This is the accepted version of this paper. The version of record is available at
https://doi.org/10.1016/j.addr.2021.04.020

Manuscript Click here to view linked References

Controlling drug release with additive manufacturing-based solutions

Shriya K Patel[a], Mouhamad Khoder[b], Matthew Peak[c], Mohamed A Alhnan[a,*]

[a] *Institute of Pharmaceutical Sciences, King's College London, London, UK.*

[b] *Drug Discovery, Delivery and Patient Care (DDDPC) Theme, School of Life Sciences, Pharmacy and Chemistry, Kingston University London, Kingston Upon Thames, London.*

[c] *Paediatric Medicines Research Unit, Alder Hey Children's NHS Foundation Trust, Liverpool, UK*

*Corresponding author at:
Institute of Pharmaceutical Sciences
King's College London
150 Stamford Street
London SE1 9NH. Tel.: +44 (0)20 7848 7265.
Email: Alhnan@kcl.ac.uk

Contents

1. Introduction....4

2. The nature of the printed matrix produced by the different 3D Printing technologies....4

2.1. Fused Deposition Modelling (FDM)....5

2.2. Selective Laser Sintering (SLS)....5

2.3. Semi-Solid Extrusion (SSE)....5

2.4. Material/Binder Jetting (MJ/ BJ)....6

2.5. Stereolithography (SLA)....6

3. Achieving different release patterns from 3D printed structures....6

3.1. Immediate Release (IR)....6

4.2. Delayed Release....8

4.3. Sustained Release (SR)....10

4.4. Pulsatile Release....11

4.5. Complex/ Stimulated (Polypill)....13

4.6. Release from 3D Printed Capsules....14

4. Mechanism of Drug Release....15

5. Opportunity with Freedom of Design and Expanding surface area....16

6. Challenges of Controlling Release from 3D Printed Structures....17

6.1. Technical Challenges....18

6.2. Regulatory Challenges....18

7. Future Trends....19

8. Conclusion....20

References:....27

ABSTRACT

3D printing is an innovative manufacturing technology with great potential to revolutionise solid dosage forms. Novel features of 3D printing technology confer advantage over conventional solid dosage form manufacturing technologies, including rapid prototyping and an unparalleled capability to fabricate complex geometries with spatially separated conformations. Such a novel technology could transform the pharmaceutical industry, enabling the production of highly personalised dosage forms with well-defined release profiles. In this work, we review the current state of the art of using additive manufacturing for predicting and understanding drug release from 3D printed novel structures. Furthermore, we describe a wide spectrum of 3D printing technologies, materials, procedure, and processing parameters used to fabricate fundamentally different matrices with different drug releases. The different methods to manipulate drug release patterns including the surface area-to-mass ratio, infill pattern, geometry, and composition, are critically evaluated. Moreover, the drug release mechanisms and mathematical models that could aid exploiting the release profile are also covered. Finally, this review also covers the design opportunities alongside the technical and regulatory challenges that these rapidly evolving technologies present.

ARTICLE INFO

Abbreviations: 3DP: 3D printing, AM: additive manufacturing, DFs: dosage forms, IR: immediate release, DR: delayed release, SR: sustained release, FDM: fused deposition modelling, EB: extrusion-based, HME: hot-melt extrusion, SLS: selective laser sintering, SSE: semi-solid extrusion, BJ: binder jetting, PB: powder-based, SLA; stereolithography, Tg: glass transition temperature, API: active pharmaceutical ingredient, QC: quality control, QA: quality assurance.

Keywords: surface-to-mass ratio, matrix, immediate, enteric, FDM, FFF, SLA, SLS, semi-solid extrusion, powder.

1. Introduction

Conventional dosage forms (DFs) are produced on a mass-scale in a 'one-size fits all' approach, without accounting for the needs of a heterogenous population. However, owing to the frequency of undesirable side effects associated with 'standard' medicines, customised medication and dosing continue to receive increasing attention [1-3]. Although controlling the active pharmaceutical ingredient (API) release to avoid peaks and fluctuation in drug pharmacokinetics has helped to alleviate side effects, the demand for a simple and flexible approach to manufacture on-demand, patient-specific, dose-tailored medicine continues to rise.

3D printing (3DP), also known as additive manufacturing (AM), is a rapid prototyping technique in which solid objects are constructed by depositing layers sequentially. 3DP technologies have received a significant attention in the pharmaceutical industry, opening the door for potential redistributed manufacturing of DFs Previous published reviews were mainly focused on individual manufacturing methods [4-7], rather than understanding and predicting the API release from complex 3D printed structures.

This review aims to describe the state of the art of manufacturing 3D printed structures with different release profiles, and to explain how the choice of materials, process nature, and the geometrical and spatial design could be used to predict and tailor specific and on-demand release patterns. The review also summarises the technical and regulatory challenges facing the control of API release from products produced using AM technologies and explores how these might evolve.

2. The nature of the printed matrix produced by the different 3DP technologies

Before describing the release profiles of 3D printed DFs, it is essential to establish the fundamental differences in the structures that 3DP technologies can construct. The fundamentally different starting materials, procedures, and variable processing parameters can yield 3D printed objects of significantly different appearance, physical, and release qualities. In this section, we will investigate the composition and the nature of matrices produced by each 3DP technology. A summary of the concept behind the different 3DP technologies along with the nature and characteristic of resulting matrices is provided in Table 1**.**

Unlike the conventional manufacturing methods for solid DFs that often produce solid structures, 3DP technologies produce defined layered structures. Fig. 1 illustrated scanning electron microscope (SEM) images of DFs created by different 3DP technologies. The layer-by-layer arrangement along with the novel matrix nature and composition have been exploited to achieve different API release profiles.

INSERT FIGURE 1

INSERT TABLE 1

The differences in the technological parameters and resulting matrices of each 3DP technology are discussed in the following sections.

2.1. Fused deposition modelling (FDM)

FDM is a polymer-rich extrusion-based 3DP method, in which a filament (based mainly on API and polymer) is melt-extruded through a nozzle by a controlled layer-by-layer process. Owing to the polymer-rich foundation (~50%) used to feed FDM 3D printers, the matrices produced are usually of high density **(**Fig. 1A**).** Whilst ensuring the matrix solidification at room temperature, the choice of material has major implications on the dissolution pattern from this matrix [8, 9]. The ideal filament polymers often have a glass temperature (Tg) in the approximate range of 30-100°C. Such a range allows the extrusion of thermoplastic matrices at an elevated temperature (90-220°C).

2.2. Selective laser sintering (SLS)

SLS is a powder-based technology in which a high energy laser is directed to draw a specific pre-configured pattern on the surface of a powder bed. This causes the fusion of particles, which mainly consists of thermoplastic polymers and API blends in a powder form. Unlike conventional powder compression methods, SLS involves the use of a loosely packed powder bed, implying significant voids within the structure following particle fusion. This leads to the formation of a highly porous void-filled matrix (Fig. 1B). Solvents can easily penetrate through the matrix voids and hence result in its rapid disintegration. Therefore, the produced matrix is ideal for fast-disintegrating or immediate-release products [10, 11].

2.3. Semi-solid extrusion (SSE)

SSE uses a pressure mechanism such as rotating screw gear(s) or pressurised air to extrude layer-by-layer a continuous stream of semi-solid material (e.g. homogenous paste/gel) through a nozzle over a moveable stage to build up 3D objects. As solvent-based method, the nature of the produced matrix depends largely on the nature of the solvent(s) used. Following the evaporation of the solvent during or after the 3DP process, evaporable solvents yield a dense matrix as seen in Fig. 1C, where

evaporable solvents of absolute-ethanol and deionised water were employed [12]. Non-evaporable solvents, on the other hand, result in more solid and rigid matrices.

2.4. Material/binder jetting (MJ/ BJ)

BJ 3DP (ink-jetting) technology involves the distribution of an ink (API and binder/binder solutions, over a powder bed which then solidifies. The process is repeated in a layer-by-layer fashion until the desired 3D DF is formed. The materials used in jetting-based technologies determine the nature of the formed matrix. While the wax-jetting method yielded a robust, compact and pore-less structure [13], the BJ method resulted in a highly porous well-bound matrix [14]. Figs. 1D and 1E show 3D printed solid DFs produced using wax-based and material-jetting approaches, respectively.

2.5. Stereolithography (SLA)

SLA involves a layer-by-layer curing of a photosensitive resin by scanning a focused UV laser. Consequently, the oligomer-based liquid resin is photopolymerised to form a cross-linked and polymer-rich structure. SLA technology is mainly used for the preparation of hydrogels, where the nature of the produced matrix is highly dependent on the concentration and molecular weight of the polymer, which in turn influences the density of the gel formed. As a result of the high degree of cross-linking, SLA technology produces pore-less, dense, and compact matrices (Fig. 1F), that often yield delayed release profiles [15, 16].

