrated the use of EC for thermal processes (HME and FDM). EC-loaded filaments were extruded and printed at around 160 °C and 200 °C, respectively. The 3D-printed disk obtained using EC filaments were found to be poorly permeable and insoluble, and drug (acetaminophen) release was found to be very slow compared to the release with other polymers studied. The authors suggested the addition of channeling agents or adjustment of printing parameter (reducing disc thickness) may enhance the permeability of the products and hasten the drug release. In another study, 3D-printed sustained-release Ibuprofen tablets with internal scaffold structures were prepared using EC polymer (Yang et al. 2018). Since, EC is hydrophobic and difficult to melt, different concentrations of various release modifiers (HPMC, PVA, sodium alginate, and xanthan gum) were added in order to adjust the drug release rate and facilitate extrusion process. HPMC was found to be the preferred release modifier for

Table 5 Overview of commercial grades of ethylcellulose (Manufacturer: Dow Chemical)

Trade names	Viscosity designation	Solution viscosity range (mPas)		T_g (°C)	T_m (°C)	T_d (°C)	Moisture content (%)
ETHOCEL Std. 4	4	3–5.5	128		168	200	< 1.0
ETHOCEL Std. 7	7	6–8	128		168	205	< 0.07
ETHOCEL Std. 10	10	9–11	132		172	205	< 0.001

the EC-ibuprofen tablet matrix since the addition of HPMC resulted in the highest and most complete drug release profile compared to other excipients (Fig. 4). The printed structure achieved complete drug release within 24 h and drug release occurred through a diffusion-erosion mechanism.

Fina et al. (2018a) employed SLS 3DP technology for the first time, to fabricate customizable drug-release 3D-printed printlets with different geometries (cylindrical, bi-layer, and gyroid lattice) using four different polymers (EC, polyethylene oxide, Eudragit (L100-55 and RL)). EC was sintered at 120 °C, with a 100 mm/s laser speed along with paracetamol (5%) to obtain the desired 3D-printed printlets. Thermal analysis revealed the absence of drug/polymer degradation; however, the crystalline drug was found transformed to its amorphous form. The study revealed that, customizable drug release dosage forms could be obtained simply by changing the geometry of the 3D-printed dosage forms, without the need to alter the formulation compositions.

In another study, DoP 3DP technique was adapted to yield doughnut-shaped multi-layered devices with a linear release profile for poorly water-soluble drug. Acetaminophen was incorporated with HPMC (as the matrix), and EC (as release retardant). The outer circumference layer of the device was bonded with a binder solution containing EC. Here, EC acted as a release retardant polymer, providing a strong adherent force with the inner drug-loaded regions and an impermeable retarding effect on drug release from the axial route, as observed in the in-vitro dissolution test (Yu et al. 2009). Above studies summarize the role of EC as a suitable feed material for characteristic applications in 3DP technology.

Hypromellose acetate succinate (HPMCAS)

In brief, hypromellose acetate succinate or hydroxypropyl methylcellulose acetate succinate (HPMCAS) is manufactured through a series of chemical reactions between two ester groups, acetic anhydride, and succinic anhydride with a low viscosity grade of hypromellose (HPMC) under controlled conditions (Yoshiro Onda and Hiroaki Muto 1980). HPMCAS consists of a cellulose backbone integrated with methyl, hydroxypropyl, succinoyl, and acetyl substitute groups (Fig. 2). HPMCAS was first commercialized in 1986 under the trade name Shin-Etsu AQOAT® by Shin-Etsu Chemical Co. Ltd. (Japan) as an enteric coating agent. Commercially, it is available in six different grades depending on fractions of acetyl and succinoyl groups present in HPMCAS and the particle size distributions (Table 6). The L, M, and H grades are chemically distinctive due to the differences in the succinoyl to acetyl group ratios (S/A ratio), and therefore, have different pH solubilities, dissolution profiles, and drug-release characteristics (Obara et al. 2013). Further, each of these grades can vary in their particle sizes: fine (F, particle size ~ 5 µm) and granular (G, particle size ~ 0.5 mm).

All HPMCAS grades are insoluble in acidic aqueous conditions or gastric fluid; however, start to swell and dissolve in buffer media with pH ≥ 5. Specifically, the L-type, i.e. AS–L, has a higher S/A ratio and dissolves in buffer with pH ≥ 5.5, whereas the H-type (AS-H) has a lower S/A ratio and dissolves in pH ≥ 6.8, and the M-type (AS-M) with a moderate S/A distribution dissolves in pH ≥ 6.0

