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Review Article

Three-Dimensional Printing of Colon-Targeting Drug Delivery Systems (CTDDS)

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ABSTRACT

In recent decades targeted drug delivery has obtained a significant interest for its ability to enhance therapeutic efficacy and reduce side effects of the drugs. Among them, colon-targeting drug delivery systems have been extensively investigated for treating inflammatory bowel diseases and colon cancer and delivering therapeutic proteins and peptides for systemic absorption. The current CTDDS are based on pH-dependent and/or timedelayed dependent release to deliver drugs to the colon without absorption from the upper Gastrointestinal Tract (GIT). Although the pharmaceutical industry has achieved a significant advancement in developing effective CTDDS, it still depends on one-size-fits-all. Consequently, the drug release by this approach will be highly influenced by the unstable GIT pH and intestinal transient time that patients with inflammatory bowel disease frequently experience which may result in premature or delayed colonic delivery of the drugs. 3D printing is a new technology that can easily build up 3D objects based on computer-aided design, consequently, it can fabricate personalized or on-demand dosage forms. Using different 3D printing techniques, printing materials and software designs of the dosage form, 3D printing can exert a high degree of control over the dose and release profile of the drug. This review highlights the most recent applications of 3D printing in the development of the CTDDS focusing on the type of the 3D printing technology, design and pharmaceutical polymers and the drug release profiles.

Keywords: 3D printing, Colon-targeting, Drug delivery, Personalised medicine, Release profile.

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INTRODUCTION

Colon-Targeted Drug Delivery Systems (CTDDS) have obtained a significant interest for the treatment of several diseases affecting the lower parts of the Gastrointestinal Tract (GIT) such as Cronh`s disease, ulcerative colitis, irritable bowel disease and colonic cancer.[1] The basic concept of the CTDDS is to prevent drug absorption from the upper GIT, so that a high concentration of the drug will be delivered to the colon with a very limited systemic absorption.[2] Consequently, this will reduce the systemic side effects of the drugs and improve their therapeutic outcome.[3] Targeting the colon would be achieved via either oral or rectal route of drug administration, nonetheless the oral administration is the most convenient.[4] Moreover, the long retention time of the colon which may reach up to 5 days making the colon a good site for systemic drug delivery. The colon drug delivery can be used to deliver drugs that are unstable in the upper GIT due to either low pH of the stomach or enzymatic degradation in the small intestine. For example gene product such as proteins, peptides and antibodies can be delivered to the colon to prevent degradation in the upper GIT and achieving systemic absorption from the colon region.[5] For development of a successful CTDDS, the GIT physiology specially the transit time from the stomach to the colon and other physicochemical properties of the drug should be carefully considered.[6] In addition, the microenvironmental properties of the colon seem different in the disease state in comparison with the healthy region. Most colonic disease is inflammatory conduction that leads to producing a high level of Reactive Oxygen Species (ROS) and inflammatory cytokines.[7] To reach an optimized colonic drug delivery system many approaches can be used including PH sensitive system, enzyme-triggered system and time-triggering system receptor-mediated system.[8] CTDDS should protect the drug from the acidic environment of the stomach, the drug should not be absorbed in the stomach or intestine and the active ingredient should not deprecate in the upper part of the GIT.[9] The drug should only be absorbed in the colon.

Several challenges are still facing the current pharmaceutical industry in developing an effective CTDDS which may include the following points. The low level of fluid in the colon is considered a challenge for the disintegration, dissolution and delivery of the drug in liquid form such as liquid-filled soft gelatin capsule will

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be very advantageous in developing effective CTDDS.[10] The colon is located in the distal part of the GIT which have also complex physiology having a wide range of pH and different transit times. The other factor is the presence of metabolic enzymes and food also complicates the GIT complexity and may affect drug stability.[11] Moreover, the current CTDDS that have been developed using conventional manufacturing approaches that produce one-size-fits-all dosage forms. This type of standard dosage forms showed some problems related to effectively deliver the drugs to the colon due to the wide variations in gastric and intestinal transit time of the medicines in different disease states.[1,12] In addition, such manufacturing approaches lack the ability to produce a customized dosage form. These challenges could fail the effective delivery of the drugs to the colonic region and innovative solutions to overcome them are very necessary. In this context, development of a personalized CTDDS to match patient's transit time or other needs is widely accepted idea in the formulation of a CTDDS. 3D printing which also called rapid prototyping or additive manufacturing is a recently emerging technology for fabrication of 3D objects using computer-aided design and 3D printers.[13,14] With the recent advancement in 3D printing machines, it become possible to precisely deposit multimaterials in a layer-by-layer fashion to develop 3D objects.[15] 3D printing has a wide variety of biomedical applications, including organ transplant, medical devices and pharmaceutical dosage form. In production of solid pharmaceuticals, 3D printing will not only offer an opportunity to develop a customized dosage form but also precise control over internal geometries and its related complex release profiles such as immediate, sustained, delayed and targeted-drug release.[16] Among this various 3D printed solid dosage forms colon-targeting tablet has gained a significant attention in the recent years due to the importance of colon targeting in treatment of colon disease.[9] This review aims to discuss the most recent advances of 3D printing technology applications in the development of drug-loaded, patient-customized CTDDS, emphasizing on the type of the 3D printing technology, dosage form design, types of polymers and the resultant release profiles.

An extensive electronic literature search was conducted on the following databases: PubMed, PMC, ScienceDirect, Google scholar and Scopus using Medical Subject Heading (MeSH) terms: 3D printing, Colon-targeting, drug delivery, personalised medicine, release profile separately or in combination. The search was performed from November 2023 to May 2024. The main criteria for including articles this research were publication date between 2000-2024 and inclusion of 3D printing, controlled drug release and/or colon drug delivery. The reviewers performed an extensive screening of the titles and abstracts for eligible articles, If the articles did not present any eligibility criteria in the title and abstract, the article was read in detail. Not all relevant publications were listed in the selected databases and the articles written in any language other than English language were not included.

Approaches of Colonic Drug Delivery

Many strategies have been investigated to formulate CTDDS. these systems should prevent the release of drugs in the stomach and small intestine and completely release them in the colon to achieve colon-targeting.[8,17,18]

pH-Dependent Systems

The pH values in the GIT are ranging from 1.2 in the stomach to 7.5 in the distal small intestine.[19] However, the pH value significantly drops to 6.4 in the ascending colon and start to elevate a gain to reach 6.6 and 7 in the transverse and descending colon, respectively, forming a pH gradient along the colon. This site-specific variation in pH has been exploited to develop enteric coated drugs formulation. Some polymers have a pH-dependent solubility, wherein they are ionized and insoluble in the acidic condition in the stomach while have the ability to dissolve when they reach a certain pH in the small intestine (5.5-7.5). Therefore, formulations coated with such polymers could be useful to deliver the drug to the colon. The polymer used should withstand the low PH in the stomach and also be able to disintegrate and dissolve in the neutral or slightly alkaline PH in the terminal ileum and colon.[11] The most used polymers in the PH-dependent coating are methacrylic acid copolymers known as Eudragit® S and Eudragit L.[19] For example, aminosalicylate drug which is an anti-inflammatory drug used in the treatment of inflammatory bowel diseases, has been coated with methacrylic acid polymers, the dissolution studies confirmed that the release profiles of the drug could be managed by changing the Eudragit® S100 and the Eudragit® L100-55 ratios in the coat, so it can be make it dissolves at a specific pH value within 5.5 to 7 range.[20] Many examples of pH-dependent CTDDS have been described in the literature such as budesonide,[21] indomethacin,[22] cyclosporine,[23] nitrendipine[24] and 5-aminosalicylic acid.[17]

Microbial Triggered Systems

The microflora of the colon is mainly composed of anaerobic gram positive cocci.[25] These bacteria have the ability to hydrolyze the undigested food polysaccharide by secreting various enzymes such as glucuronidase, xylosidase, galactosidase, nitroreductase and deaminase. These enzymes can be used to develop a CTDDS by incorporating a specific moiety or polymer that is substrate to one of these enzymes in the formulation. The addition of such substrate will be either as coating or in form of a prodrug. The combination between the substrate moiety and the active drug will render it as an inactive non-absorbable prodrug. This prodrug form will be activated enzymatically when reaches the colon releasing the active drug.[11] The azo bond between sulphapyridine and -amino-salicylic acid in sulphasalazine undergoes a reduction in the colon by colonic bacteria and there is many prodrugs have been designed on azo bond hydrolysis.[26,27] Amino acid-containing drugs that consist of polar groups like amino group or hydroxyl group have been also used in the designing of colon drug delivery

as the colon microflora hydrolyze the drug-amino acid linkage and release the active moiety in the colon.[28] Conjugating drug moieties to sugar to form glycosides has been used for selective drug delivery to the colon, the glycoside bond is hydrolyzed by bacterial enzymes in the colon like glycosidase, galactosidase and cellobiosidase enzymes.[29] Also, the linkage of drug moieties to glucuronic acid has been used to deliver drugs to the colon as the linkage is hydrolyzed by glucuronides in the colon.[30]

Time-Dependent Systems

Delayed/pulsatile release approach has been used to target the release of drugs to the colon after preprogrammed time.[1,3,8,18] The lag time should have been preprogrammed to equal the time of the oral dosage form to pass through the gastrointestinal tract and reach the colon. The time required is difficult to predict however lag time of 5 hr is usually considered.[11] In a previous study, theophylline colon-targeted device was developed for pulsatile delivery of theophylline using pH and time-dependent release. The device is composed of an insoluble hard gelatin capsule body filled with enteric coated theophylline microcapsules and sealed with a hydrogel-forming polymer; the entire device was also enteric coated. Following the administration, the outer enteric coat will protect the entire device from the gastric medium. In the small intestine, the enteric coat will dissolve and the hydrogel plug will swell creating a lag time equal to the intestinal transient time. After the swelling lag time the hydrogel plug will eject releasing the microcapsule in to the colon and the pH sensitive coat of the microcapsules will produce a controlled release of the theophylline in the colon over 24 hr.[31]