3. Achieving different release patterns from 3D printed structures

Although 3D printed structures share common ingredients with powder compressed and film coated tablets, the inherently different properties of 3D printed structures dictate fundamentally different release profiles. Furthermore, the newly introduced 3DP manufacturing approaches can also be easily adjusted to optimise the API release through the selection of appropriate polymers [17-20], geometry modification [21-24] and matrix compartmentalisation [25-27].

3.1. Immediate release (IR)

Approximately 40% of drug delivery products are taken orally, of which 70% are IR DFs [28]. Immediate release is traditionally attained by compressing powders with an appropriate disintegrating agent, enabling rapid disintegration and dissolution [29-34].

Powder-based (PB) 3DP methods (e.g. BJ, SLS) have been assessed for their potential to produce IR DFs. These 3DP technologies allow for the creation of a highly porous structure with the presence of low-density, void-filled inter-particulate spaces, where API and filler particles are loosely or partially adhered [14, 17, 35-37]. PB 3DP has an advantage in allowing for greater tablet porosity to be attained in comparison to tablets produced *via* powder compression [17, 38]. Such structures are difficult to mimic using conventional tabletting methods without compromising the physical integrity and mechanical strength of the tablets. When introduced to the dissolution medium, water can easily penetrate through these structures, resulting in rapid disintegration and IR profiles. This obvious advantage of powder-based 3DP technologies has been exploited for the production of highly fast disintegrating tablets [14]. The first FDA approved 3D printed tablet, Spiritam®, was produced by PB technology (ZipDose®) that enabled an immediate disintegration in 10 seconds, whilst containing high doses (1000 mg) of piracetam [39].

Such a porous structure could also be fabricated using SLS 3DP, in which IR profiles could be achieved [40]. While the control of API release profiles can be attained in PB 3DP technologies through manipulating the solvent/binder concentration and amount, controlling API release in SLS should be balanced with the requirements of matrix formation. API loading has shown to affect its release profile in SLS 3D printed structures [41]. Indeed, higher API loading was associated with higher energy absorption, more particle fusion, and hence slower release characteristics.

For SSE, achieving a fast disintegrating and dissolving moiety in a polypill structure required the use of a large amount of disintegrant (>55% of total IR compartment weight in the polypill) [25], which is excessively higher than the recommended percentage of 1-20% of disintegrants used for conventionally produced tablets [42, 43]. On the other hand, adding disintegrants to the composition of the filaments fed into FDM printers proved ineffective. Sadia et al. proposed that during the thermal heating in hot-melt extrusion (HME) for the production of these filaments, the liquified polymer may coat the disintegrant particles, sealing their pores and hence preventing swelling [21]. This contributed to the failure to induce tablet disintegration and accelerated API release. A similar phenomenon was also observed with cellulose-based filaments [22].

Several attempts have been undertaken to achieve IR from DFs produced through extrusion based (EB) 3DP technologies (i.e. SSE and FDM). These were mainly based on altering the DF design and surface area-to-mass (SA/M) ratio through the use of perforating channels within the tablet design [21], varying the infill pattern [23, 44-47], and producing different geometries [48] or designs [49], as shown in Fig. 2 and discussed in further detail in Section 5.

INSERT FIGURE 2

It is worth noting that in FDM 3DP, the polymer choice is usually confined to a small number of biodegradable thermoplastic polymers, e.g. polyvinyl alcohol (PVA) [50] and polylactic acid (PLA) [51]. Such polymers tend to have a relatively high Tg (yielding a solid structure at room temperature), which is associated with longer polymer chains and stronger inter-chain interactions. Therefore, the polymer-rich matrices that FDM 3DP technology generates, along with the high Tg polymers used, are more likely to result in extended-release profiles [52, 53]. Polymer-rich methods such as FDM have been shown to result in a highly tortuous structure with reduced porosity of the materials in comparison to oral tablets produced *via* conventional compression technology.

One approach to achieve IR from relatively high Tg polymers is through the use of ionizable polymers such as Eudragit® EPO, a cationic methacrylate-based polymer with MW of 47,000g/mol and a Tg of 52°C [54]. Using FDM 3DP, Sadia et al. reported the manufacturing of four different APIs incorporated within Eudragit® EPO-based DF. At gastric pH, the dimethylaminoethyl side chains of Eudragit® EPO are ionised, increasing the polymeric chain spaces, and leading to polymer erosion and immediate API release. *In vitro* release studies showed that all Eudragit® EPO-based DFs release >85% of the incorporated APIs within 30 minutes [8]. It is worth noting that the potential of 3DP to allow for single-step tablet production has captured the attention of pharmaceutical companies. Unlike conventional tablets whereby several steps (mixing, granulation, drying, compression and film coating) are involved, Merck and AMCM recently announced their goal to simplify and shorten tablets production processes by applying SLS 3D printing at commercial scale [55] .

Another approach to engineer 3D printed IR DFs is through the use of IR polymers with relatively low Tg. Okwuosa et al. combined the advantages of water-soluble polyvinylpyrrolidone (PVP) [49, 56], with FDM 3DP at a lower operating temperature (110°C) [57]. This approach allowed the release of 85% of the API within the first 30 minutes, complying with the USP standards for IR DFs. However, poor stability of the resulting hydroscopic PVP-based polymeric matrices has been reported [58].

SLA 3DP proved difficult to be used to produce IR DFs. In fact, the polymer-rich cross-linked matrices formed *via* this technology are more suitable for producing controlled-release DFs [16]. Upon water contact, these DFs swell and the loosening of the cross-linked matrix is required in order for the API release to occur, resulting in controlled release profiles [59]. *In vitro* studies of API release from SLA 3D printed hydrogels have shown that API release is dependent on water content. This can be exploited to accelerate API release by increasing water content in these hydrogels [60].

4.2. Delayed release (DR)

DR DFs are frequently used to achieve a site-specific drug delivery in the gastrointestinal tract and/or to protect API(s) susceptible to degradation in the hostile nature of the gastric environment. Conventionally, an acidic polymer coating (thickness ~30-100 µm) is applied to the protected the core

(e.g. tablets, pellets) in the stomach acidic environment. This coating then dissolves when intestinal pH is reached (pH >5.5). However, applying such an approach for 3D printed DFs has proved challenging due to the difficulty of building relatively thin and sealed barriers using the current resolution of 3DP technologies.

Two approaches have been employed to achieve such a demanding task: 3DP of a solid enteric matrix (i.e. monolithic system) or the simultaneous dual 3D printing of a shell-core structure (i.e. reservoir system). Fig. 3 shows different examples of DR formulations produced *via* 3DP.

INSERT FIGURE 3

An early attempt to achieve DR was through using PB 3DP in which Eudragit® L100 (an enteric methacrylate polymer) was used to produce a coating with a thickness of 200 µm. Such a thick coating was necessary to inhibit the API release in the acidic medium. However, a slow pH-response was observed in the intestinal phase. The release from this structure was proposed to be governed by the rate of polymer erosion [37]. Using FDM 3DP, monolithic tablets for delaying the release of paracetamol were manufactured [61]. Three different grades of a semi-synthetic polymer, hydroxypropyl-methylcellulose acetate succinate (HPMC-AC), different drug loadings (up to 50%) and different infill patterns were assessed. While the three tablets complied with the USP criteria for DR formulations, with less than 10% API release after the first two hours in acidic medium, the tablets showed a slow response to pH change with 80% API release over >4 hours.

To achieve a faster release in intestinal medium, a hybrid solution was proposed where budesonide 3D printed PVA-based tablets were coated with Eudragit® L100 using a fluidised bed coater [62]. Okwuosa et al. proposed a single process using two-colour FDM 3DP where a core-shell structure was developed [63]. Eudragit® L100-55 filaments were used to 3D print an enteric shell surrounding PVP-based 3D printed cores with IR properties. To achieve sufficient inhibition of API release in the gastric phase, a minimum of three layers (~500 µm in thickness) of the enteric coating was required (Fig. 3B). This thickness is significantly higher than typical enteric coating thickness. The study demonstrated the potential of fabricating patient-specific pH-responsive tablets in a single step as well as the potential of 3DP to produce products with different coating thicknesses by digital input, using the same staring materials. A similar method was also used to protect pantoprazole using 3D printed shells based on cellulose acetate phthalate or Eudragit® L100-55 (Fig. 3C) [64].