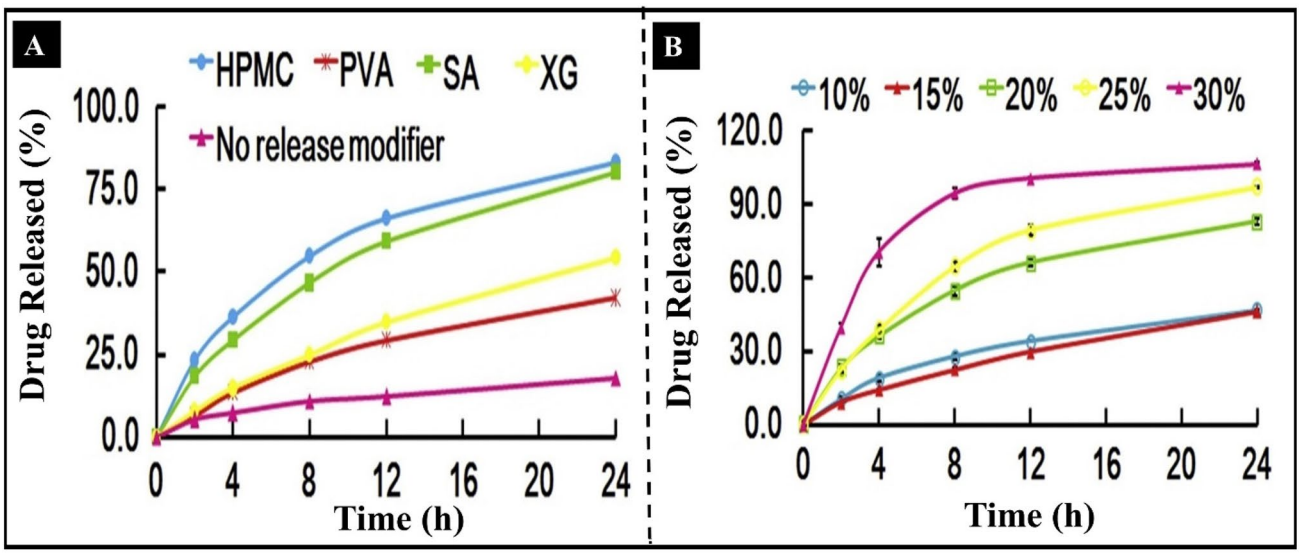

Fig. 4 **a** Influence of different types of release modifiers on drug release profiles (ibuprofen: EC: release modifier = 20:60:20); **b** Influence of different concentration of HPMC release modifier on drug release behavior (n = 6) (reprinted with permission from Yang et al. (2018). Copyright© 2018 Elsevier Ltd.)

Table 6 Overview of commercially available grades of HPMCAS (AquaSolve™ HPMCAS)

Grades of HPMCAS	Acetyl (%)	Succin-oyl (%)	Methoxy (%)	Hydroxy-propyl (%)	T_g (°C)	T_d (°C)	Soluble pH	Examples (trade names)
LF and LG	5–9	14–18	20–24	5–9	119	258	≥5.5	AFFINISOL™ HPMCAS
MF and MG	7–11	10–14	21–25	5–9	120	267	≥6.0	AFFINISOL™ HPMCAS
HF and HG	10–14	4–8	22–26	6–10	122	276	≥6.8	Shin-Etsu AQOAT®,

(Table 6). The MW of HPMCAS is around 55–93 kDa (Debotton and Dahan 2017) and the viscosity ranges from 2.4–3.6 mPa·s. HPMCAS has a larger thermal processing window than other commonly used cellulosic polymers as it degrades at an elevated temperature from approximately between 258 and 276 °C. Further, HPMCAS is primarily an amorphous polymer with T_g close to 120 °C and has moderate melt viscosity, thus making it suitable for thermal manufacturing technologies such as HME and 3DP (Sarode et al. 2014). Noxafil® by Merck (2013) was the first commercialized brand to incorporate an amorphous solid dispersions of HPMCAS-loaded posaconazole (an antifungal drug) prepared using melt extrusion technology (EMA 2013).

HPMCAS is widely used for numerous pharmaceutical applications including, as a solubility enhancer (Ueda et al. 2014), film-forming agent (Siepmann et al. 2006), and controlled/sustained-release agent (Kojima and Nakagami 2002; Debotton and Dahan 2017). In addition, it is commonly used to inhibit drug crystallization through the preparation of amorphous solid dispersions (ASDs), leading to enhanced solubility and the dissolution of poorly water-soluble drugs (Friesen et al. 2008). Primarily, HPMCAS is most used for enteric coating purposes to deliver acid-liable drugs that degrade in the stomach or drugs that show better therapeutic outcomes in the lower regions of the GI tract, which have higher pH (Qiu et al. 2009). However, the quality of the enteric coating mainly depends on the nature of the API and coating polymer, coating parameters (thicknesses, uniformity), and in-vitro/in-vivo test conditions. For these reasons, conventional enteric coatings bear a risk of premature drug release, unpredictable lag time, uncontrolled drug release kinetics, increased tablet hardness, drug-excipient incompatibility, instability and toxicity (Qiu et al. 2009).