Pressure Dependent Systems

The pressure generated via muscular contraction of the gut has also been utilized to trigger drug release in the colon. The colon has the higher luminal pressure inside the GIT due to the process of stool formation, therefore the system has been developed to release the content in response to the raised pressure of the colon and resist the pressure of the upper GIT.[32] Ethylcellulose has been used as a water-insoluble polymer to develop such CTDDS.[33]

CODES™ Technology

CODES™ is a novel CTDDS that was developed to overcome some of the time-dependent system or PH-dependent system related limitations.[34] The basic concept of CODES™ is to mix between the pH-sensitive and microbial sensitive methods. The CODES™ is composed of a core tablet containing an active drug with lactulose and coated with two polymeric layers. The outer layer is an enteric coat layer to protect the subsequent layer the acidic pH of the stomach. The inner coat layer is an acid soluble layer (such as Eudragit E) to withstand in the alkaline pH of the small intestine and produce a lag phase equal to the small intestine transient time. Once the tablet reaches in the colon, the microflora enzymes will degrade the lactulose and lower the pH, resulting in dissolving the acid soluble coat layer and releasing the drug into the colon.[35]

3D printing of Pharmaceuticals

The scientific community has recently been more interested in additive manufacturing, or Three-Dimensional (3D) printing, in a variety of fields, including pharmaceutics. 3D printing is an emerging technology aiming at manufacturing of 3D constructs in a layer-by-layer deposition pattern.[36-39] The process is started by designing the construct using one of the computer-aided design software and slicing this shape into many layers represented by a numerical code containing all the necessary information related to the printing pattern. When the code is launched into the printer, it will exactly guide the printing pattern in x, y and z directions.[37] This deposition pattern, in addition to other factors such as the nozzle diameter and materials parameters, offers a high capacity of precise control over single or multiple materials disposition. Moreover, the controlled layer-by-layer deposition of materials will perfectly control the internal micro/ macro architecture of the construct. Therefore, numerous benefits come with this method of production, which combines a variety of 3D printing techniques. Most important is the ability of this technique to produce personalized or on-demand dosage forms that cannot otherwise be easily produced by the traditional manufacturing approaches.[40,41] Personalized dosage form that contains a patient-customized dose or rate of drug release is the corner stone of the future medicine as it may reduce the dose requirement and cost and improve the treatment outcome.[42] In the traditional manufacturing approaches of medicines, production of such patient-specific modifications in the dose, dosage form or the rate of drug release requires too many modifications in the formulation and manufacturing process. However, by using the 3D printing technology this aim could be more easily achieved by simple manipulation of the software design or ink composition.[43] 3D printing technology has been successfully adopted to modify the rate of drug release from the dosage form by careful customization of the shape or porosity of the dosage form.[44] 3D printing has also the ability to combine multiple drugs into a single dosage form, reducing the number of medicine per patient, improving their compliance specially in elderly patients who have multiple medicines[45] Moreover, owing to their ability to precise control over deposition multiple materials, 3D printing has the ability to produce complex dosage forms having multi-doses and release profiles by printing multiple drugs and excipients and utilizing various coatings[46] or loading with (micro/nano) particles.[47] Finally, this technology has a high reproducibility rate compared to traditional manufacturing procedures.[48]

Undoubtedly, one of the biggest benefits of 3D-printed medications is the ability to tailor treatment to each patient's requirements, putting the patient back at the heart of the drug's manufacturing.[49] The production of oral solid dosage forms such as tablets that include synthetic pharmaceuticals have demonstrated a high

potential for 3D printing. A significant milestone was achieved in 2015 when the US Food and Drug Administration approved for the first time a 3D-printed tablet (SPRITAM) which is an orally disintegrating tablet of levetiracetam produced by ZipDose Technology (Aprecia Pharmaceuticals, Langhorne, PA, USA).[50] There are several types of printers and additive manufacturing processes could be useful in 3D printing of pharmaceuticals such as powder binding, photo-polymerization, inkjeting and extrusion 3D printing.[16] Each has unique characteristics, benefits and drawbacks. In spite of the above mentioned advantages of 3D printing in the field of pharmaceutical production and many of these techniques has been successfully adopted in 3D printing of various solid dosage form, many challenges are still available toward making these techniques more feasible for most drugs and dosage forms. The high printing temperature that is required by some of printing methods to melt the polymeric ink may cause degradation of many active ingredients. In addition, the converting the pharmaceutical excipients into printable ink can be used by 3D printers or 3D printing of a targeted dosage forms are still among challenges that need to be addressed.[51,52] Fused Deposition Modeling (FDM) is one of the most widely utilized methods for pharmaceutical applications for simplicity, availability and cost effectiveness.[53] Using Computer-Aided Design (CAD) software, the appropriate dosage form is first digitally designed. These designs are then translated into STL files, which direct and operate the printer. The FDM printer is supplied with drug-containing thermoplastic polymeric filament, which is typically made by Hot-Melt Extrusion (HME). It then extrudes the molten components, layer by layer, to create the three-dimensional structure.[37,54]

Types of 3D printing technologies

3D printing or also called additive manufacturing is quickly rising to prominence as a very well-known and cutting-edge technologies. 3D printing technologies include a variety of manufacturing processes to build up 3D object by the selective layer-by-layer placement of material. Schematic illustration summarizes the most common type of 3D printing technologies that could be useful in pharmaceutical industry, including material extrusion, material jetting, binder jetting multiplication, selective laser sintering and stereo lithography.[55-57]

Material Extrusion

Extrusion-based printing is among the most prevalent and least expensive methods of 3D printing material.[39] Semisolid extrusion and Fused Deposition Modelling (FDM) are the two main kinds. The preprinting substance is continuously extruded through a nozzle in both methods. The nozzle and/or platform is moved in the x, y and z dimensions, or both, to create the predesigned geometry.[58] Extrusion printing can now be achieved with semisolid extrusion techniques on a wide range of materials (called printing ink) and temperatures, including drugs, proteins and viable cells (known as "bioprinting").[59] Semisolid extrusion printers can print a range of inks using mechanical or pneumatic extrusion forces in addition to heat. In these systems, the rheological characteristics of the printing ink and the post-printing solidification process need to be carefully considered to print structures with acceptable shape fidelity. Consistent extrusion of the ink from the printing nozzle requires ink to possess the appropriate viscosity. Where very viscous ink may lead to irregular or non-continuous extrusion while too soft ink may cause poor printing resolution and could not tolerate the building load, in both cases this may lead poor printability fidelity. Ideal ink for extrusion-based printing should have a shear thinning property like other the non-Newtonian fluid behavior which allow viscosity reduction and extrusion upon exposure to shear force inside the nozzle, at the same time the viscosity will return back to the preprinting value immediately after extrusion.[60] Solidification can happen via chemical or physical processes following the extrusion. For instance, freshly printed layers of photo-linked hydrogels can be cross-linked by printers equipped with UV lamps. As an alternative, the crosslinking agent could be printed concurrently with the print resources.[61] When designing materials for semisolid extrusion prints, these gelation processes play a crucial role in the design process.

Usually, the z- and x-axe movements are activated with utmost precision, down to one micron. Fused deposition modelling is essentially constrained in terms of feature resolution by the size of the nozzle for extrusion. Fused deposition nozzles typically have a diameter of 400 microns.[58] Because lower-viscosity materials spread during semisolid extrusion, feature resolution is typically rather poor.as printed.[58] Extrusion printing's feature resolution can be increased to 10 microns with the use of hybrid approaches.[62] These printers produce a much smaller filament stream by applying an electric force to the extruded filament. These hybrids, dubbed "electrospinning," are offered for sale and are the greatest resolution extrusion-based techniques at the moment.[63]

Material Jetting

Material jetting 3D printer (also called inkjet 3D printer) works on a similar principle to well-known 2D inkjet printers. The print head and printing substrate are moving in the x, y and z axes for printing 3D objects. Inkjet printers are printing low viscosity fluids, wherein droplets of fluid with controlled volume are ejected to predetermined places to create 3D object. There are two type of inkjet printers based on the type of the force ejecting the droplets from the printhead, they are thermal and acoustic inkjet printers. Post-printing cross-linking is essential for successful printing. Similar to semisolid extrusion, the procedures of cross-linking consist of ionic, thermal, photo and pH-dependent effects.[60] This technique's ability to print multiple materials simultaneously, even those with different physicochemical properties, is one of its biggest advantages.[64] Material jetting is employed in