Another approach involved the use of FDM 3DP coupled with an automated gel-dispensing syringe to fabricate an enteric DF [65]. In this study, a gel based on API and hydroxypropyl methylcellulose (HPMC) as an infill material, was incorporated into an Eudragit FS 30D-based enteric 3D printed skeleton (Fig. 3D). While the system showed tight control of API release in the gastric phase, on change to pH 7.5 API release increased, suggesting complete dissolution of the enteric film [65].

Whilst conventionally enteric coatings are typically 20-100 µm in thickness, an additional step in the processing is required for coating. 3DP allows for an in-built coating in a single process [63, 64, 66]. Moreover, 3DP allows the production of 'cage structures', which can include tablets, and modify the drug release or retention time as required [67-69].

4.3. Sustained release (SR)

Conventionally, SR is achieved through the use of biocompatible polymer matrices (i.e. monolithic systems) or using a rate-controlling membrane (i.e. reservoir system) [70-72]. Hydrophilic matrices, are one of the most widely used, proving effective for various reasons, including design simplicity, stability, ease of scale-up and administration.

3DP has demonstrated a significant potential to provide a platform for manufacturing controlled-release DFs (Fig. 4). Using a large portion of polymers of relatively high Tg, FDM 3DP is naturally suited to manufacture DFs with extended-release properties [50, 62, 73-84]. Initial trials incorporated PVA, a polymer whose filament is commercially available, as water-soluble domains to build supporting parts for 3D printed objects. Several attempts have been carried out to understand the mechanisms of API release from these 3D printed structures. *In vitro* API release was deemed to be mainly dependent on the erosion of the PVA matrix [50, 80, 85]. The API release from such water-soluble and swellable polymeric matrices is mainly controlled by two mechanisms: surface erosion (polymer dissolution) and drug diffusion [70, 74, 86]. The dominant mechanism depends on the type of DF, the nature of the excipients, and the API solubility.

The choice and properties of polymers used in 3DP, especially the aqueous solubility, influence the APIs sustained release mechanism. Naturally, water-insoluble polymers, for example ethylcellulose and polycaprolactone, tend to produce release kinetics driven by drug diffusion [87]. On the other hand, soluble polymers, such as HPMC and PVA yield a SR release based on matrix erosion.

HPMC, a hydrophilic polymer, swells and dissolves in water allowing SR of the API [88]. HPMC-based matrices are considered as swelling controlled systems, where the release rates are controlled by the rate of dissolution medium penetration and matrix swelling [89]. Upon contact with the dissolution medium, the Tg of the system is reduced, due to the penetration of water plasticiser into the network of the polymeric chains [90]. In some cases, the matrix showed hydrogel formation on the surface in addition to the swelling behaviour, leading to further delaying the API release [91]. These hydrophilic polymers are also available in low MW grades, suggesting their suitability for dissolution enhancement and IR application. However, they often have a relatively low Tg, which does not necessarily meet the thermoplastic properties for thermal extrusion needed for several 3DP processes, e.g. FDM [92-94]. Boetkar et al. concluded that the release of nitrofurantoin was dependent on the

loading amount of Metolose® 60SH (polylactic acid (PLA) and HPMC based feed materials), the higher the load the greater the release [95].

Eudragit® RL and RS are synthetic non-biodegradable, non-absorbable, non-toxic, and amorphous polymethacrylate polymers [96] that are commonly used for time-controlled release purposes [97]. API release is achieved by diffusion either through pores in the polymeric coating or through the hydrated polymer matrix [98], leaving a ghost tablet. Since Eudragit® RS has low permeability and Eudragit® RL has high permeability, combining them at different ratios allows for specific target permeability and API release following pH-independent swelling [99-103].

INSERT FIGURE 4

Manufacturing DFs with 3DP is more suited for tablets rather than pellets. Only one example currently exists for production of SR pellets [104]. Such multi-unit dosage systems have clinically shown a more reproducible transit time with regards to release [105-107]. In the future, the advancement of 3DP technologies could benefit from producing capsule structures with enclosed multi-unit.

The ability of 3DP to produce DFs that mimic API release from commercially available SR products have been instigated. Using EB 3D printing, Khaled et al prepared HPMC-based SR tablets comparing the release profiles with commercial bilayer tablets manufactured using conventional compressed methods [4]. The study reported that the 3D printed tablets (using HPMC at 14% w/w) matched the guaifenesin SR release profile of commercially available tablets. In another example, FDM 3D printing technology was also used to fabricate MR budesonide DFs [62]. 3D printed budesonide caplets were finally coated with an enteric polymer (Eudragit® L100) layer using a fluidized bed coater. Budesonide release was compared with two commercial budesonide products: Entocort® and Cortiment®. While Entocort® showed rapid budesonide release in the upper small intestine conditions, Cortiment® yielded a delayed and very slow release. Interestingly, the 3D printed caplets started budesonide release in the small intestine medium and continued in a sustained manner throughout the distal intestine and colon, suggesting their potential in the treatment of inflammatory bowel disease.

4.4. Pulsatile release

Many diseases, such as rheumatoid arthritis and bronchial asthmas, are regulated by the human circadian rhythm, requiring drug administration at certain times of the day [108, 109]. DFs that offer modified/pulsatile release can synchronise with the circadian rhythm, therefore with the symptomology of such diseases. Traditionally, pulsatile release tablets have been made through altering drug design and employing polymer coatings, which act as functional barriers to control API release rate [110-112]. 3DP offers a unique ability to produce tablets of complex structures in which a pulsatile release profile could easily be achieved through matrix compartmentalisation and modifying the design approach [26,

27, 113-115]. Different 3D printed design profiles and the corresponding pulsatile release profiles are shown in Fig. 5.

INSERT FIGURE 5

Melocchi et al. explored the use of FDM for the manufacturing of capsular devices with pulsatile release profile using swellable polymer hydroxypropyl cellulose (HPC) [113]. HPC yielded a release lag phase when used as the substrate for enteric coating. Upon water inflow, the 3D printed capsular device formed a gel barrier around the capsule shell, hindering solvent penetration into the capsule cavity for ~120 minutes. The dissolution tests showed a lag phase of approximately 60 minutes before a rapid and complete API release in < 10 minutes.

FDM 3DP was also used to design dual-pulsed release capsules, consisting of walls of different thicknesses, sections, and composition, that allowed multiple release kinetics [26]. The capsular device consisted of a soluble compartment yielding IR and a delayed swellable/erodible compartment for pulsatile release. With different compartment assembly, two distinct pulse release patterns were obtained, with one or more lag phase (Fig. 5A2). In line with the circadian nature of chronic asthma, floating pulsatile theophylline tablets were developed with a pre-determined lag time of 6 hours [116]. The shell thickness affected tablet pulse release, with tablets of thicker shell demonstrated a pulse release at ~4 hours, whilst thinner shell gave a pulse release at ~1.5 hours [116].

An innovative approach was carried out by Melocchi et al. printing a 'Lego-inspired' capsular device (Fig. 5B) [114]. One-, two-, and three-pulse release profiles were attained using compartmentalisation. The breakup of the compartments provided different release profiles; prompt release (IR), on pH change release (DR) or after tuneable lag-times release (pulsatile-release). Simple alteration of the design approach and composition allowed for multiple release kinetics to be obtained with a single DF. The performance of each individual compartment was dependent on the composition and thickness of its own wall, whilst unaffected by composition and number of adjoined compartments.

While this approach holds great promise, the issue of the resolution of 3DP of the barrier wall is a challenge. The resolution of 3DP is dependent on the tip diameter and 3D printer operating settings, which in turn define the dimensions of each layer. Resolution difficulties are associated with controlling the layer deposition process and the tendency of material to expand post-deposition. Achieving a wall thickness greater than the nozzle diameter (typical size of 300-800 µm) requires adjacent layers to be more closely deposited, which can lead to nozzle blockage or printing failure.

EB 3DP technologies, which rely on a nozzle-based mechanism to build layers of different thickness, face the challenge of maintaining a reproducible and consistent material flow. During the 3DP process, there is a need to alternate between stopping and restarting the printhead when printing layers of varying thickness. Therefore, these are likely to be limitations on the reproducibility of EB in the manufacture of pulsatile release DFs. However, in comparison to conventional technology such as

powder compression or injection moulding, creating complex structures with 3DP proved a facile alternative approach to mimic pulsatile release from conventional tabletting [25, 117].

4.5. Complex and polypill DFs

Polypills provide the prospect for improved medication adherence and combination therapies [118-123]. Furthermore, polypills help personalise dosages and release profiles of multiple APIs independently within one dosage form. However, they are complex DFs that face the challenge of co-ordinating APIs release, both individually and in synchrony. Here, 3DP holds significant potential on providing a modular solution using different modalities to allow simultaneous and independent API release at different times and sites from a single DF.