Recently, FDM 3DP and HME technologies have been investigated to address the limitations of conventional polymeric coatings Goyanes et al. (2017). reported a strategy to fabricate gastro-resistant 3D-printed paracetamol tablets without the need for an enteric coating. Several drug-loaded filaments (5–50%) were prepared using three different grades of HPMCAS (LG, MG, HG), a plasticizer (methylparaben 5–15%), and a lubricant (magnesium stearate 5%) extruded through a single screw filament extruder (80–110 °C). The printing of HG and MG-grade filaments was carried out at 180 and 185 °C, respectively, comparatively lower than the temperature used for LG-grade filaments (190 °C). Significant thermal degradation of the drug and excipients was absent. Drug release from the 3D-printed tablets was largely influenced by the HPMCAS grades (LG > MG > HG) (Fig. 5a). More remarkably, all the 3D-printed tablets showed delayed drug releases (< 10% drug release for first 2 h in pH 1.2), thus making HPMCAS based 3DP approach suitable for drug delivery in lower GI tract regions (e.g. intestines or colon).

Lu et al. (2018) investigated the physicochemical properties of melt-extruded HPMCAS. HPMCAS was found extrudable between a low and high temperature range of 130–180 °C without any notable degradation; however, significant thermal degradation was reported at 260 °C. Further, Sarode et al. (2014) studied the physicochemical behaviour of different HPMCAS grade polymers (LF, MF and HF) for HME processing, specifically T_g, solid-state functional group properties, crystallinity, solution viscosity, and moisture content. The authors reported an absence of significant thermal degradation during thermal analysis of drug and carriers; however, an increase in yellowness was observed as the extrusion temperature and HME processing speed increased (Fig. 5b). The MF-grade had the best flowing property, the LF-grade was found to be the most stable for thermal extrusion, and the HF-grade had the slowest dissolution rate. In another study, a similar trend was reported showing a faster and almost complete drug release after 12 h from FDM 3DP tablets with LG- and MG-grades, while slower and incomplete drug release (> 24 h) was observed with tablets containing HG-grade HPMCAS (Goyanes et al. 2017).

In general, plasticizers are added to a polymer-drug blend to reduce the T_g, and melt viscosity, resulting in improved melt flow properties, thereby facilitating the melt extrusion process. Some commonly used plasticizers for the extrusion of drug-polymer mixtures are TEC, triacetin, different grades of polyethylene oxides (PEO and PEG), Tween® 80, stearic acid (SA) and glycerol (Pietrzak et al. 2015; Skowyra et al. 2015; Alhijjaj et al. 2016; Giri et al. 2020). Klar and Urbanetz (2009) specifically recommended the use of TEC plasticizers for HPMCAS. The H-grade HPMCAS has low melt viscosity compared to the M- and L-grades; thus, melt mixing and extrusion of the H-grade is comparatively