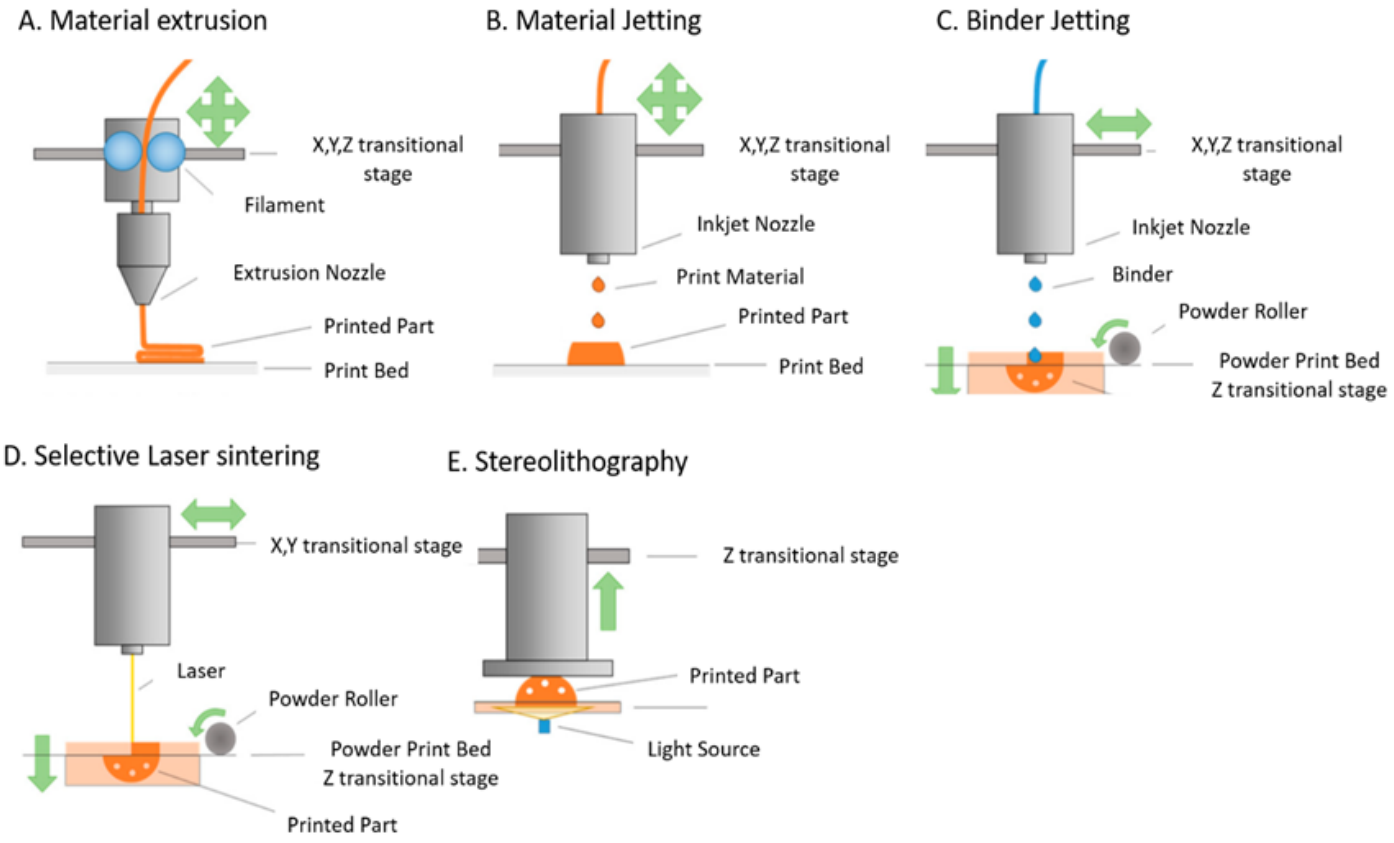

Figure 1 : Typical mechanisms of additive manufacturing. Layer-by-layer material deposition is the defining characteristic of additive manufacturing techniques. Thermoplastic materials are typically deposited by material extrusion (A), although semisolid materials can also be deposited mechanically and by pneumatic means. contents. Binder jetting (C) and material jetting (B) both use well-known inkjet heads; in material in binder jetting, only a binder is fed through the nozzle; in jetting, the entire print material is placed in. The support of the powder bed provided by binder jetting is a benefit, as it eliminates the requirement for support systems or replacement materials. The selective laser sintering process also uses this mechanism. (D), where a laser selectively fuses the powder bed. Lastly, selective stereo lithography (E) creates the desired part by polymerizing a liquid resin vat. The figure is adapted from reference (49).

bioprinting of viable cells as well as small molecules such as drugs.[60] The printing resolution and the final shape fidelity are strongly influenced by the droplet size, fluid rheological features and print speed. Therefore, these parameters should be precisely optimized. Droplets tend to spread out before they are completely cross-linked when they land on the print, which reduces the resolution of the inkjet. Furthermore, the most distinct features are typically printed parallel to the direction of the inkjet.[39]

Manufacturers of inkjets claimBinder Jetting

While in material jetting the printing depends on jetting of the ink on the printing substrate to build a 3D object, binder jetting uses a liquid binder to bind a powder substrate at a predetermined places to create the 3D object Each layer of the object is created by applying a layer of powder across a printing surface.[39] The binder is then deposited in the required geometry using an inkjet head. After that, the powder bed is lowered, fresh powder is applied and a second layer is selectively bound. High powder volumes may be needed for this technique, but sacrificial materials are not necessary because the powder bed can support the emerging part.[65] One benefit of this technique is that it allows for the printing of multiple materials using different binding agents. Furthermore, porous structures are easily created during this manufacturing process, which frequently takes place at room temperature. Not only can metals and ceramics be used frequently, but polymers can also be printed. For improved mechanical properties, materials printed in this manner need to undergo post-printing processing, such as chemical treatment. Based on the size of the powder particles, powder binder printers can print objects with a high resolution feature, down to 50-micron.[39]

Selective Laser Sintering

While binder jetting and selective laser sintering work similarly, the latter uses a laser beam to fuse powder particles rather than a liquid binder. This mechanism limits the number of materials that can be printed using a laser. Although thermoplastic polymers are commonly in laser sintering 3D printing, particularly in biomedical applications, metals and ceramics are still widely used.[66] Particle size will affect final print mechanical properties, efficiency of particle spreading and feature print resolution,

so careful selection of the powder particle size is crucial.[67] The material has a major influence on the feature resolution of selective laser sintering. Compared to other 3D printing techniques, selective laser sintering is a high-resolution technique that can produce resolution as small as 30 microns,[68] though some report feature resolutions in the range of 100 microns.[54] Similar to binder jetting, the printed objects are typically porous and require post-printing processing to achieve mechanical strength and smooth surfaces. Furthermore, selective laser sintering typically requires no support materials and is quick and affordable.

Stereolithography

Stereolithography is the earliest type of additive manufacturing.[69] It uses the same methods as photolithography, which came before it. The basis of stereolithography is the way light interacts with photopolymer resins. To achieve the desired geometric pattern, a large barrel containing resin is first exposed to radiation from either a top or bottom. The light source is positioned beneath the resin tank with a transparent base in the bottom-up technique, which uses smaller resin volumes (Figure 1).[58] After curing the first layer, the building platform moves upward. Then, another layer undergoes a similar polymerization process. On the other hand, in top-down stereolithography, the part needs greater volumes of material to stay completely submerged because the building platform is moving downward for every layer.[70] Other stereolithography-related techniques include Digital Light Processing (DLP) and Continuous Liquid Interface Processing (CLIP).[58] Stereolithography printing can produce a high resolution printing technique. However, light leakage may cause some non-specific polymerization, resulting in some print quality.[71] Post-curing, post processing and sacrificial support structures are frequently needed during the printing process. A restricted range of materials can also be employed, with photocurable polymers being one of the most common ones.[58] A more expensive but more specialized form of stereolithography called two-photon polymerization allows for higher feature resolution. Two laser beams are used in two-photon polymerization to polymerize resins. These devices are capable of producing features with a resolution of 120 nm Figure 1.[72,73]

3D printing of controlled release pharmaceuticals

Recently, it has become well-known that the key of the future medical care is to provide a personalized drug delivery system. Personalization of the disease treatment not only include the tailoring of the patient's dose but it can be extended to the production of a more complex dosage forms such as multiple drug dosage forms, independent multiple release profiles and site-specific drug delivery or targeting drug delivery systems.[74,75] 3D printing has been extensively investigated as a manufacturing tool to produce such dosage forms, wherein traditional manufacturing methods have been founded to be less flexible and more expensive to produce similar dosage forms. The first clinical application of the 3D printing in the medical industry is the production of a rapid disintegrating tablet of Levetiracetam for personalized oral drug delivery. This rapid disintegrating tablet (Spritam®) was the first FDA-approved 3D-printed medication which was produced using binder jetting 3D printer to create a highly porous rapid disintegrating tablet.[76,77] Various strategies have been adopted by 3D printing to control the drug dose and the rate and site of the drug release. Manipulation of the infill density is one of the simplest ways to control the rate of drug release from a 3D printed dosage forms by creating a geometric changes (porosity). Material extrusion parts are typically printed by first depositing an outer shell, which is then filled with predetermined infill geometry (a part with 100% infill produces a solid part, while a part with 0% infill leaves the part completely hollow).[78] Many studies have investigated the effect of surface area/volume ratio on the release profile of tablets and the results have shown that increase surface area to volume ration significantly increases the rate of drug release from the 3D printed tablet[78,79] Verstraete *et al*. showed that faster release profiles are achieved with lower infill percentages when using oral drug delivery.[80]

The control of the rate of drug release from a 3D printed tablet could also be achieved by selecting the type of the polymer or polymers blend which work as a carrier for the drug, wherein the rate of a drug release from a polymeric matric is highly depending on the physicochemical properties of the polymer such as solubility, particle size, type of the polymer and percentage incorporated in the formula.[81] In 2015, Alhanan *et al.* has successfully developed a FDM 3D printing method to print immediate and controlled release theophylline tablets using pharmaceutical polymers. In this study eudragit E and hydroxypropyl cellulose (grade SSL) were used to produce immediate release tablets while Eudragit RL and RS and their mixture were used to print extended release theophylline tablets (up to 16 hr) (Figure 2)[82] It was possible to slow down theophylline release following the addition of Eudragit RS. This might have been related to the lower number of quaternary ammonium groups in Eudragit RS in comparison to Eudragit RL, which makes Eudragit RS less permeable to water.[18] In another similar study, hot melt extruder and FDM 3D were successfully used to produce filaments and print immediate release tablet of pantoprazole using pharmaceutical grade polymers. Where the tablet printed using filament containing polyethylene glycol (grade 6000) and pantoprazole 10% (without plasticiser) exhibited the faster dissolution rate more than 90% within 30 min.[83] These studies have clearly shown how the selection of the 3D printing polymers could change the rate of the drug release.