In this context, two different and well-defined release profiles (IR and SR) were achieved *via* a compartmentalisation strategy [25], in a five-in-one dose regime produced by EB 3DP [25]. A polymer-rich matrix loaded with three APIs was extruded in segmented compartments providing SR. The other two APIs were combined with disintegrants and extruded directly on the top of the tablet architecture to provide IR. In addition to polymer choice, polymer content influences the release profile; as polymer content increases, lag times increase with a corresponding decrease in API release rate [36].

A significant advantage of 3DP over conventional technology is the ability to produce complex structures. Sun et al. fabricated customizable tablets to achieve any desired APIs release profile [7]. The tablet consisted of three components; two with a surface eroding polymer with and without API and one containing an impermeable polymer [7]. The tablet was protected by an impermeable polymeric layer on all sides except for an opening on one side. When immersed in aqueous medium, the polymer (with and without the API) eroded through the side with the opening. With a one-dimensional release, the rate of API release was dependant on the shape of the drug-containing polymer. The unique structure made of 5-long segments of the drug containing polymer achieved five pulses overtime. Such approach assumes that the DF, particularly the opening part, is consistently immerged in gastric and intestinal media. However, several studies have shown that the gastrointestinal tract is mainly filled with voids and pockets of liquid [124]. Therefore, it is essential that this concept is tested *in vivo.*

Pereira et al. explored the significance of polypill architecture on API release [125]. Monolithic tablets that contained four APIs produced a slower release than the smaller tablets that contained an individual API, which can be attributed to a smaller SA/M ratio of the polypill. The API release appeared to be dependent on individual API solubility. The position of each individual API layer within the multi-layered stacked format of the polypill was shown to affect the produced release profile. APIs in the inner layers were released by the diffusion through the outer layers, following the erosion of the outermost layers. The arrangement of drugs within the polypill format thus can be optimised to achieve desired API release profiles.

A multi-layered stacked polypill with six APIs was SLA 3D printed with different geometries and material compositions [126]. Although different API layers were successfully printed, Raman microscopy analysis showed the API diffusion across the layers occurred depending on their amorphous or crystalline properties. Therefore, quality control (QC) testing throughout the manufacturing process must be taken to ensure the intended release profile is maintained.

4.6. Release from 3D printed capsules

More recently, functional containers in the form of capsules that can control API release according to capsule design and shell composition have been designed and manufactured using 3DP technology. Conventional methods for producing both hard and soft capsules consist of API and excipient blends enclosed in a shell (~0.6-0.9 mm thickness), with adjuvant materials added such as plasticizers, preservatives, colouring agents, disintegrants and lubricants. Conventionally, gelatine has been used almost solely as material for capsule shells, due to its unique physicochemical properties. To address gelatine limitations, such as the animal source and ethnic dietary laws, temperature and moisture sensitivity, non-gelatine capsules have been formulated using collagen hydrolysis from animal origin or cellulose [127-129].

3DP has enabled capsules to be produced with complex shapes and challenging dimensions, with curvatures, cavities, and intricacy at the hundreds of microns size (Fig. 6) [103, 130-133].

INSERT FIGURE 6

3D printed capsules offer flexibility, customization and cost-related benefits as shell components can be developed and extemporaneously assembled regardless the nature of the encapsulated formulation [26]. Using computer-aided design (CAD) software, Nober et al. designed a hermetic capsule closure system (Fig. 6C) [134]. The printable filaments made of Eudragit® L100-55, PEG400, and PLA were produced by a twin-screw extruder. The 3D printed enteric capsules met the European Pharmacopeia (EP) criteria for enteric products, regardless of thickness of the shell.

Shell thickness has shown to alter the release profile obtained from 3D printed capsules. Smith et al. used a 3DP approach to prepare PVA capsule shells, where shells were filled with either a solid or liquid vehicle containing the API (Fig. 6D) [131]. It was demonstrated that controlling the wall thickness allowed delaying the API release until the time point at which the target-site was reached. Interestingly, the induction time of API release was controlled from 12 to 198 minutes. Such a wide time interval is currently unattainable through commercially available technology. Varying the onset of API release allowed probing site-specific drug delivery in the gastrointestinal tract of beagle dogs. The analysis of pharmacokinetics of API release from these capsules indicated a direct *in vitro, in vivo* relationship (IVIVR).

Okwuosa et al. assessed the effect of shell thickness and polymer choice on the release profile obtained from 3D printed capsules (Fig. 6B) [132]. IR and SR profiles were achieved with the use of different polymers. Eudragit® EPO, yielded an IR profile with over 85% API (dipyridamole) released before 30 minutes. This could be attributed to the rapid ionization of the cationic chains of the methacrylate polymer at low pH and the high solubility of dipyridamole in gastric medium. On the other hand, extended release was obtained using shell system made of Eudragit® RL, an insoluble and permeable polymer, allowing for a reservoir-based controlled-release system. The effect of shell thickness on API release was also observed; the rate of API release decreased with increased shell thickness. This was mainly due to the prolonged diffusion pathway, extending time for API release. It is worth noting that controlling the thickness to such precision is a unique advantage of 3DP, where API release is simply altered through digital modifications without any change in formulation composition.

Tailored release patterns for multiple APIs in a single DF was achieved through compartmentalisation, avoiding interference between APIs [27]. Controlling API release was also achieved through digital exploitation of the shell thickness and the size of the rate limiting pores (Fig. 6A). A combined design approach allowed for achieving target API release profiles with variable orders and configurations. This digital programming could be implemented in dose individualisation to achieve multiple pharmacokinetic profiles.

Altering capsule geometry has been shown to be fully customizable method to alter behavioural properties, such as dosing, type and duration of API release [115]. A capsule was 3D printed consisting of three parts: two surface-eroding matrices (one with and one without the drug) and a coating. The versatile fabrication of 3D printed moulds of different shapes and sizes allowed for altering API release profiles from API-containing matrix [115].

4. Mechanism of drug release

Controlling API release from the DF is based on physicochemical and mathematical principles which can be modified to control the temporal and spatial release profile [135]. Several mechanisms were established to describe API release: diffusion, dissolution, erosion, etc. [136]. Mathematical models are important tools to evaluate the API release processes *in vivo* and *in vitro* [137]. API release can be predicted theoretically with measurement of physical parameters, the amount and type of API, polymer and adjuvants, as well as the size and shape of designed DF [138].

While 3DP advances in manufacturing DFs are still being studied, many mathematical models that were used to predict and describe desired drug release from conventional dosage forms may still apply. Table 2 provides a summary of the expected API release mechanisms with the mathematical models that can be used to predict and accordingly alter the API release for the different 3DP technologies. The future approach to using 3DP to produce controlled release DFs lies in the complete digitisation of the release profile. This could be achieved through mathematical modelling of the API

release first, followed by printing the corresponding DF with target release profile [27]. Fig. 7 provides a summary of different variables (3DP technology, material composition, infill pattern and percentage, CAD and multicolour 3DP) that contribute to in vitro drug release from 3D printed DFs.

INSERT TABLE 2

INSERT FIGURE 7

5. Opportunity with freedom of design and expanding surface area

3DP shows superiority over conventional methods with flexibility in terms of size, shape, and texture of the printed object. Digital modelling allows for a new level of freedom at the design stage. The shape of the 3D printed DFs is no longer dependent on size and shapes of the compressing tools (i.e. dies and punches) used in conventional tablet pressing. Producing such complex geometries *via* powder compaction have been exceptionally challenging and requires frequent change of tooling. The change in the shape, geometry and structure of 3D printed DFs directly influence the API release kinetics [13, 139-147]. One main predictor for *in vitro* API release from DFs is the SA/M ratio of the dosage form. Indeed, 3DP offers different means to alter the SA/M ratio and consequently yield different release patterns (Fig. 8).

INSERT FIGURE 8

The effect of DF geometry on API release was investigated in paracetamol-loaded (4% w/w) PVA 3D printed tablets [85]. As predicted, API release was mainly dependent on the SA/M ratio of the 3D printed DF. Indeed, the API release was slower with DF shapes in the following order: pyramid, torus, cube, sphere, or cylinder. Increasing the SA/M ratio facilitates water access to the surface of the DFs and API diffusion to the dissolution medium, improving the tablets dissolution profile [80, 81, 148]. The study, however, did not recognise that the shape of the DFs changes through erosion throughout the dissolution process.