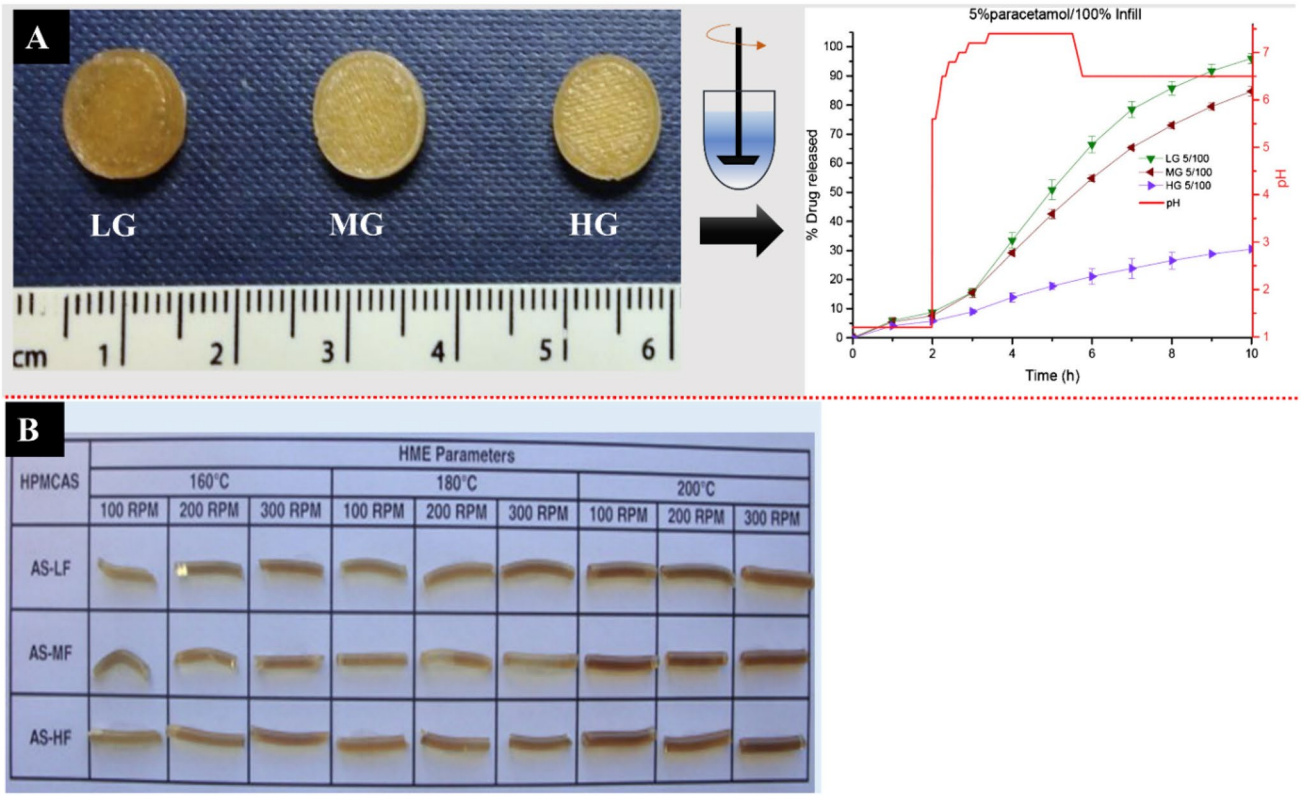

Fig. 5 **a** Drug release profile from the 3D-printed paracetamol tablets containing different HPMCAS grades (reproduced with modifications from Goyanes et al. (2017). Copyright© 2017 Elsevier Ltd.); **b** Photograph of HME extrudate filaments at different processing conditions (reprinted with permission from Sarode et al. (2014). Copyright© 2015 Elsevier Ltd.)

easy even at lower temperatures. For HPMCAS, it is recommended to conduct melt extrusion at a temperature below 180 °C to prevent polymer decomposition and cleavage of the ester group (Obara et al. 2013).

Microcrystalline cellulose (MCC)

Briefly, MCC is prepared through acid hydrolysis of cellulose fibers at a boiling temperature (~ 105 °C) until the "level-off" degree of polymerization is achieved for cellulose (Battista et al. 1961). It appears as a white crystalline powder which is insoluble in most organic solvents and forms an aqueous colloidal suspension in water. MCC has an MW of 10–220 kDa (Debotton and Dahan 2017) with a T_m (Emcocel® 90 M) of 260–270 °C and dissolves in buffers with pH 5.0–7.5 (Rowe et al. 2009). MCC is commonly used as a binder, diluent, or filler in the manufacture of oral solid dosage forms, i.e. tablets or capsules (de la Luz Reus Medina and Kumar 2006). It is listed as a "generally regarded as safe" substance in the FDA inactive ingredients database. The role of MCC in a dosage form depends on the concentration used; for example, it acts as a binder (20–90%), disintegrant (5–15%), anti-adherent (5–20%), diluent (20–90%), and adsorbent (20–90%) (Rowe et al. 2009). Commercially, MCC is available in different grades with different particle sizes under different brand names for various applications such as Avicel® PH 101, Vivapur® 101, and Emcocel® 50 (smaller particle size, ~ 50 µm), grade 200 (larger particle size, ~ 180 µm), grade 102 (~ 100 µm), and grades 301 (~ 50 µm) and 302. The different grades of MCC are used as direct compression binders, for wet granulation, to improve powder flowability (larger particle-size grades), for weight uniformity in tableting, as fillers for capsules, and as emulsifiers or viscosity modifiers for liquid preparations (Nofrerias et al. 2019; Yohana Chaerunisaa et al. 2019).

MCC has been extensively used as a disintegrant in traditional pharmaceuticals (tablets) (Yohana Chaerunisaa et al. 2019). Disintegrants are added to accelerate break/disintegrate the bulk tablet upon exposure to a medium (e.g. water or GI fluid), resulting in rapid drug release. Khaled et al. (2014) fabricated guaifenesin bi-layer tablets with both immediate and sustained-release layers, using a extrusion 3D printer (Fab@Home). MCC and sodium starch glycolate were used as disintegrants, whereas HPMC 2910 and HPMC 2208 were used as binders for printing the immediate (> 20% drug release in 30 min) and sustained-release layers, respectively. The authors reported that the friability, weight

variation, hardness, and thickness of the printed formulations were comparable to those of marketed tablets and were within acceptable standard ranges in accordance with the US Pharmacopoeia (Fig. 6a). Later, the same group Khaled et al. (2015a) utilized MCC (Pharmacel® 102) as a squeeze and pushing agent along with different grades of HPMC (K100 M) polymer to develop a 3D-printed multiple-dosage system named "polypill" comprised of three different drugs (captopril, nifedipine, and glipizide) with definite release profiles compartmented into a single tablet using a pneumatic extrusion 3D printer (Fig. 6b). Further, Rowe et al. (2000) used MCC powder (Avicel PH 301) as disintegrant agent along with different grades of Eudgragit® polymer for the preparation of 3D-printed oral dosage forms with pulsatory drug (diclofenac) release profiles (Fig. 6c).