In many cases, such as with painkillers, immediate-release profiles are preferred. The increased surface area to volume ratio for the prints is what led to Verstraete's release profile results. Crucially, Kyobula *et al*. also showed that wettability is a requirement for this process.[84] Compared to their counterparts with cavities larger than 600 microns, spaces and cavities smaller than 600

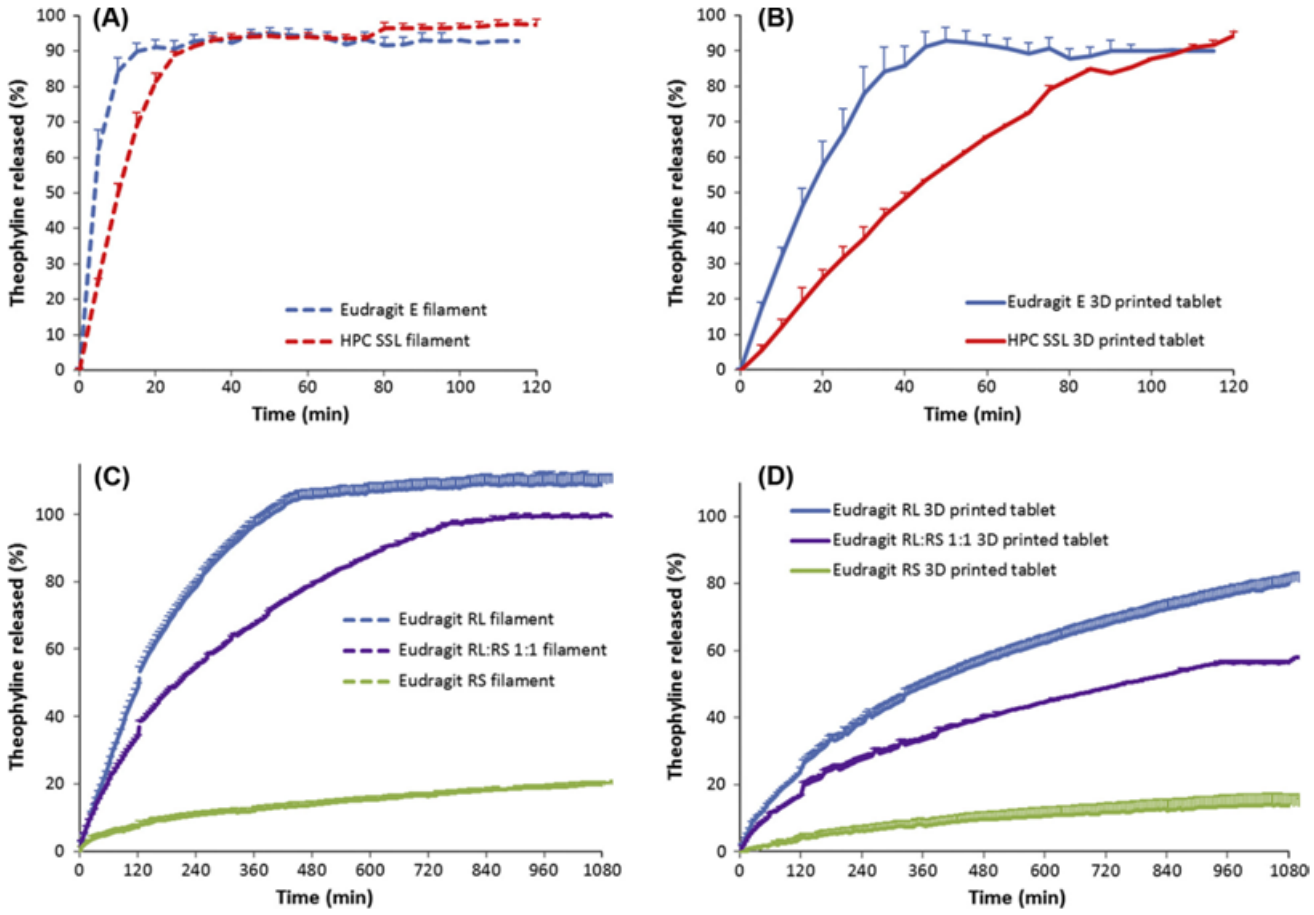

Figure 2 : Impact of FDM based 3D printing on *in vitro* release of theophylline compared to original filament using (A and B) immediate release polymers: Eudragit E and HPC SSL and (C and D) extended release polymers: Eudragit RL, Eudragit RS and their 1:1 mixture. The figure was adapted from reference (82).

microns were less wettable and produced longer release times. The relationship between infill, the creation of micro-geometry and release profile is reported in other literature.[85]

3D printing technology not only offers a control over the rate of a drug release but also a site-specific drug release dosage forms has been developed using 3D printing approach. Many studies have investigated the feasibility of the 3D printing technology to fabricate gastro-flotation tablets which are also considered a site-specific release dosage form of the drugs in the stomach. The concept behind using 3D printing to produce floating dosage form is to print a low density solid tablet so it can float in the stomach and increase the retention time.[86] Li *et al.* demonstrated that gastro-flotation tablets could be customized with a range of infill percentages. In this study, a novel floating tablet of dipyridamole was printing using lattice shape infill with different density to create a tablet mass lower than that of the stomach content, so it will float in the stomach. Extrusion-based 3D printing was used in the print of the floating tablet and hydroxypropyl methylcellulose hydroalcoholic gel with microcrystalline cellulose was also used as an ink of the printing. The different infill tablet produced more 70% release of the drug within 8 hr and floating time of upto 8 hr compared to the commercially sustained release tablet which produced only 38% release in the stomach, suggesting enhanced bioavailability of the floating dosage form.[87] In another study, FDM 3D printing was used to fabricate gastroretentive-floating pulsatile tablet. Where the printing filament was manufactured from Hydroxypropyl Cellulose (HPC) and Ethyl Cellulose (EC) using hot melt extruder. A core-shell tablet was created with a shell having different geometries (shell thickness, wall thickness and infill density). The core-shell tablets showed a good floating behavior and the a lag time for the pulsatile release of the drug was 30 min to 6 hr.[86] A similar article was also conducted to create gastro-floating tablet of theophylline using FDM 3D printing.[88]

Moreover, the capacity of 3D printing to fabricate customized dosage forms containing multiple drugs each with identified release profile was also investigated. Khalid *et al.* has successfully printed a single tablet contains five drugs with a defined two release profiles, called polypill. In this work, extrusion-based 3D printing was used to print pravastatin, ramipril, atenolol, aspirin and hydrochlorothiazide in a single polypill. Wherein, aspirin and hydrochlorothiazide were printed in the top cap of the polypill providing an immediate release profile whereas

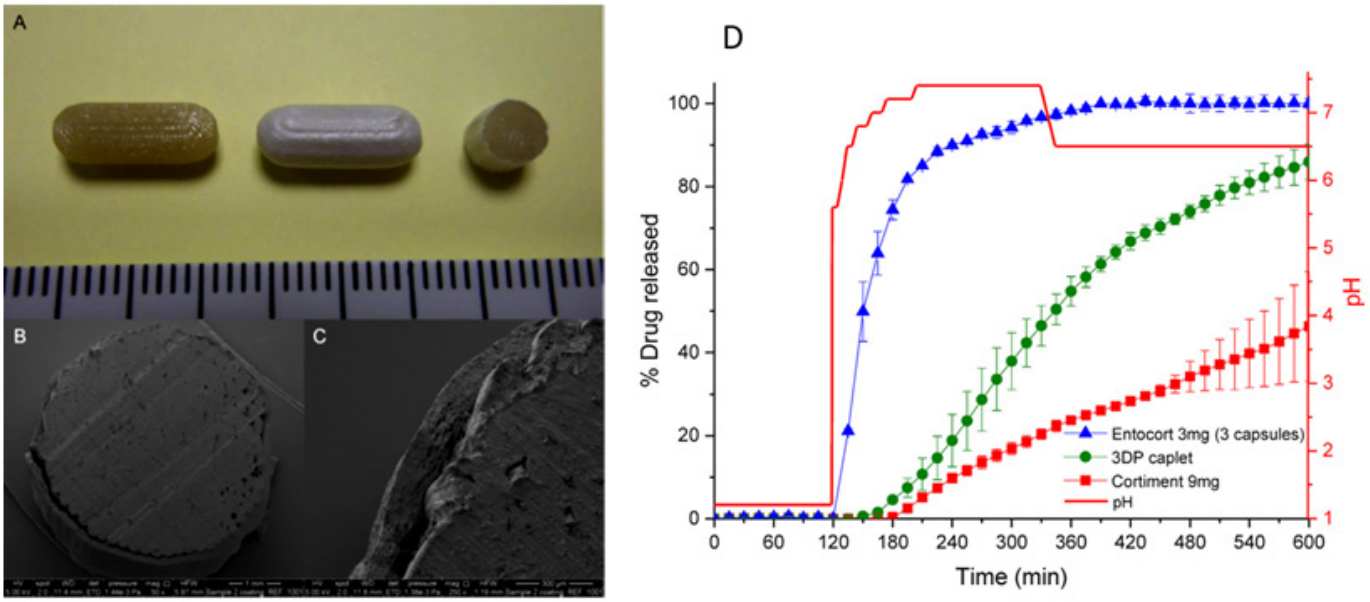

Figure 3: Images and release profile of 3DP fabricated caplets (A) from left to right, caplet prior to coating, caplet after coating and cross section of coated caplet (scale in cm); (B, C) SEM images of internal structure of cross-section of a coated-3D printed caplet. (D) Drug release from Cortiment1, Entocort1 and coated 3D printed caplets in 0.1 M HCl for 2 hr followed by physiological bicarbonate buffer under dynamic pH conditions (pH 5.6-7.4 and then 6.5) controlled by the Auto pH SystemTM. Red line shows the real-time pH values. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article. The figure was adapted from reference (92).