The modification of the infill percentage in 3D printer setting is a simple digital approach to alter the SA/M ratios. To achieve different structures, the infill can be adjusted from 0% (shell with a hollow core) to 100% (fully solid). It is worth noting that the 3D printed structure often involves the use of one or more shell-layers (also known as outliner). This will not only affect the SA/M ratio but also the overall density of the 3D printed DF and the inlets for the penetration of dissolution medium [149]. Reducing infill percentage has been shown to accelerate API release from the printed DFs [24, 149-159]. In FDM 3D printed tablets, different infills (50% and 75%) yielded different release profile (32% and 26% API release after 8 hours, respectively) [73]. Similarly, in PVP IR pantoprazole tablets,

printed *via* FDM 3DP, an infill of 50% decreased the time for complete API release to 3 minutes, compared to approximately 10 minutes for 100% infilled tablets [49].

Several studies used innovative and unconventional design approaches that not only altered the SA/M ratio, but also changed the way tablets interact with the dissolution medium (Fig. 2). In order to accelerate API release, Sadia et al. used a design approach based on perforating channels in parallel or at a right angle to the caplet long axis [21]. The impact of this design was reflected on the *in vitro* dissolution; while block tablets showed slow release, channels of 0.8-1.0 mm allowed a significant increase in theophylline release (Fig. 2A2). Dissolution data showed that a channel size of ≥0.6mm was required to accelerate API release to such a level to meet pharmacopeia criteria for IR products.

3DP was also used to fabricate moulds to cast tablets with designed disintegration profiles. Ajmal et al. [160] designed four different moulds using CAD software. 3D printed PLA tablets were designed with break lines to control disintegration into a defined number of sections. The API release studies confirmed that tablets disintegrated according to design, where tablets with greater number of sections released the API at a faster rate than those with fewer sections.

One challenge of the dissolution of 3D printed designs, is the swelling of the polymeric structures, following aqueous medium uptake, that can lead to closure of the 'built-in' pores. To overcome this challenge, Isreb et al. printed oral theophylline DF with a 'radiator-like' design (Fig. 2E) [161]. The novel design architecture facilitated a 7-to-8-fold increase in SA/M ratio and facilitated API release, whilst preventing the formation of a thick permeation gel-layer, which would slow API release.

In addition to increasing the SA/M ratio, product design can also accelerate the disintegration of the printed DFs. Arafat et al. provided a unique design consisting of a caplet shape with built-in gaps [22]. The design contained nine repeating blocks that were interconnected using three bridges, allowing for eight gaps. Upon introduction to gastric medium, the 1 mm spaces caused the tablet to break into mini structures within 4 minutes, meeting the USP criteria for IR products (Fig. 2D). In the future, such design approaches could aid personalising release profiles without formulation modification [21-24, 161-175].

6. Challenges of controlling release from 3D printed structures

The current position of controlling release from 3D printed structures presents challenges that need to be addressed for the rapidly advancing technology to progress towards on-demand manufacturing. The challenges facing 3DP, the associated impact on API release profile, and recommendations and future trends have been summarised (Table 3). These challenges can be subdivided into technical and regulatory challenges.

6.1. Technical Challenges

The fact that 3DP technologies rely heavily on polymer is a major challenge facing controlling API release from 3D printed complex structures. Currently, limited polymers are both available and accepted for use in these technologies [45, 176]. Although several pharmaceutical grade polymers have been extensively evaluated for 3DP applications in recent years, further work is still required to extend the technology and allow the application to a broader range of APIs and clinical indications.

The reproducibility of the API release profile of 3D printed tablets is another challenge [177, 178]. The impact of the stability of the pharmaceutical ink used to 3D print DFs on API release profile is still unclear. Similarly, the stability of the final 3D printed structure throughout shelf-life and how this could affect the intended release profile is still to be assessed. Furthermore, the technologies involving a post-printing drying process require a thorough assessment to ensure that drying time does not alter the properties of the DF, including API release profiles.

There is currently limited literature describing the stability of the printed products as well as pre-products [179]. Moreover, whilst 3D printers can produce structures of granular details, the resolution for printing medicines is relatively low [63, 180]. Currently, 3D printers are not optimised for pharmaceutical grade materials. To achieve a precise DF design with smooth finishing, high-resolution equipment needs to be developed. This needs to be balanced with overall efficiency and production time-per-unit. As it stands, the technology requires development to include pharmaceutically acceptable materials to allow printing at a greater resolution, and therefore tighter control of the API release profile.

6.2. Regulatory challenges

Although 3DP is developing rapidly from a pharmaceutical perspective, essential quality challenges associated with manufacture and regulation remain. The realisation of new opportunities with controlling the release profiles of 3D printed DFs can only be achieved through satisfying the compendial and regulatory standards. Due to the large number of factors affecting the quality of computationally designed DFs and the safety of their use, the appropriate regulatory requirements are yet to be clarified. Currently, there are no standardised regulations concerning the design, manufacturing process and quality testing considerations for 3D printed DFs.

While conventional DFs rely on providing sufficient QC of the end product, applying such approach for 3D printed products in small batches and on demand manufacturing scenarios is impractical [181-184]. This will both slow down and increase the cost of batch release. Therefore, a shift towards quality assurance (QA) for the produced batch is anticipated, whereby QA of the processes involved in 3DP is the foundation of assurance of the quality and safety of the final product(s). Such approach could be borrowed from biological products of short shelf-life, where real time release is adopted [185].

Several technical variables might have major impact on the variability of API release from 3D printed structures. These include variable layer thickness, inaccurate positioning during printing, 3D printer head clogging, inconsistent binding between layers, and the friability of final tablets. Quality defects commonly associated with 3DP include banding (ripples on a products side caused by the vibration in the x-y plane during printing), leaning (drift in the x-y plane), warping (distortion caused by thermal expansion), delamination (caused by missing binder solution layers) and collapse (where tablet porosity is lost) [186]. These defects may not only impact the DFs uniformity and aesthetics, but also can negatively affect the reproducibility of API release.

With an increased number of stakeholders, and familiarity of technologies in the pharmaceutical field, it is expected that the quality concerns and regulatory ambiguity about 3D printed DFs will be clearer in the future.

7. Future trends

Introducing the production of 3D printed controlled release DFs into clinical practice could pave the way for a revolution in personalised medicine. This will allow for individualised and programmable drug delivery. It is clear that this field is still in its infancy and several adaptations and advancements are yet required to translate the power of this technology into real-world benefits.

To overcome the regulatory limitations discussed in Section 6.2., clearer guidelines for 3D printed DFs are required. Regarding QC, measurements to ensure 3DP procedure aligns with principles enforced by regulatory bodies and means to manage and minimise the associated risks are yet to be fully established. Following the introduction of HME technology in the pharmaceutical fields, several pharmaceutical grade polymers that are specially developed for HME were introduced to market. Similarly, the number of approved of 3DP-grade versions of pharmaceutical grade polymers suitable for 3DP is now likely to grow. In fact, medical grade PLGA-based filaments for FDM 3D printing have already been released [187].

In parallel, materials capable of allowing higher printing resolution are required to enable greater control over the DF release profile. It is anticipated that *in silico* simulation will play a greater role in the field, allowing for the release profile to be predicted through material modelling and computer simulation. To date, there has been limited *in silico* 3DP for pharmaceutical applications, generally involving a certain aspect of the printing process [188-196]. Digitising the entire process, however, will reduce the likelihood of batch-to-batch variation, and hence allow for increased reproducibility of 3D printed DFs. In the ideal world, producing controlled release DFs *via* 3DP will reach a position where optimised release profile can initially be dialled, followed by designing and 3DP of DFs, leaving room for infinite geometries.

Such *in silico* simulation has been carried out by Novák et al. [197] who used virtual prototyping and parametric design to solve the issue regarding designing the tablet geometry and its internal structure resulting in a specified release profile [153]. Basic structural motifs were combined providing a close release profile estimation by linear combination of the pre-calculated release profiles

digitally. Similarly, Fina et al. prepared zero-order release formulations *via* FDM 3DP, showing that simple design modifications with a prolonged release core surrounding an insoluble shell to allow the 3D printing of SR formulations with tuneable zero-order release kinetics [153]. With improved resolution of future 3D printers, it is expected that the importance of such design strategies will grow.

INSERT TABLE 3

8. Conclusion

The past decade has witnessed an accelerated interest in pharmaceutical 3DP, particularly for use as personalised DFs, with well-defined release-controlled profiles. It is of great interest to understand and predict API release from these novel 3D printed structures. This will allow for programmable and personalised medicine to evolve, enabling the minimisation of side effects associated with the standardised doses usually produced by conventional manufacturing approaches.

Several 3DP technologies have produced different structures that consequently have resulted in different release profiles. API release was dependent on the choice of materials, designed geometry, infill percentage, SA/M ratio and other process-specific parameters. Currently, the use of these technologies still faces technical and regulatory challenges including shortage of compatible materials, low resolution, and the lack of information on the reproducibility and stability of pre- and final products. As QC of API release of the end product is still a major challenge for on-demand 3DP manufacturing, adopting a QA approach for real time batch release could be a solution. The availability of a wider range of compatible materials, better understanding of quality challenges and improved resolution of the next generations of 3D printers are likely to fully realise the potential of engineering and personalising drug release from 3D printed DFs.