In another study, Sadia et al. (2016) used MCC as a filler to facilitate filament extrusion; however, the prepared filaments exhibited poor flowability during printing, resulting in discolouration, and incomplete printing of the structures. Maintaining the printer nozzle temperature at 135 °C led to the thermal degradation of MCC. On contrast, semi-solid extrusion does not require filament preparation for 3DP and thus, the drug and carriers are not subjected to stress or a thermal environment unlike in FDM. Therefore, this approach could be a viable alternative for preparing 3D-printed dosage forms of thermosensitive APIs that cannot be formulated using FDM. Li et al. (2018) used MCC (MCC PH101) as an extrusion molding agent for extrusion-based 3DP, and HPMC K4M and HPMC E15 as polymeric carriers to yield 3DP gastro-floating tablets of dipyridamole.

Other cellulose derivatives

Cellulose esters are commonly used in pharmaceutical formulations as enteric and film coatings, extended release agents, diluents/fillers for tablets or capsule, taste-masking agents, and semi-permeable coatings in osmotic drug delivery (Rowe et al. 2009). These cellulose derivatives show good film-forming properties and are generally water insoluble or soluble in buffer media with pH > 5. Cellulose esters are categorized into organic and inorganic groups and the former is more important for pharmaceutical applications. Cellulose acetate (CA) and cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), HPMCAS, and cellulose acetate butyrate (CAB) are some of the most commonly used organic cellulose esters. Inorganic cellulose esters, for example, cellulose sulphate and cellulose nitrate, are rarely used for pharmaceutical purposes (Shokri and Adibki 2013). Cellulose esters are non-irritant, non-toxic, and biodegradable polymers and have long been

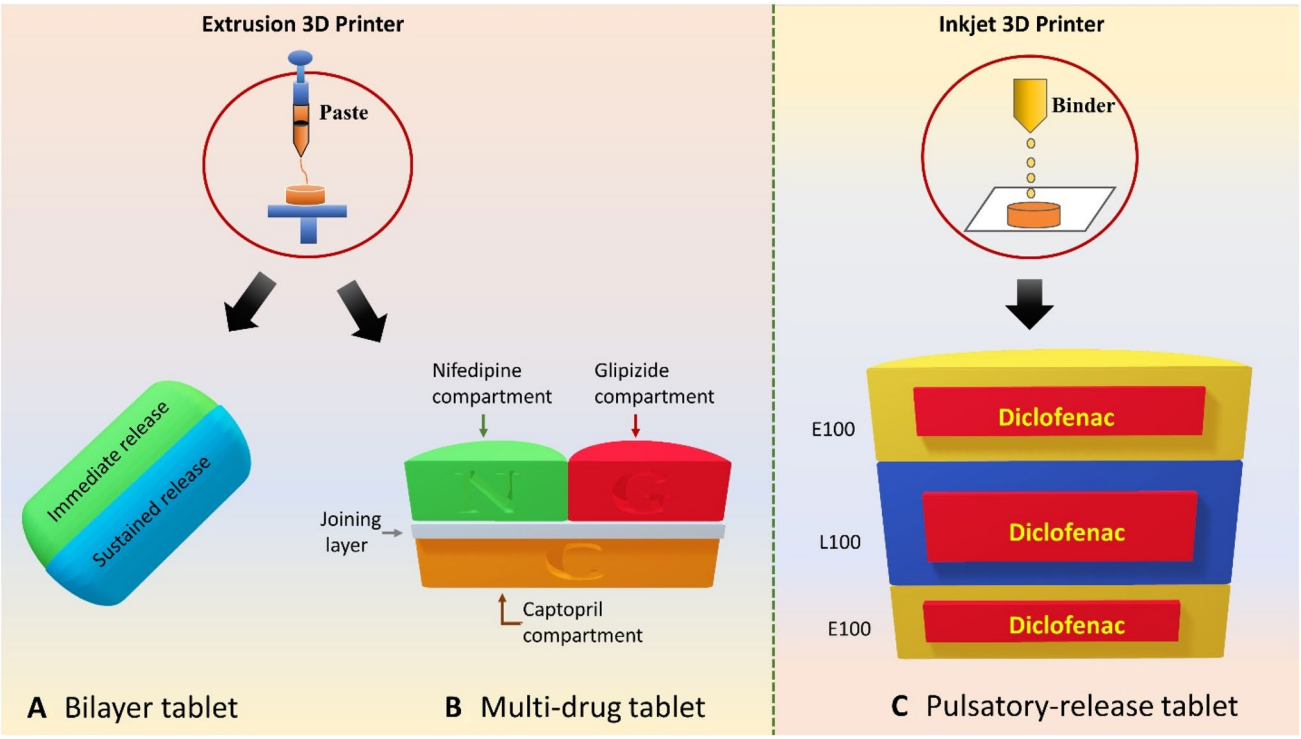

Fig. 6 Schematic illustrations of different types of 3D-printed dosage systems: **a** bilayer tablet and **b** multi-drug tablet prepared with extrusion-based 3D printer, and **c** pulsatory-release tablet fabricated with inkjet-based 3D printer

utilized for numerous drug delivery purposes; however, only a few studies have investigated their applications for 3DP.