the other drugs were printed in separate chambers within the body of the tablet using hydrophobic polymer cellulose acetate which provide sustained release profile of these drugs.[89] Recently, commercially available Polyvinyl Alcohol (PVA) filaments were used as a drug carrier for 3D printing of oral tablets via FDM.[90,91] These commercial PVA filaments can be loaded with drugs either by soaking them in an alcoholic solution of the drug or by chopping the filaments and mix them with the drug and re-extrude them via hot melt extruder. Although the later offers higher loading capacity of the drug, limited number of drugs can be loaded using hot melt extruder due to the thermal degradation that may occur during extrusion.[36] Skowyra *et al.* investigated the feasibility of using an FDM-based 3D printing to fabricate extended release, patient-tailored prednisolone tablet. In this study, ready-made PVA filament was loaded with prednisolone by soaking in methanolic solution of prednisolone for 24 hr, wherein methanol caused swelling of the PVA filament allowing prednisolone to diffuse into PVA filament. *In vitro* release study revealed that approximately 80% of prednisolone was achieved after 12 hr for 2 and 3 mg tablet and 18 hr for 4, 5, 7.5 and 10 mg, suggesting a dose dependent extended drug release which could be useful in the development of CTDDS.[90] In 2015, Goyanes *et al.* also used the commercial PVA filament to fabricate an extended release caplet of budesonide using FDM 3D printing. The PVA filament was cut in to small pieces and mixed with budesonide. The mixture was then extruded by hot melt extruder to produce 1.75 mm in diameter drug-loaded PVA filament which was used to print budesonide-loaded caplet. After printing, the caplet was coated with eudragit L100 enteric coat which prevents drug release in the stomach. Ultimately, the enteric coated PVA caplet provided a lag time for the drug release, showing not more than 20% release in the first 6 hr of the *in vitro* dissolution test as shown in Figure 3. This time is almost equivalent to the *in vivo* gastric and intestinal transient time, suggesting the potential of this procedure to produce colon-targeted dosage form.[92]

Many other studies have investigated the capacity of the 3D printing to create a controlled extended release drugs, however the rate of the drug release was controlled by controlling the structure of the tablets. In 2009, Yu *et al.* has developed a zero-order release tablet using 3D printing. In this work, a doughnut-shape multilayers drug delivery device was printed.[93] The doughnut-shape was selected based on a mathematical model suggested that a tablet with a central hole could provide a constant drug release rate due to the controlled surface area during erosion.[94] The doughnut tablet was printed using extrusion based printing and HPMC and EC were used as printing ink and to provide controlled drug release. The tablet was fabricated with upper and lower layers EC to obtain impermeable layers while the inner core was printed from drug-loaded EC (2%) to create a slower release rate from the exposed surface. Theoretically, doughnut shape geometry allows a decrease in the surface area due to the outward releasing portion and the increase in the surface area of the inward releasing portion to produce a zero-order release (Figure 4).

3D Printing of oral Colon-Targeting Drug Delivery Systems (CTDDS)

Table 1 summarizes the most recent CTDDS that were developed using 3D printing technologies emphasizing on the type of 3D printing, polymers used and the proposed colonic delivery strategy. Moreover, the time to 10% release of the drug ($t_{10\%}$) and the time to 80% release ($t_{80\%}$) were also presented as indicators of the lag time phase (time prior to release) and the release time, respectively. Wherein, a lag time of around 5 hr is necessary to match the gastric and intestinal transit time and ensure colonic delivery of the drug. These data will be very useful to assess the performance of the performance of the CTDDS and highlights the factors that could influence release profile. In general, the current strategy to 3D print CTDDS depend on developing a shell/core structure. The shell (drug-free) is contributing to produce the lag time phase while the core (drug-loaded) will determine pattern of the colonic release of the drug (immediate or sustained). However, not all the studies include printed core and some of them the core in injected inside the printed shell either manually or automatically during the printing process. Therefore, the 3D printed CTDDS can be classified in to shell-3D printed tablets (sometimes called capsular device or printfill) and shell/core/drug-3D printed tablets (Figure 5).

Regarding shell-3D printed tablets, although different 3D printing technologies has been used HME with FDM 3D printing is the most commonly used technology to print a hollow or low infill shell that would be used as a container of the drug. Various strategies have been employed to develop a programmed shell to dissolve after a specific time producing the lag phase, include using pH-sensitive polymers such as methacrylate copolymers, using polymers blends at various ratios and controlling the shell wall thickness. In 2018, Linares *et al.* investigated the feasibility of the combined FDM 3D printing and Injection Volume Filling (IVF) system to develop a CTDDS of theophylline. Although FDM is one of the most common 3D printing techniques for its simplicity and its good level of accuracy and reproducibility, the major limitation of this technique is incompatibility with the thermosensitive drugs due to the high temperature that the drug could experience during the formation of the drug-loaded thermoplastic filament and 3D printing process.[95] Therefore, in this study to overcome the problem of degradation of the thermosensitive drugs, a 3D bioprinter combing FDM printing and IVF has been used to fabricate the CTDDS. This multi-head printing system allowed efficient and simultaneous multimaterials 3D printing which make it possible to inject the thermosensetive drug in to the FDM printed scaffold avoiding the risk of thermal degradation. Consequently, to create a colon targeted printfills using this system, the printing process started with FDM printing of a porous PLA printfill with solid bottom (two layers), when the PLA printing reaches 18 layer the IVF started injection of a theophylline-loaded HPMC hydrogel. Next, a second IVF injector starts to print a set volume of eudragit FS30D, a pH-sensitive polymer, to seal the top of the printfill, delaying the release of the theophylline from the printfill. *In vitro* release study of the final printfill showed that no drug release at pH 1.2 within 2 hr, however after 2 hr when the pH of the dissolution medium is changed to 7.5 there was a sudden increase in the amount of the released theophylline due to the dissolution of the enteric polymer seal of the printfill, reaching about 65% of

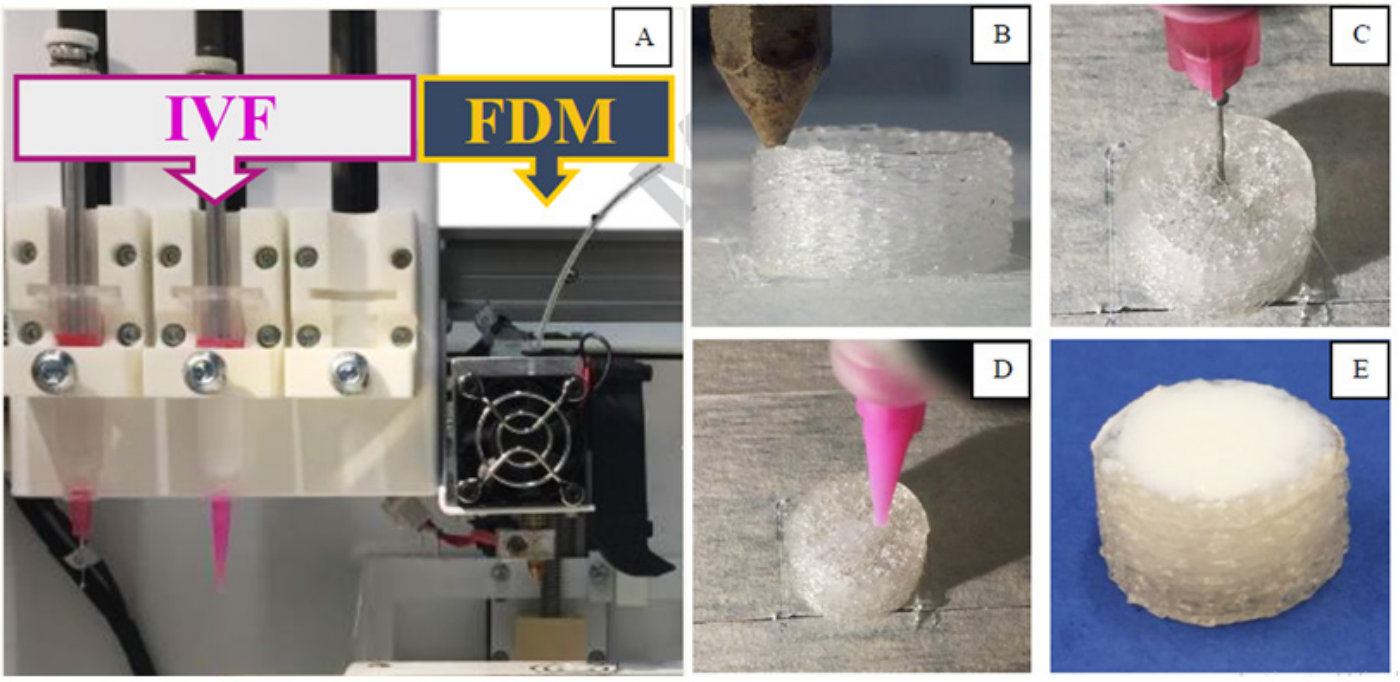

Figure 4: A) 3D printer with FDM and IVF technologies; B) Extruder of FDM technology; C) Syringe of IVF technology injecting the drug–loaded gel; D) Syringe of IVF technology injecting the delaying release polymer; E) Final printfill obtained. The figure was adapted from reference (96).

Table 1: 3D Printed drugs in form of CTDDS dosage forms.