List of Figures

Fig. 1. Cross-sections of dosage forms produced by different 3D printing (3DP) technologies. A) Fused deposition Modelling [8], B) Selective Laser Sintering *[40]*, C) Semi-Solid Extrusion [12], D) Wax Jetting [13], E) Material Jetting [14], F) Stereolithography [163] and G) Conventional tablets [198] made by tablet pressing. Apart from Figure 1-D which was obtained using a µCT, all images were captured using a scanning electron microscope.

Fig. 2. Visualisation of how adjusting the design shape of the dosage form can affect the release profiles. A1) Sadia et al. [21] channelled tablet approach to aid faster release showing the effect of channel size on dissolution profile, B1) Fanous et al. [23] IR dosage forms with bespoke complex internal geometries, C1) Donut shaped tablets yielding immediate release profiles with different infill patterns and the observed effect on drug release shown by Wang et al. [24], D1) Arafat et al. [189] Gaplet design to accelerate disintegration, with effect of spacing shown and E1) Isreb et als novel radiator-like design [151]. A2, B2, C2, D2, and E2) In vitro release of the APIs from these structures in dissolution test

Fig. 3. Visual representation of methods employed to achieve delayed release (DR) profiles – with images of their structure and the release profile obtained as a function of pH. A1) FDM 3D printed tablet from enteric polymers by single filament [59], B1) shell-core delayed release tablet *via* FDM 3DP [61], C1) Dual extrusion printed acid- and thermo-labile pantoprazole tablets [62] and D1) Enteric coated colon-specific drug delivery produced *via* FDM and injection volume filling [63]. A2, B2, C2 and D2) In vitro release of the APIs from these structures in pH-change dissolution test.

Fig 4. Examples of extended- release profiles from 3D printed dosage forms. A) Skowyra et al. fabrication of ER patient-tailored prednisolone tablets *via* FDM 3DP [75], B) Pietrzak et al. flexible-dose dispenser ER 3D printed tablets [76], C) Cheng et al. 3D printed ET tablets using hydroxypropyl methylcellulose hydrogels [78], D) Zhang et al. 3DP coupled with Hot-melt extrusion enhanced ER profiles.

Fig. 5. Examples of pulsatile release profiles from 3D printed dosage forms. A1) Maroni et al. multi-compartment capsular device for two-pulse oral delivery [26], B1) Melocchi et al. lego-inspired capsular device [105], C1) Pereira et al. multicompartmental cardiovascular polypill capsule with four model drugs for bespoke drug release [27], D1) Sun et al. approach to obtain fully customizable release profiles for personalised medicine [7], E1) Patent zero-order drug release profile and F1) Goyanes et al. tunable zero-order release 3D printed tablets [143]. A2, B2, C2, D2, E2 and F2) In vitro release of the APIs from these structures in dissolution test.

Fig 6. Visual representation of different examples of 3D printed capsules: A) Okwuosa et al. liquid capsule of different core volumes with Eudragit® EPO coating for immediate release [122] , B) Smith et al. PVA capsule shells of different wall thickness to delay API release [121], C) Nober et al. hermetic closure system of different polymers to obtain delayed release capsules [124] , D) Pereira et al. multicompartmental cardiovascular polypill capsule with four model drugs for bespoke drug release [27].

Fig. 7. A concept map that summarises the main exploitations to achieve different API release profiles (immediate, delayed, sustained, controlled, or pulsatile release) from 3D printed dosage forms.

Fig. 8. Different methods to design and optimise drug release patterns from 3D printed dosage forms: A) Manipulating the external structure using novel innovative design approaches such as the Gaplet [22], channel [21] and radiator-like [151] designs, B) Manipulating the internal structure using different infill patterns and percentages, C) Manipulating the size and structure of the dosage form.

Table 1. Summary of the different 3DP technologies: formation mechanism, composition, nature and resolution of form DF.

3D printing technology	Typical Matrix Composition	Concept	Nature of Matrix formed	Typical Resolution	References
Fused Deposition Modelling (FDM)	Active pharmaceutical ingredient (API), polymer, filler, lubricant and stabilizer.	Polymer-rich filament is melt-extruded through a hot nozzle in a controlled layer-by-layer manner.	Polymer-rich structure (~50%) of relatively high glass transition temperature (Tg) polymer species.	80-200µm [199]	[9, 50, 80, 156, 200]
Selective Laser Sintering (SLS)	API, thermoplastic polymer (powder form), light absorbing agent (salt, metal, or lake dye), and a filler (optional).	Powder-based technology – laser fuses thermoplastic polymer resin, drawing layer-b-layer a specific pre-configured pattern on the surface of a powder bed.	Loosely packed powder bed yields significant voids following particle fusion. Highly porous, void-filled matrix.	20-150µm, depending on particle size [201]	[10, 40, 202]
Semi-Solid Extrusion (SSE)	API, polymer/matrix, filler, evaporable or non-evaporable solvent (optional), plasticiser/solvent and a lubricant (optional).	Rotating screw gear or pressurised air extrudes semi-solids (e.g. homogenous paste) through a nozzle over moveable stage in a layer-by-layer fashion.	Dense and rigid matrix. Depends on solvent nature: evaporable - dense matrix forms; non-evaporable - solid, rigid structure forms.	100-500µm, depending on size of the nozzle tip [203]	[4, 12, 25, 117, 204]
Binder Jet/Powder Based (PB)	API, carrier fluids, binder, surface tension and viscosity modifiers.	The ink (binder(s) and/or API(s) binder solution) sprayed over a powder bed in a layer-by-layer fashion until 3D DF is printed.	Void-filled, porous printed matrix forms.	~100µm [205]	[37, 206, 207]
Stereolithography (SLA)	API, oligomer, liquid polymer, photo-initiator.	Curing of a photosensitive oligomer-based resin by scanning a focused ultraviolet laser in a layer-by-layer fashion.	Dense, void-less, polymer rich, cross-linked structure. Hydrogel forms for aqueous polymer solutions.	16-100µm [208]	[15, 60, 126]

Table 2. A summary of the predicted/ typical release profile and mechanism from DF produced by the different 3DP technologies, and the challenges presenting utilising these technologies.

Technology	Material Composition/ Substrates	Predicted/ Typical Release mechanism	Applicable mathematical models and factors affecting drug release	Challenges
Fused Deposition Modelling (FDM)	Soluble polymer based	Matrix erosion: API is dispersed within a polymeric matrix. API release is controlled by the polymer intrinsic properties. In dissolution medium, polymer surface erosion leads to API release, mainly governed by the kinetic of degradation [135].	Higuchi's model [209] (water soluble and low soluble APIs) Hopfenbergs model (surface-erosion) [210]. API release controlled by polymer properties, e.g. composition, molecular mass, matrix thickness.	• Difficulty to achieve immediate release [52, 57]. • Limited number of polymers available to produce compatible filaments [50, 80].
	Insoluble polymer based, e.g. ethyl acetate and Eudragit® RL + RS	Diffusion-based: API molecules diffuse through the pores of the polymeric matrix. Release rate decreases as a function of time as API in the central domains travels a longer diffusion path [211].	Korsmeyer-Peppas [71] (if mechanism is unknown or more than one involved). Other mechanisms: Fickian Zero-order model and Non-Fickian models, e.g. first-order release, Hixon and Cromwell [212] were suggested (when release is dependent on particle surface area).	• Limited loading capacity (≤50%) [62, 156]. • Limited number of polymers available to produce compatible filaments [45].

Selective Laser Sintering (SLS)	Polymer-based	Erosion and dissolution: API released by the polymeric erosion providing controlled release. API release governed by thickness and dissolution rate of polymer.	Noyes-Whitney relationship [213]. Factors such as penetration rate of the dissolution medium into the matrix, degree of porosity, wettability of system and surface topography of particles control the rate of API release [214].	• Limited to polymer of certain glass transition temperature [40, 51]. • Requires API compatibility with photoabsorbent material
Semi-Solid Extrusion (SSE)	Soluble polymer matrix	Erosion and diffusion based: Upon contact with the dissolution medium the polymer surface erodes, and the active agent is released by diffusion.	Higuchi [209] (water soluble and low soluble drugs incorporated into semi-solid and/or solid matrices). Fickian Zero-order model and Non-Fickian models, e.g. first-order release, Hixon and Cromwell [212].	• Residual solvent can affect release profile. • Requires disintegrant at a much higher percentage than conventionally required which can impact the obtained release profile.
	Insoluble polymer matrix	Diffusion based: API molecules diffuse through the pores of insoluble polymeric matrix.	Fickian zero-order, non-Fickian models, e.g. first-order release - Hixon and Cromwell [212].	• Residual solvent/drying can affect the obtained release profile
Binder /Material Jetting (BJ/MJ)	Wax based jetting	Dissolution and diffusion: API diffuses out the matrix, with the process moving towards the interior. Release rate can be altered by increasing the amount of API or the wax concentration, and/or incorporation of hydrophilic polymer [215].	API release related to the square root of time accounting for the volume and length of the openings of the porous matrix. The release of drug from a homogenous matrix system can be controlled by varying the initial concentration of drug matrix porosity and tortuosity, the type and solubility of polymer-forming the matrix.	• Compatible materials are wax based that may hinder drug release [216].