CA is commonly used as a capsule diluent, filler, enteric coating, and taste masking agent (Dias and Duarte 2013). CA is a white to off-white polymer that can be obtained as a powder, pellets, or flakes and is available in different grades with varying physical properties and average MWs ranging from 30-60 kDa. CA is compatible with plasticizers such as PEG, triacetin, TEC and diethyl phthalate (Phuong et al. 2014). It is tasteless and soluble in dichloromethane-ethanol blends, acetone–water blends, and di-methyl formamide (Rowe et al. 2009). Pattinson and Hart (2017) prepared a viscous yet flowable feed material of CA for extrusion-based 3DP. They dissolved CA powder (25–35% w/w) in acetone and the resulting fully dense paste was used to print miniature eyeglass frames and a rose. Acetone evaporates as soon as the ink passes from the nozzle, allowing solidification of the extruded paste. The extrusion quality was found to be improved by using a lower amount of high MW CA feedstock. The authors indicated that the printed product possessed good mechanical strength (Young's modulus (*E*) and strength (σ) of 2.2 GPa and 45.0 MPa, respectively).

In another study, Khaled et al. (2015b) demonstrated a cardiovascular treatment regimen consisting of five drugs incorporated in a single system with two different and well-defined release mechanisms. CA served as a permeable carrier for the sustained-release of atenolol, paravastatin, and ramipril while aspirin (ASA) and hydrochlorothiazide (HCT) were formulated for immediate-release. This study exploited the inherent hydrophobic nature of CA to form a hydrophobic shell for the physical separation of different cardiovascular drugs and thereby avoid incompatibility issues. The implementation of such a multidrug "polypill" system with different drug release profiles opens a new avenue for the delivery of customized multi-drug regimens in the near future.

CAP is another organic cellulose ester derivative primarily used as an enteric or film-coating agent in tablets or capsules as well as in controlled or delayed-release formulations (Dias and Duarte 2013). Kempin et al. (2018) employed dual-extrusion 3DP to fabricate an inner tablet core of the acid- and thermolabile drug pantoprazole sodium with an external coat of gastro-resistant polymer (CAP, Eudragit L100-55, or HPMCP). The filament extrusion and printing temperature for CAP was 110–112 °C and 140–145 °C, respectively, and the corresponding temperature for HPMCP were 129–131 °C and 165 °C. The tablet core of pantoprazole was printed at a comparatively lower temperature. An in-vitro dissolution test of the coated tablets revealed the absence of drug loss and thermal analysis revealed insignificant drug degradation. This work is helpful to understand that it is possible to develop bespoke dosage forms of thermolabile drugs with careful selection of suitable polymers and plasticizers even using thermal methods such as FDM 3DP and HME (Table 7).

Challenges and considerations

Material choice is a key consideration when designing a pharmaceutical dosage form. The inherent thermoplastic characteristics, modest T_g, and large thermal processing window of cellulose makes it suitable for broad applications in 3DP. However, cellulose and its derivatives, as base polymers have various determinants that needs to be considered during thermal processing. For example, cleavage of the acetyl and succinoyl groups of HPMCAS is likely to occur during energy intensive processes, leading to physical and chemical instabilities in the polymer and the developed products (Obara et al. 2013). Therefore, the judicious selection of carriers and printing methods, and the optimization of processing conditions are key factors in the formulation of cellulose-based 3DP dosage forms with desired specifications.

Extrusion temperature is a crucial parameter for filament preparation, which is largely governed by T_g, and the T_d (degradation temperature) of the polymer as well as the selected drug (Li et al. 2017). Heat and shear stress generated during HME processing and FDM 3DP extrusion can cause thermal degradation of the materials used. Most polymers generally have a T_m at which the drug start to degrade, leading in low drug loading in the final product or product failure due to chemical changes in the API. For example, Goyanes et al. (2015b) found that more than half of the API (4-ASA) degraded following the printing process. Researchers have attempted different approaches to circumvent drug/polymer loss or degradation such as the addition of plasticizers or other excipients to ease material processing or the use of different non-thermal 3DP techniques (e.g. pneumatic or mechanical pressure-assisted extrusion). Beck et al. (2017) suggests an alternative strategy using two novel technologies (FDM 3DP and nanotechnology). Using this combination, the drug was not subjected to heat and the technique can thus be applied for thermolabile drugs.

Another strategy to prevent API/polymer degradation or drug loss during extrusion and/or printing, is the addition of plasticizers to a drug-polymer mixture. Plasticizer lower the T_g value for processing and help with flowability for extrusion (Repka and McGinity 2000). For example, CA possesses a high T_g and therefore cannot be melt-processed as raw material to avoid decomposition before melting. Phuong et al. (2014) proposed the use triacetin or triacetin-diacetin as the suitable plasticizers to reduce the T_g of CA, thereby reducing its processing temperature. Some of the commonly used plasticizers include TEC, SA, various grades of PEG, propylene glycol, diethyl phthalate, triacetin, and maleic anhydride. In addition, API may also act as a plasticizer in

Table 7 Summary of 3D-printed pharmaceuticals prepared with different cellulose-based polymers and 3DP technologies