Sl. No	Drug	3D printing technology	Polymer (s)	HME temperature (C°)	3D printing temperature (°C)	Colon-targeting Strategy	$t_{10\%}$	$t_{80\%}$	References
1	Theophylline	FDM plus IVF.	Body: PLA; lid: eudragit FS30D; core: chitosan particles.	Commercial PLA filament.	200	pH-dependent plus microbial dependent (chitosan).	2.3	6.8	96
2	Camptothecin	FDM plus IVF.	Body: PLA; lid: eudragit FS30D; core HPMC hydrogel.	Commercial PLA filament.	201	pH-dependent plus microbial dependent (chitosan).	3.5		97
3	5-flurouracil	HME plus FDM.	Shell: combination of eudragit L100 and Eudragit S1, core: chitosan-coated alginate beads.	eudragit L100-55/ eurdagit S100 combinatios: 150-165.	182	pH-dependent plus microbial dependent (chitosan).	6	24	98
4	N-acetylglucosamine	Injection molding plus droplet extrusion.	Shell: Blend Eudragit FS 100 plus PLA; Core: methyl cellulose hydrogel.		160	pH-dependent plus time-dependent.	4.5	23	99
5	Live bacterial suspension.	DIP and FDM.	Body and cap: PCL, P (CL-LA) or P (CL-GA), Lock: PVA coated with eudragit S100.	Commercial PVA filament.	210	pH-dependent.	4-5	5-7	100
6	Theophylline, budesonide and diclofenac.	HME and FDM.	Core:PVP; shell: eudragit L55-100.	PVP filament: 90; eudragit L100-55: 125.	PVP: 110; eudragit L100-55: 185.	pH-dependent plus time-dependent.	2-3	3-4	102
7	Caffiene	HME and FDM.	Core: PVA and HPC; shell1:HPC; Shell2: eudragit L100	PVA:185; HPC: 160; eudragit L100: 165	PVA:185; HPC: 160; eudragit L100: 166	pH-dependent plus time-dependent.	4.5-5.5	5.5-6.5	105
8	5-aminosalicylic acid.	HME and dual FDM.	HPMCAS and PVA.	HPMCAS: 150; PVA:180.	HPMCAS: 195; PVA:190.	pH-dependent plus time-dependent.	4.3	> 8	106
9	Mesalamine	HME and dual FDM.	Core: Kollidon SR; shell: combinations HPMC-HME and eudragit L100.	Kollidon SR: 200; combinations HPMC-HME and eudragit L100: 170.	190-215	pH-dependent plus time-dependent.	8	24	107

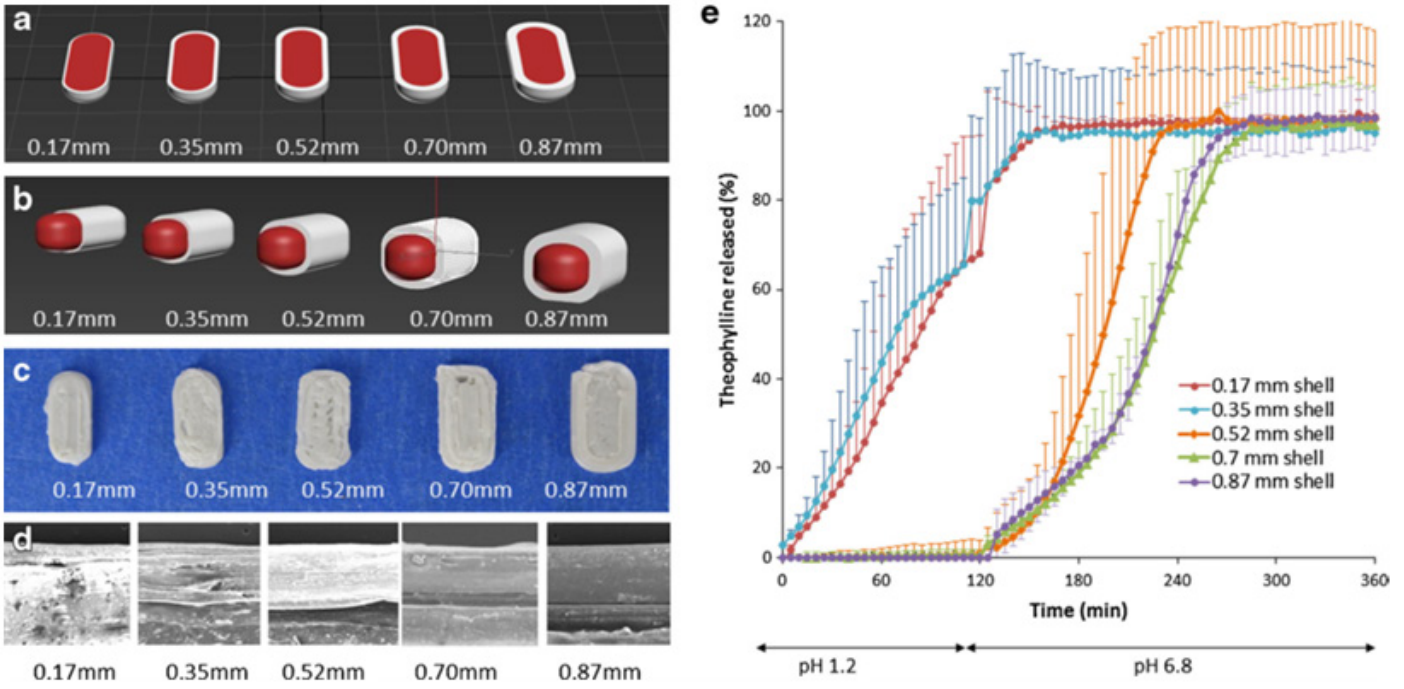

Figure 5: (a and b) Rendered images (Autodesk 3DS Max) of shell-core designs with increasing shell thicknesses (0.17, 0.35, 0.52, 0.70 and 0.87mm). (c) Images of 30% completed shell-core designs with theophylline core and increasing Eudragit L100-55 shell thickness. (d) SEM images of the surface of the tablets. (e) Impact of shell thickness of 3D printing on in vitro release pattern of theophylline from 3D printed tablet in USP II pH change dissolution test. The figure was adapted from reference (102).

the dose released within the first 5 hr.[96] The study has successfully developed a pH-dependent colonic delivery printfill, however the release profile of theophylline from the printfill is suggesting a premature release of the drug as about 65% of the drug released before 5 hr of the release time which is equivalent to gastric plus small intestine transient time.[4] This means that more than half of the dose will be released in the small intestine and the rest of the dose will reach the colon.

Later in 2021, another similar study to develop a CTDDS of the anticancer drug camptothecin was published. In this new study, exactly the same PLA printfill was developed using FDM with IVF 3D printing machine, however camptothecin-loaded chitosan micelles were mixed with printable ink and injected into the printfill rather than injection of the drug -loaded hydrogel. The new printfill has combined two colonic delivery strategies, first the pH dependent due to the presence of the eudragit FS30D seal and the second is the chitosan micelles which could delay the release of the camptothecin until reaching the colon. In the colon, the chitosan will act as a substrate of the bacterial enzymes leading to release of camptothecin in the colon. *In vitro* release study showed that no drug release within the first 2 he at pH 1.2, only 3% of the drug released at pH 6.8 at time point 4 hr and the drug release started to increase gradually when the pH was changed to 7.4 at time point 5 hr, suggesting that the developed printfill could delay the drug release until the drug reaches the colon.[97] A similar study was also conducted in 2018 to 3D print colon-targeting tablet which is composed of a pH-responsive tablet containing 5-fluorouracil-containing alginate/chitosan beads. The printing process include printing of a hollow (infill 30%) pH-responsive tablet using various ratios eudragit L100-55: eudragit S100. The hollow pH-responsive tablet was loaded with a 5-flourouracil-containg alginate /chitosan beads and closed with a PLA lid.[98]

In 2023, Asadi *et al.* conducted a study to print a CTDDS using extrusion based 3D printing and hydrogel injection. In this study, the author has investigated the printability of a polymeric blend composed of pH-responsive polymer (eudragit SF100) and biodegradable polymer polylactic acid (PLA) to print the tablet shell. During the printing, the shell was filled with an N-acetyl glucosamine-loaded methylcellulose hydrogel. Among the various blend ratio 60/40, 70/30 and 80/20 eudragit FS100 to PLA, 80/20 ratio of eudragit FS100 to PLA showed the most stable and reproducible printing. Further, the study has investigated various shell infill and different hydrogel concentrations. *In vitro* release study revealed that tablet printed of 80/20 of eudragit FS100 to PLA and filled with N-acetyl-glucosamine-loaded methyl cellulose 3% hydrogel achieved the most desirable release profile for colonic targeted drug delivery, less than 20% of the drug released after 5 hr of the study. This work has also proved that optimization of the shell composition alone is not enough to program the release profile to match the desired release but the core hydrogel concentration had a detrimental effect (Figure 6).[99]

Very recently, 3D printing technology was used to develop CTDDS to deliver aqueous suspension rather than solid dosage forms.