	Powder-based jetting	Disintegration and dissolution: powder-based jetting produces porous, void-filled structures with inter-particulate spaces. Upon contact with dissolution medium, water penetrates the matrix resulting in rapid disintegration and IR.	Mathematical model applicable shows correlation between API release and the square root of time which accounts for the volume and lengths of openings in the porous matrix.	• Reproducibility of drug release from dosage forms depends on drying.
Stereolithography (SLA)	Liquid polymer	Swelling and diffusion: drug diffusion through the hydrogel swollen matrix. On contact with water the hydrogel matrix swells, the cross-linked network loosens, and API is released in a controlled manner. API release depends on the swelling rate and extent of the hydrogel.	API diffusivity in hydrogels [217] can be modelled using Lusting and Peppas' relationship (drug diffusivity and hydrogel network structure) [218] and Korsmeyer and Peppas' correlation [219] (moving boundary phenomena with hydrogel swelling). Decreasing cross-linkable polymers and/or increasing non-cross linkable components and water in the initial resin can modulate the hydrogel characteristics such as water uptake, pore size and therefore release profile [220].	• Hydrogels shrink and thus can change the observed release profile [15, 59]. • Regulatory concerns for using photo initiators. • Compatibility is required between API and initiator. • Slow drug release makes its more suitable for implant rather than oral dosage forms [15, 221].

Table 3. A summary of challenges, future trends and potential and opportunity of 3DP for producing controlled-release DF.

3DP challenges	Impact of challenge on release profile	Future trends	Opportunity upon overcoming limitation	References
Limited number of compatible, commercially available approved polymers.	Limited range of 3D printed DF.	Testing a wider range of existing polymers for their use in 3DP technologies. Development of new grades of approved pharmaceutical excipients specially optimised for 3DP.	Achievement of reproducible release patterns, especially for immediate release. Shortened development time and approval.	[45, 176]
Requiring high concentration of polymer.	Release profile heavily impacted by the high concentration of polymers required in the 3DP technologies, producing a low drug loading.	Development of new polymers with behavioural characteristics that suit the wide range of release kinetics or that can be used in lower concentrations.	Agility at controlling the release profile without having to factor in the polymer concentration.	[222, 223]
Limited knowledge on stability of pre-product (pharmaceutical ink) and final product of 3DP.	The stability of pre-product (filaments, inkjets, substrates and cartridges) is to be established.	Better understanding of the stability of initial and final products and the link to process parameters and selected materials.	Stable pre-product will generate a reproducible drug release. Ideally, paired with *in silico* simulation for prediction and pre-design of release profile as desired.	[181, 224]
Release profile reproducibility.	Reproducibility of drug release is not established.	Better understanding of the variability of initial and final product and its link to process parameters and selected materials.	Dialling the release profile as desired would open the door for an infinite number of geometries and freedom of design for the production team.	[177, 178]
Low resolution of 3D printed dosage forms	Currently 3D printers are designed for larger objects than solid DF.	The technology and materials need development to allow 3DP at greater resolution.	High resolution 3D printed dosage form with better aesthetics. New opportunities for drug release controlled by design and multiple drug release starting from the same materials.	[63, 180]
Quality control (QC) and quality assurance (QA)	No clear regulatory route for QC and QA specific for the release of 3D printed dosage forms. QC for end-product involves time-consuming *in vitro* dissolution test.	Better understanding of quality challenges affecting drug release. QA means replacing QC of end product. Fast QC means for dissolution testing.	Rapid release of small batch production.	[181-184]

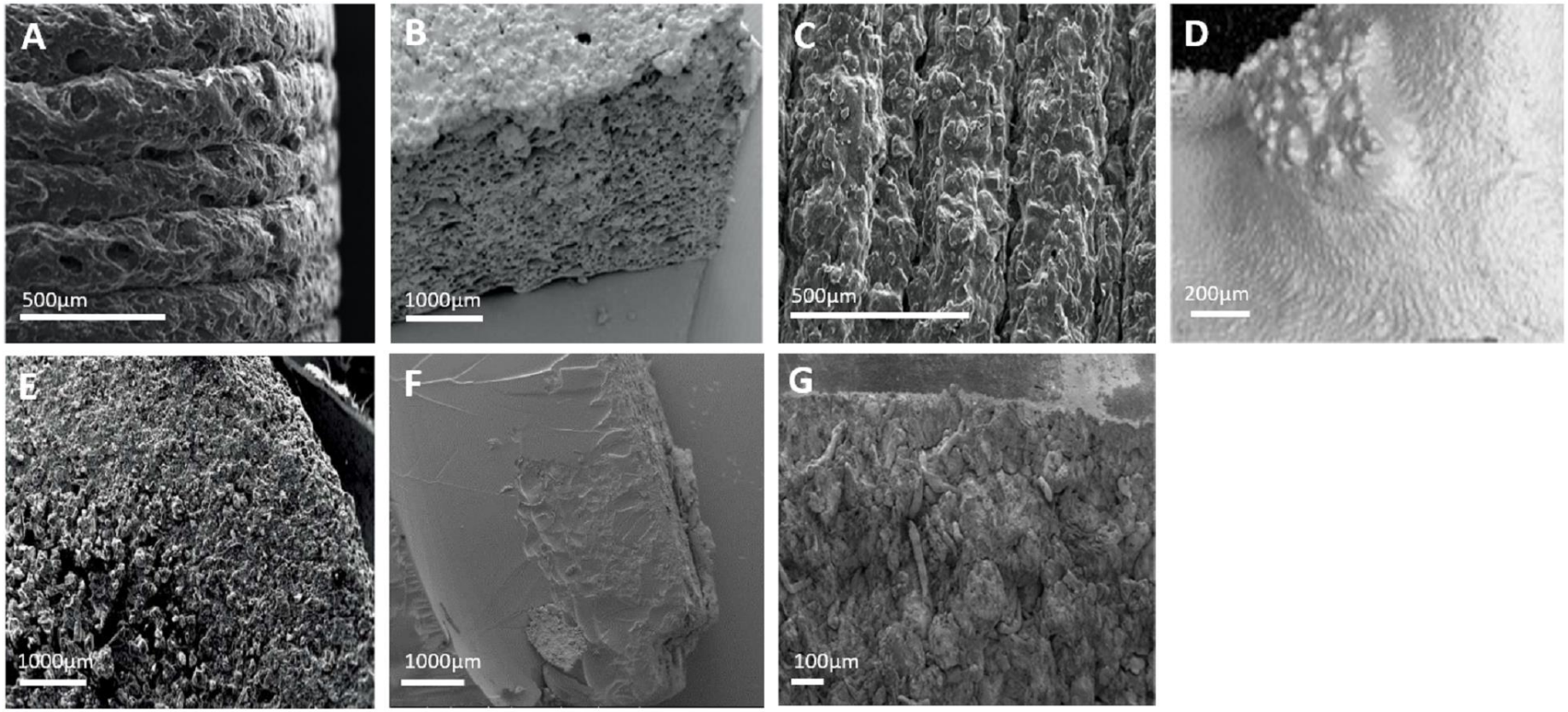

Fig. 2. Cross-sections of dosage forms produced by different 3D printing (3DP) technologies. A) Fused deposition Modelling [8], B) Selective Laser Sintering *[40]*, C) Semi-Solid Extrusion [12], D) Wax Jetting [13], E) Material Jetting [14], F) Stereolithography [163] and G) Conventional tablets [198] made by tablet pressing. Apart from Fig. 1-D which was obtained using a µCT, all images were captured using a scanning electron microscope.