Polymer(s)	API(s)	Drug loading (extrusion temp. °C)	3DP method (Print temp. °C)	Application	References
HPMC (K4M, K15M, K100M)	Glipizide	Single screw HME (155)	FDM (170)	Extended release	(Khizer et al. 2019)
AFFINISOL™ HPMC HME 15LV	Diltiazem	Single screw HME (135)	FDM (170–180)	Immediate, extended, delayed and episodic absorption release	(Kadry et al. 2018)
HPMC (Metolose 90SH-15000SR)	Catechin	Drug dissolved in ethanol/water	Semi-solid extrusion	Personalized therapy	(Tagami et al. 2019)
HPMC E5, EC N14, HPC LF and HPC EF	Acetaminophen	Twin screw HME 160 °C (For HPMC 180 °C)	FDM (200)	Controlled drug release	(Zhang et al. 2017a)
HPMC E5	Paracetamol	Drug mixed with polymer	SLS (135)	Personalized therapy	(Trenfield et al. 2018)
HPMC K4M, HPMC E15 & MCC PH101	Dipyridamole	HPMC hydro-alcoholic gel mixed with drug and other excipients	Extrusion based printer	Gastro-floating sustained-release	(Li et al. 2018)
HPMC	Tricalcium silicate	Slurry formation	Extrusion based printer	Complex scaffold printing	(Wu et al. 2019)
HPC-SSL	Theophylline	Twin-screw HME (120)	FDM	Immediate release	(Arafat et al. 2018)
HPC	Theophylline	Twin-screw HME (150)	FDM (210)	Controlled release Floating tablets	(Giri et al. 2020)
HPC (Klucel LF), EC N14 & Avicel PH® 102	Theophylline	Twin-screw HME (165)	FDM (190)	Gastro-retentive Floating Pulsatile Drug Delivery	(Dumpa et al. 2020)
HPC (SL, SL-FP, SSL and SSL-SFP) grades	Caffeine	Polymer as binder solution and premixed with API	Powder bed 3DP	High drug loading capacity with fast drug release	(Infanger et al. 2019)
HPC (Klucel™ EXF)	Domperidone	Twin Screw HME (145–150)	FDM (210)	Intragastric floating system	(Chai et al. 2017)
Ethyl cellulose & HPMC K100-LV	Ibuprofen	Twin-screw extruder (100–120)	FDM(174–182)	Sustained release	(Yang et al. 2018)
EC & HPMC E100	Acetaminophen	Drug mixed with polymer	Powder bed 3DP	Controlled release	(Yu et al. 2009)
EC N7	Paracetamol & Ibuprofen	Drug mixed with polymer	SLS (120, 50 mm/s)	Customizable release "mini-printlets"	(Awad et al. 2019)
HPMCAS (LG, MG & HG grades)	Paracetamol	Filament extrusion using a single-screw HME (80–110)	FDM (190)	Modified release 3D-printed tablets, (suitable for drug delivery to lower GIT)	(Goyanes et al. 2017)
HPMCAS, HPMC, Eudragit® RL & Kollicoat® IR)	Acetaminophen & Furosemide	Twin-screw HME for drug-loaded polymeric filament (180)	FDM (200)	Tunable drug delivery based on material (polymer) composition	(Melocchi et al. 2016)
HPMCAS-MG, Affinsiol™15 cP, Kollicoat® IR, Kollidon® VA64,	Haloperidol	Filaments via twin-screw HME (150–170 °C)	FDM (210)	3D-printed tablets for rapid drug delivery	(Solanki et al. 2018)
HPMC 2910, HPMC 2208 & MCC PH 102	Guaifenesin	Drug mixed with polymeric gel to form a paste	Pneumatic extrusion (Fab@Home)	Bi-layer (an immediate and sustained-release) guaifenesin tablets	(Khaled et al. 2014)

Table 7 (continued)

Polymer(s)	API(s)	Drug loading (extrusion temp. °C)	3DP method (Print temp. °C)	Application	References
MCC, HPMC 2208	Captopril, Nifedipine & Glipizide	Printable ink (paste) made of drug & polymers	Pneumatic extrusion	Multi-drug, multi-functional polypill tablets	Khaled et al. (2015a)
MCC PH 301, Eudragit® E100, Eudragit® RLPO	Diclofenac	Drug deposited in polymer powder bed	Binder inkjet 3DP	3D-printed oral dosage forms with complex release	(Rowe et al. 2000)
MCC PH 101, HPMC K4M & HPMC E15	Dipyridamole	Drug mixed with polymer gel to form a paste	Extrusion-based 3D printer	3D-printed gastro-floating tablets	(Li et al. 2018)
MCC PH 301, Eudragit® E100, Eudragit® RLPO	Fluorescein	Drug deposited in polymer powder bed	Binder inkjet 3DP	3D-printed tablets with varying lag times and release rates	(Katstra et al. 2000)
CA	Toluidine blue & rose Bengal	CA mixed with drug powder to make a printing dope	Extrusion-based 3D printer	Direct printing of antimicrobial objects with adequate strength and high toughness	(Pattinson and Hart 2017)
CA, HPMC 2208, Lactose, PVK 30	Atenolol, Pravastatin, Ramipril, Aspirin, Hydrochlorothiazide	Drug-excipients powder was blended and mixed with ultrapure water to form a paste	Extrusion-based 3DP	Multi-active solid dosage form "polypill" containing five APIs in a single tablet with immediate and sustained release profiles	(Khaled et al. 2015b)
CAP, HPMCP, PEG 6000, PVP K12, Eudragit	Pantoprazole sodium	HME for preparing drug loaded filament	Dual-extrusion FDM	3D-printing of gastro-resistant tablets containing thermo- and acid-labile drugs	(Kempin et al. 2018)