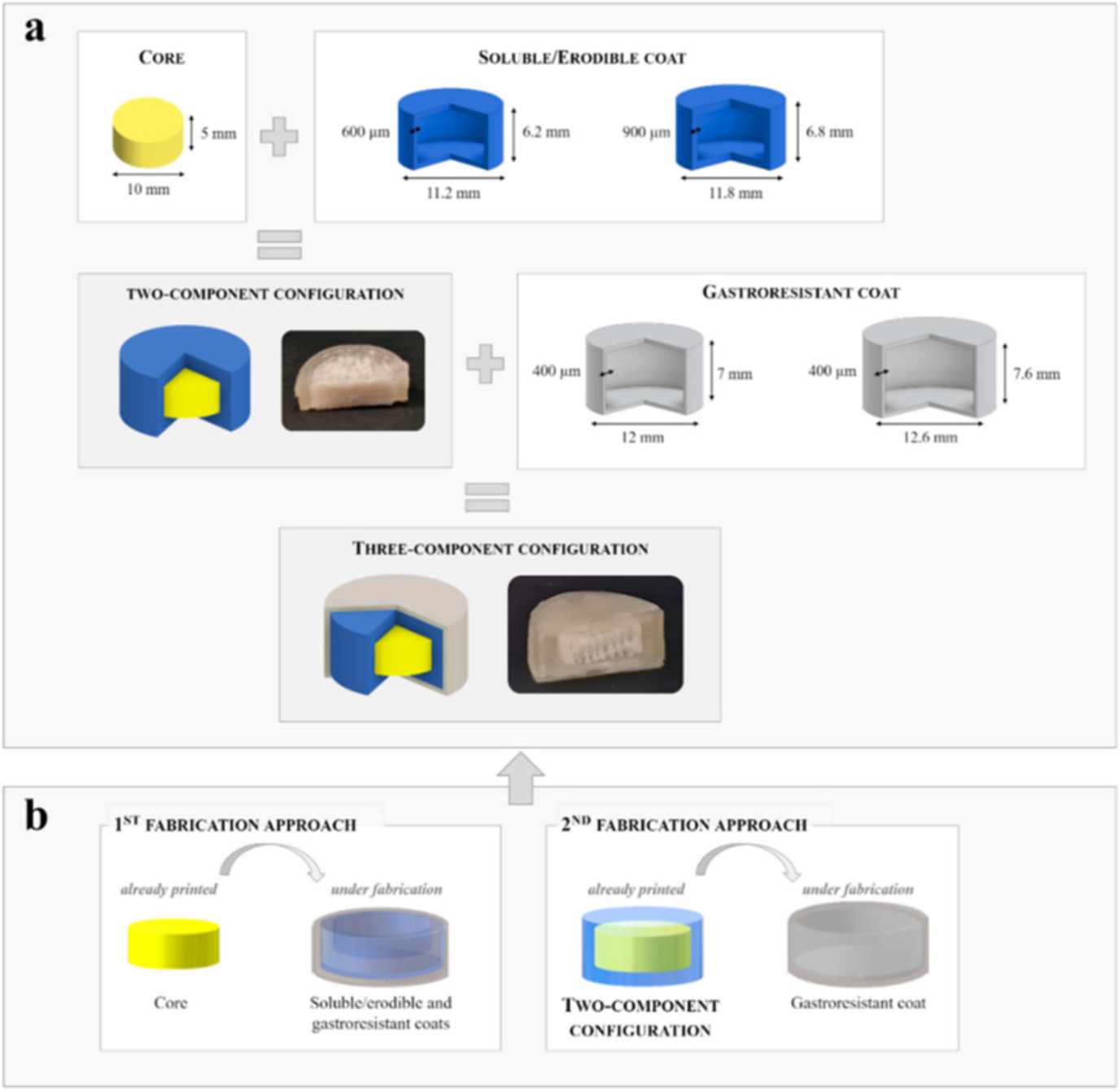

Figure 6: (a) Outlines and photographs of the configurations of the Chronotopic™ system including CAD files with dimensional details of the parts to be combined and (b) outline of the fabrication approaches envisaged for printing the three-component configuration. The figure was adapted with permission of reference (105).

The printed colonic targeted capsule was filled with aqueous suspension of live bacteria and exhibited sufficient stability in GIT compared to the traditional liquid filled capsules. The new capsular device composed of biodegradable but water resistant body and lid and enteric coated lock connecting the body and the lid. The water resistant parts of the capsules were printed by Digital Light Processing (DIP) 3D printing using three in-laboratory synthesized polymers, including PCL (polycaprolactone) and its Linear Copolymers P (CL-LA) (polycaprolactone-co-lactic acid) and P (CL-GA) (polycaprolactone-co-glycolic acid) to obtain different mechanical properties. These polymers were also methacrylated and mixed with photo initiator before DIP 3D printing. The lock was printed from a water-soluble polymer (polyvinylalcohol) and then coated with enteric polymer (eudragit S100) using FDM 3D printing to close the body and the lid. The results show that capsules printed from different copolymers exhibited tuneable mechanical properties but all can withstand the stress experienced during passing through the GIT. Furthermore, the capsules were relatively resistant to proton diffusion, an important feature for protecting the bacterial

suspension from the harmful acidic conditions in the stomach. *In vitro* dissolution tests and *in vivo* imaging in a beagle dog confirmed that the capsules have the desirable release profile for colonic delivery, where the capsules content released in the distal small intestine and colon.[100]

In the second group of the 3D printed CTDDS, the whole tablet including the drug-loaded core is printed. Although this procedure is could be harmful to the thermosensitive drugs and limit the list of drugs compatible with this procedure, it has higher capacity in producing various personalised dosage forms and provide higher chance to control over the release profile of the drug and include multiple drugs each with defined release profile in a single dosage form. Moreover, 3D printing of a drug could have other advantages such as producing of solid dispersion or co-crystal form of the drug to enhance solubility of the CBS class II and IV drugs.[101] The performance of the shell/core/drug 3D printed will also depend on the shell characteristic as discussed above in addition to the characteristic of the printing core (type of the polymer and infill density) and compatibility of the drug with these process. Researchers have developed various procedures to 3D print core-shell tablets with release profiles targeting the colon. In 2016, Okwuosa *et al*. has developed a complex core-shell enteric tablet using HME and FDM 3D printing. The tablet was printed by a dual head FDM 3D printer to simultaneously print the shell and the core of the tablet using different polymers. Pharmaceutical polymers Polyvinylpyrrolidone (PVP) and methacrylic acid co-polymer were used to print the core and the shell, respectively. The filaments for both core and shell were prepared hot-melt extruder and talc and Triethyl Citrate (TEC) were used as a filler and plasticizer, respectively. The study focused on exploring the effect of shell thickness and the impact of printing resolution on the release profile of model drugs (theophylline, budesonide and diclofenac). Moreover, thermal stability of the drugs was also investigated using Thermogravimetric Analysis (TGA) and Differential Scan Calorimetry (DSC). The result showed that low thickness (0.17 and 0.35 mm) will not resist the gastric pH and result in a premature drug release while the thicker shells (0.52-0.81 mm) resulted in a better control over the drug release. The shell thickness to control drug release is much higher than the required coat thickness by fluid-bed or pan coater (30-100 µm), suggesting difficulty to prevent drug release by 3D printing using 1 or 2 layers. TGA and DSC also proved the thermal stability of the drugs in the printing conditions (printing temperature is 185°C). The release profile of the all drugs in this study showed $t_{10\%}$ and $t_{80\%}$ values of 2-3 hr and 3-4 hr, suggesting an enteric release of the drugs rather than colon-targeting release.[102] The failure of the current shell/core tablet to produce colon-targeting is due to the type of the polymeric matrices for the shell and the core, wherein the type of the pH sensitive polymer of the shell and the solubility of the polymeric matrix are determinant factors of the release patterns of the drugs. The work has shown a high potential to be to produce CTDDS.

In 2021, Melocchi *et al.* has used HME and FDM to fabricate a complex shell-core Chronotopic™ system for pulsatile and colonic delivery of caffeine. The study has thoroughly investigated the feasibility of the FDM printing to produce personalised, on-demand chronotropic system. The concept of the chronotopic™ system depends on 3D printing of a drug-loaded core surrounded by swellable/erodible chronotropic shell. When the swellable/erodible shell reacts with aqueous medium, it forms a gel layer that undergoes slow dissolution/erosion, providing a lag time before the release of the drug depending on the shell thickness (pulsatile configuration). For colonic delivery of the drug the core/shell tablet was further surrounded by an additional shell composed of enteric soluble polymer to provide gastro-resistant property to the tablet (colon-targeting configuration). For printing of such complex multi-materials tablet, a dual printheads FDM printers was used. Furthermore, this Chronotopic™ system required formulation of a drug-free and drug-loaded printable filaments using pharmaceutical grade polymers, a list of the filament compositions is provided in Table 1.

The development of drug containing formulations based on pharmaceutical grade polymers and suitable for formation printable filament by hot melt extruder and FDM 3D printing has already been described in other studies.[103,104] However, in this study a new challenge has been addressed which represented by using a dual-arm printer which required to alternate two/three different formulations during fabrication of the pulsatile/colon-targeting tablet. Printability of the above polymeric filaments was carefully optimised by using different printing resolutions (limited and fine-tuned resolutions) to attain the required shell thickness with respect to the digital design. Fine-tuned resolution showed better printability and reproducibility in printing the required shell thickness. Uncontrolled penetration of aqueous fluids trough adjacent layers not completely sealed was preliminary excluded by testing shells filled with water sensitive paper strips. *In vitro* release study was used to test the lag time (indicated by $t_{10\%}$) provided by the outer shell, middle shell and the core separately or in pulsatile and colonic delivery configurations. The outer gastro-resistant shell which printed using Eudragit L100-55 -based filament (400 µm thickness) offered no drug release in the acidic release medium (pH 1-2) and approximately 2.5 hr and 11 min $t_{10\%}$ and pulse time, respectively. The middle shell (900 nm thickness) which is printed using Hydroxyl Propyl Cellulose (HPC)-based filament exhibited 4 hr and 9.5 min $t_{10\%}$ and pulse time, respectively. The core of the Chronotopic™ system was designed to provide an immediate release of the drug release after the lag phase. Two types of the filaments were investigated for FDM printing of the core, including PVA and HPC based filaments, moreover the filaments included plasticiser and disintegrant to achieve the desired release. Cores with different infill density (50, 80 and 100%) was also investigated. With all the formulations, the desired release profiles were obtained by decreasing the infill to 50%, independent of the presence of an

adjuvant in the formulation. Finally, the optimised formulations and printing process independently identified for both core and shells were used in FDM 3D printing of the pulsatile and colonic delivery configurations. The desired release profiles for each one were also confirmed using the *in vitro* release studies.[105] The results of this study clearly showed that increasing the shell thickness will increase the lag time, moreover the presence of two shells (pH sensitive and swellable/erodible shell) allowed better programing of the lag time to produce either controlled pulsatile or colonic delivery release, compared to the above mentioned studies.

In 2023, a bicompartmental colon-targeting device of 5-aminosalicylic acid was developed using FDM 3D printing. The biocompartmental device was printed using dual-nozzle FDM 3D printer. Hydroxypropylmethyl Cellulose Acetate Succinate (HPMCAS) and Polyvinyl Alcohol (PVA) were selected as matrix-forming polymers of the outer pH-dependent and the inner water-soluble compartments, respectively. The results showed a biphasic drug release profile with only 5.7 wt% and 8.2 wt% drug released at pH values of 1.2 and 6.8, respectively. Suggesting that most of the drug payload released after 5 hr.[106] In another recent study in 2024, hot melt extruder and FDM 3D printer were as also used to print a hybrid core/shell colon-targeting tablet of mesalamine. Filaments composed of various ratios of eudragit L100 and Hydroxypropyl Methyl Cellulose (HME-grade) (HPMC-HME) was investigated for printing the shell of the tablet, while Kollidon SR was used for printing the mesalamine core of the tablet. Optimal filament ratios were identified as 50:50 for the core and 30:70 for Eudragit L-100 to HPMC HME L100 for the shell which achieved the desired release profile for colon delivery of mesalamine (less than 5% released in the first 5 hr).[107] Comparing the results between different reviewed studies shows that 3D printing technology exhibited a high degree of flexibility to fabricate CTDDS with personalized or programmed lag time and the release duration ($t_{10\%}$ and $t_{80\%}$, respectively) to match patient specific need. The release pattern in such formulations can be customized based on the type of the printing polymer specially the dissolution pH value of the pH sensitive polymers, other excipients and the design of the structure (such as the shape, shell thickness, core infill density). For example, patients with inflammatory bowel diseases may have unstable gastric and intestinal transit time, therefore, CTDDS having shorter or loner lag time may be required to for effective colon targeting in those patients. Moreover, the bowel diseases may include the terminal part of the small intestine; in this case CTDDS with short lag time (2-4 hr) may be desired. In other cases, the bowel disease may be located in the descending colon, in this case long lag time and sustained release could be desired Table 2 .