some cases. Prasad et al. (2019) reported that an increase in the paracetamol concentration causes a significant decrease in the melt viscosity of the drug-carrier blend, possibly due to the plasticizing effect of paracetamol.

In general, cellulosic polymers swell when subjected to heat and pressure under extrusion conditions. This rheological changes resulting from the thermal conditions, i.e. elevated temperature and shear due to screw speed, shows a "die swell" phenomenon, thus increasing the actual filament diameter as compared to the diameter of the extruder nozzle die (Crowley et al. 2007; Giri et al. 2020). The physical characters of the filaments such as toughness should also be considered, as the gears/rollers of the 3D printer exert pressure during material feeding. Khizer et al. (2019) reported that filaments with a breaking distance (toughness) of less than 1.5 mm were too brittle to load into a 3D printer (Khizer et al. 2019).

Cellulosic polymers are reported to have relatively high melt viscosity, which generate high torque within the extruder (Gupta et al. 2016; Meena et al. 2014). However, a very low melt viscosity will prevent extrudate formation and material release from the die. Therefore, the selection of a suitable melt viscosity range for extrusion is crucial. Kolter et al. (2012) suggests an optimal viscosity range between 1000 and 10,000 Pas for melt extrusion of polymers.

Further, it is recommended to avoid the use of pure water in the preparation of cellulose-based paste feedstock (HPMC gel) for semi-solid extrusion 3DP. Water causes excessive hydration and excess polymer swelling, resulting in the formation of highly viscous and poorly flowable paste, ultimately leading to nozzle blockage. Instead, the use of hydro-alcohol solvents prevents excessive gel hydration and inhibit excessive shrinkage of the prepared formulation (Khaled et al. 2014; Missaghi et al. 2009; Shah et al. 1996).

Cellulose and its derivatives absorb moisture from the environment upon storage for prolonged period; for example, HPMCAS potentially absorbs moisture and undergoes hydrolysis to yield acetic and succinic acids. It is therefore recommended to keep in-house prepared polymer-loaded filaments in an airtight containers or zipper bags containing silica gel packets. In addition, any moisture present in cellulose-loaded filaments can be removed by preheating the filaments (~ 50-60 °C for roughly 30 min) before printing, which might otherwise cause the nozzle blockade. In case of nozzle blockade, the nozzle can be cleaned by heating the chamber at a high temperature (~ 250 °C for 2–3 min). Then the nozzle needs to be unscrewed, and any residue present inside can be removed using a brash brush and/or by immersing the nozzle(s) in a suitable solvent (~ 2–3 h), depending on the solubility characteristics of the last printed material. For example, if the nozzle is clogged after printing with ABS material, it should be removed from the printer head and put in acetone for few hours. The acetone might remove/dissolve the clogged material and enable it to be cleared with a needle.

Conclusion

The introduction of 3DP technology has added a new dimension to pharmaceutical manufacturing. The technology is particularly advantageous for personalized drug therapy, as it offers a high degree of control and flexibility in dosing and design, spatial and temporal drug release, on-site and on-demand manufacturing capability, and cost-effectiveness. Though 3DP technology is set to revolutionize the development of medicines and further the concept of patient-specific therapeutic regimens, this technology is in its early stages in the pharmaceutical field. A number of factors such as printable materials, printer resolution and speed, production cost, feasibility for industrial scale-up, regulatory requirements, and clinical safety concerns need to be assessed to make 3DP technology viable for pharmaceutical industries.

Research on a wide range of materials that are compatible and safe for 3DP continues to increase. Since the properties of the feed material greatly influence the characteristics of the final 3DP products such as mechanical strength, drug loading, surface morphology, and drug-release behavior, proper attention is essential while choosing the appropriate printable polymers. Based on the literatures examined in this review, cellulose and its derivatives are regarded as suitable polymers with a huge potential for applications in 3DP multifunctional drug-delivery devices. Further work to make these polymers extrudable and printable at a lower extrusion temperature might enable the printing of thermolabile drugs, currently regarded as a major obstacle for FDM 3DP technology. This review provides a better understanding of the thermal and rheological properties of cellulose polymers, their role and functions in 3D-printed dosage forms, and an overview of challenges and considerations. It will therefore assist researchers in the successful fabrication of 3D-printed pharmaceuticals utilizing cellulose and its derivative polymers.

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Compliance with ethical standards

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