Challenges and limitations

Although 3D printing technology has made a significant progress in the field of personalized pharmaceutical fabrication and many studies have been published about the development of a novel pharmaceuticals including CTDDS, many challenges are still facing the application of 3D printing for commercial production of CTDDS and translation in to clinical application.[108] Many of these challenges are technical related to the compatibility of the drug with a specific printing technology. Among various 3D printing technologies, FDM 3D printing has attracted the pharmaceutical scientists for production of CTDDS for its accuracy and reproducibility. However, most of the commercially available polymeric filament are not suitable for 3D printing of CTDDS.[109] Therefore pharmaceutical polymers that are used in formulation of conventional CCTDS need to be processed by hot melt extruder to formulate filaments that are mechanically suitable for FDM 3D printing.[36,82,110] However, two challenging problems may be related to this process, first the drug and polymer are subjected to a high temperature could reach more than 200°C during both hot melt extrusion and FDM 3D printing, shortening the list of drugs and polymers that could tolerate this high temperature without degradation. Some studies have suggested adaptation of pharmaceutical polymers with low glass transition temperature for FDM 3D printing, expanding the spectrum of drugs that can be printed using 3D FDM printing.[95,111] Moreover, formulation of a drug-loaded filament by hot melt extruder may require other pharmaceutical excipients such as lubricant, fillers and plasticizers which could affect the release profile of the drugs. For example: eudragit L100 and eudragit S100 are pH-sensitive enteric polymers that are dissolve at pH above 6 and 7, respectively, however, the addition of other excipients such as plasticizer or diluent may influence the pH threshold of polymers solubility.[112] Some reports have also suggested the use of other printing techniques such as the extrusion-based 3D printing which is not depend on thermoplastic polymers and does not require high temperature to print, so it is compatible with thermos sensitive drugs. Khalid *et al.* has conducted many studies to establish 3D printing approach of pharmaceuticals using extrusion-based 3D printing, avoiding the use of FDM 3D printing. In these studies, the author has managed to convert different pharmaceutical-grade excipients such as diluents, binders and gel forming agents in to viscous smooth paste suitable for extrusion-based 3D printing.[113-115] In 2015, Khalid *et al.* has used extrusion-based 3D printing to print polypill contains three drugs (captopril, nifedipine and gliclazide) each with identified release profile. In this study, Hydroxylpropyl Methyl Cellulose (HPMC) hydro alcoholic gel was used as a printing ink which further mixed with the active drug ingredients, fillers and osmogene to form a viscous extruded paste suitable for extrusion-based 3d printing. Captopril compartment was design to create an osmotic pump and the resultant release profile showed an extended release with less than 20% of the drug released in the first 5 hr, suggesting the potential of this procedure to create CTDDS.[89] Other technical challenges that should be considered during 3D printing of CTDDS include resolution, reproducibility and scalability.[102,116] It

Table 2: Formulation of filaments and extrusion parameters.[108]

Formulation	T (C°)	Screw speed (rpm)	Torque (N.cm)
HPC	160	80	50
EDR+25% TEC	165	80	120
(PVA+15% GLY)+10% CFF	185	70	110
(PVA+15% GLY)+10% CFF+30% EXP	190	70	150
(PVA+15% GLY)+10% CFF+30% AMY	190	70	140
(HPC SSL+5% PEG 400)+10% CFF	160	100	45
(HPC SSL+5% PEG 400)+10% CFF+30% EXP	160	100	65

HPC: Hydroxy propyl cellulose, EDR: Eudragit L100-55, TEC: Triethyl citrate, PVA: Polyvinyl alcohol, GLY: Glycerine, CFF: Caffiene, EXP: Sodium starch glycolate, AMY: High-amylose maize starch, HPC SSL: Low viscosity hydroxypropyl cellulose, PEG: Polyethylene glycol.

was also demonstrated that the printer's feature resolution had an impact on the release profile, with low-resolution printing producing coating layers that were thicker than the nominal dimension. Hang and colleagues have shown that in the case of multilayer tablets, the release mechanisms rely on multiple parameters, such as the percentage of infill and the thickness of the shell.[117]

Moreover, pharmaceutical challenges may retard the development of effective CTDDS. Most of the previously 3D printed CTDDS are depending on coating with pH-sensitive polymers and the swellable/erodible polymers to delay the drug release. However, adaptation of other colon targeting strategies such microbial-triggered release for 3D printing could allow formation of more efficient CTDDS using 3D printing. This strategy needs coating the drug with insoluble coat that act as a substrate of the enzyme released by microflora in the colon or binding the drug molecules to this substrate forming a prodrug that release the drug in the colon. He *et al.* has developed a novel reactive prodrug ink formulation strategy for inkjet 3D printing of controlled release dosage forms and implants. Three different ibuprofen attached reactive prodrugs were synthesized through an esterification reaction to produce IJ3DP printed tablets Controlled release was achieved by mixing the synthesized reactive prodrug with different mole ratios of hydrophilic co-monomers. During printing and exposure to UV radiation, these formulations produced co-polymerized products with different hydrophilicity and thus different release rates.[118] Similar 3D printing strategy could be a used prodrug for microbial-based colonic delivery.

Finally, the challenges could be related to quality control and FDA-approval of the formulations produced by 3D printing technology. Quality control requires non-destructive and practical techniques. This has already been resolved through the use of several Process Analytical Technologies (PATs) to consistently regulate the quality of the product and the process.[52,119] Further, a significant retardation to using 3D printing in developing pharmaceutical formulations is the absence of a regulatory body. The FDA issued guidance in 2017 outlining regulatory necessities for the manufacture of medical devices. Currently, various FDA-approved 3D printed medical devices are available on the market; however, only one FDA-approved 3D printed pharmaceutical product (SPRITAM®) is available.[38]

CONCLUSION

3D printing is an emerging technology that has been recently introduced in drug industry for its high capacity and flexibility in fabricating personalized dosage forms. Although pharmaceutical industry has achieved tremendous advancement in the recent years its application in producing personalized dosage forms especially those with targeted or multiple release profiles is still limited. 3D printing has the capacity to digitally control the printing materials, shape, size and internal architecture of the printed structure. These properties along with layer-by-layer printing fashion has made it feasible to produce novel dosage forms with personalized dose, drugs combinations and different or targeted release profiles. Although only one 3D printed drug has been approved by FDA, 3D printing has been successfully used to produce various dosage forms with immediate and extended-release profiles, wherein the rate of the drug release was controlled by selecting the suitable printing polymers and by controlling the printing infill percentage. Reducing the infill percentage with increase the surface area/volume ratio providing faster release rate. Furthermore, 3D printing has been used to fabricate oral tablets with a drug release profile targeting the colon (CTDDS), which means these tablets has a lag time of around 5 hr before drug release is started. FDM is the most commonly used 3D printing technology in printing CTDDS for its accuracy and low cost, however it requires adaptation of pharmaceutical grade polymers such pH-sensitive polymers and swellable erodible polymers to formulate mechanically strong and flexible filaments suitable for FDM 3D printing. In addition, these processes include subjecting the drug to high temperature which may cause its degradation. 3D printing of CTDDS could depend on using pH sensitive polymers such as eudragit L100 and eudragit S100, time-dependent release (delayed/pulsatile release) and microbial-dependent drug release. Several

challenges are need to be solved before we can see wide spectrum of licensed drugs in the market are produced by 3D printing technology including development of 3D printing approaches and formulation that are more compatible with drugs, reducing the risk of drug degradation, improving the quality control of the 3D printed products and finally establishment regulatory body for approval of 3D printed products.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study is a review article, no human or animal participants or case reports were included in the study.

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The authors declare that there is no conflict of interest.

ABBREVIATIONS

CTDDS: Colon-targeting drug delivery system; **GIT:** Gastrointestinal tract; **ROS:** Reactive oxygen species; **MeSH:** Medical Subject Heading; **FDM:** Fused deposition modeling; **HME:** hot melt extruder; **DLP:** Digital light scattering; **CLIP:** Continuous liquid interface processing; **$t_{10\%}$:** Time to 10% release of the drug; **$t_{80\%}$:** Time to 80% release of the drug; **HPC:** Hydroxypropyl cellulose; **EC:** Ethyl cellulose; **PVA:** Polyvinyl alcohol; **HPMC:** hydroxypropyl methyl cellulose; **IVF:** Injection volume filling; **PLA:** Polylactic acid; **PCL:** polycaprolactone; **P (CL-LA):** Polycaprolactone-co- lactic acid; **P (CL-GA):** Polycaprolactone-co-glycolic acid; **TEC:** triethyl citrate; **TGA:** Thermogravimetric analysis; **DSC:** Differential scan calorimetry; **GLY:** Glycerine, **CFF:** Caffiene, **EXP:** Sodium starch glycolate, **AMY:** High-amylose maize starch; **HPC SSL:** Low viscosity hydroxypropyl cellulose; **PEG:** Polyethylene glycol; **HPMCAS:** Hydroxypropylmethyl cellulose acetate succinate.

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