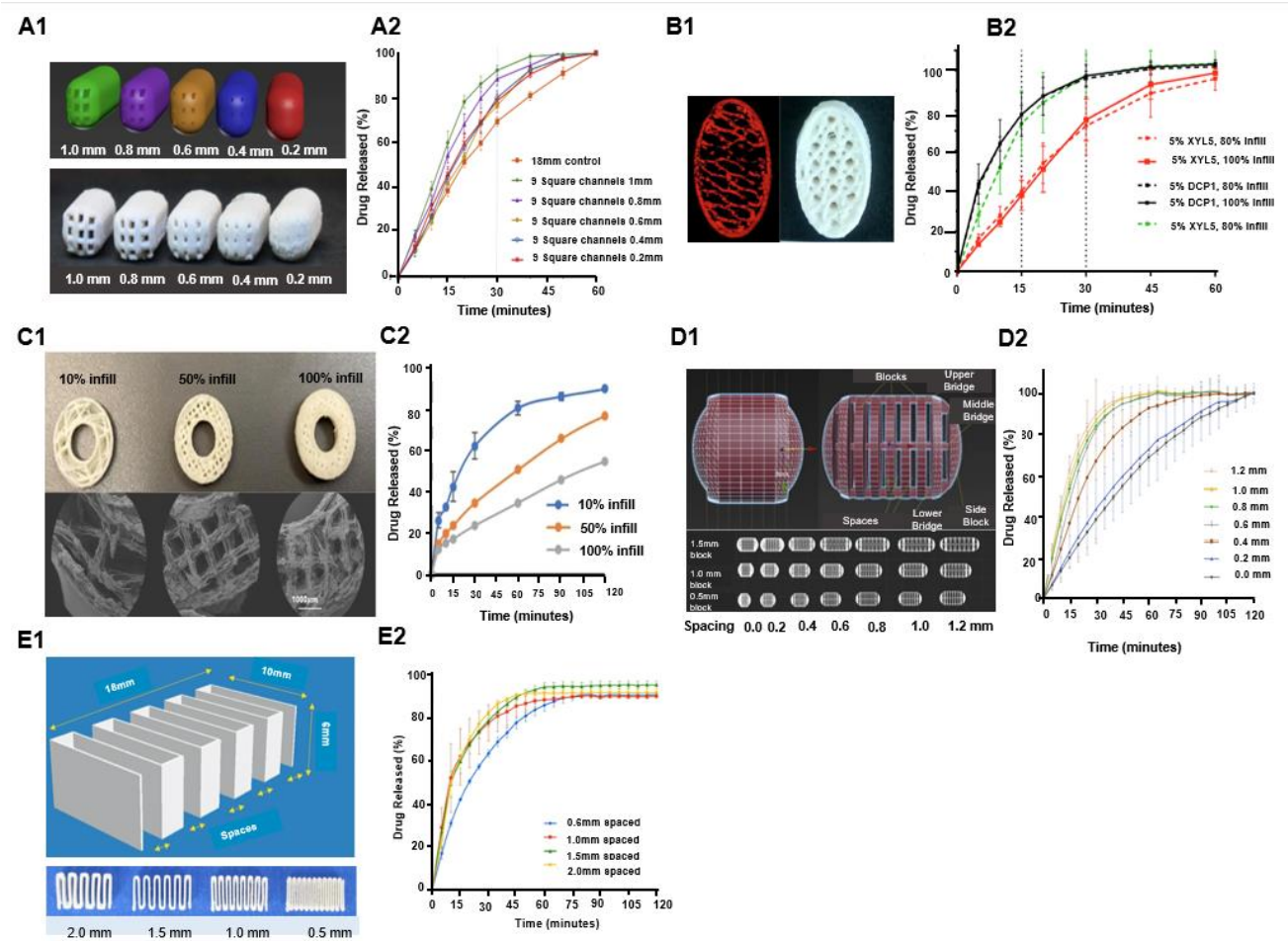

Fig. 2. Visualisation of how adjusting the design shape of the dosage form can affect the release profiles. A1) Sadia et al. [21] channelled tablet approach to aid faster release showing the effect of channel size on dissolution profile, B1) Fanous et al. [23] IR dosage forms with bespoke complex internal geometries, C1) Donut shaped tablets yielding immediate release profiles with different infill patterns and the observed effect on drug release shown by Wang et al. [24], D1) Arafat et al. [189] Gaplet design to accelerate disintegration, with effect of spacing shown and E1) Isreb et als novel radiator-like design [151]. A2, B2, C2, D2, and E2) In vitro release of the APIs from these structures in dissolution test

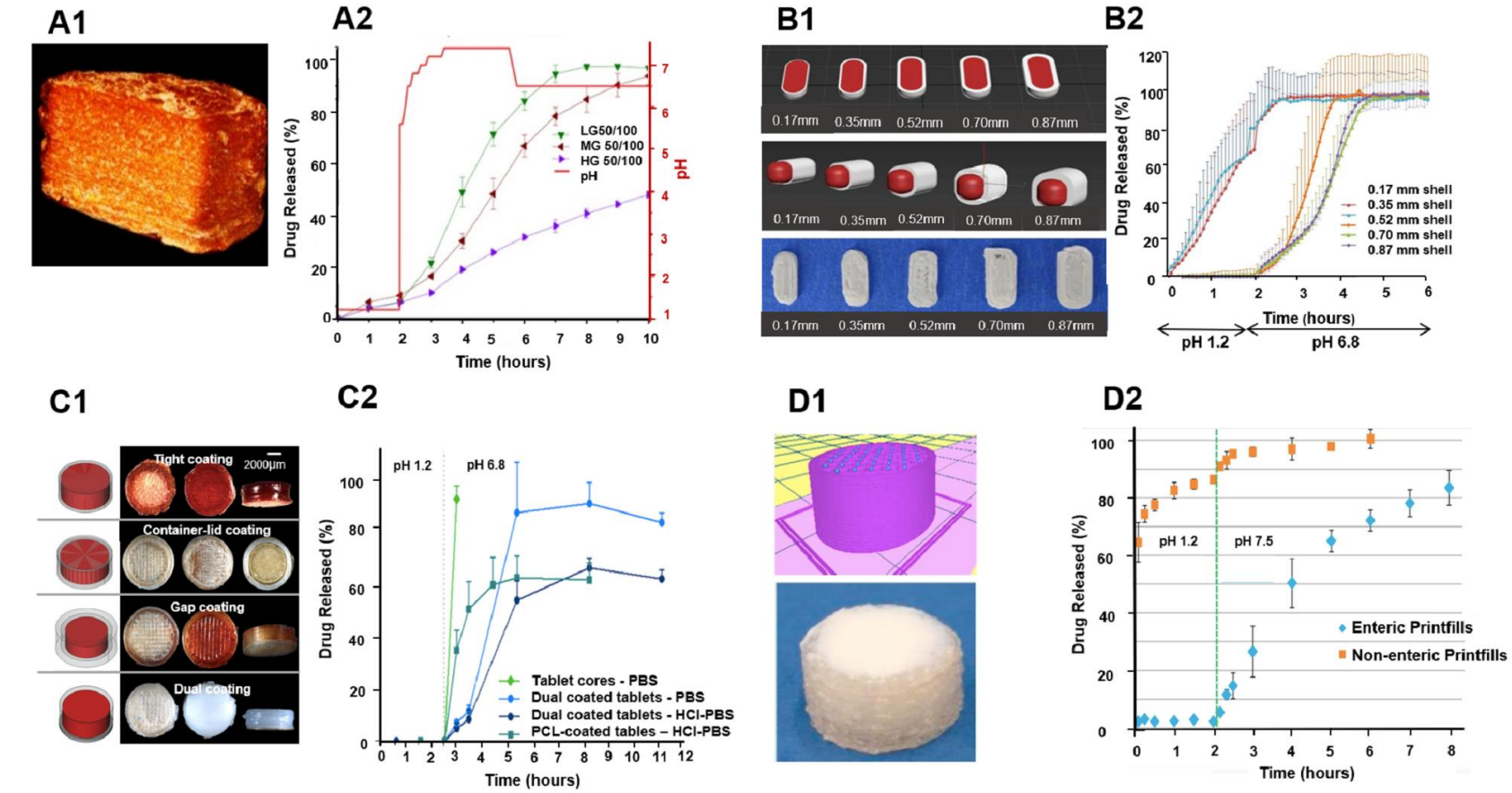

Fig. 3. Visual representation of methods employed to achieve delayed release (DR) profiles – with images of their structure and the release profile obtained as a function of pH. A1) FDM 3D printed tablet from enteric polymers by single filament [59], B1) shell-core delayed release tablet *via* FDM 3DP [61], C1) Dual extrusion printed acid- and thermo-labile pantoprazole tablets [62] and D1) Enteric coated colon-specific drug delivery produced *via* FDM and injection volume filling [63]. A2, B2, C2 and D2) In vitro release of the APIs from these structures in pH-change dissolution test.

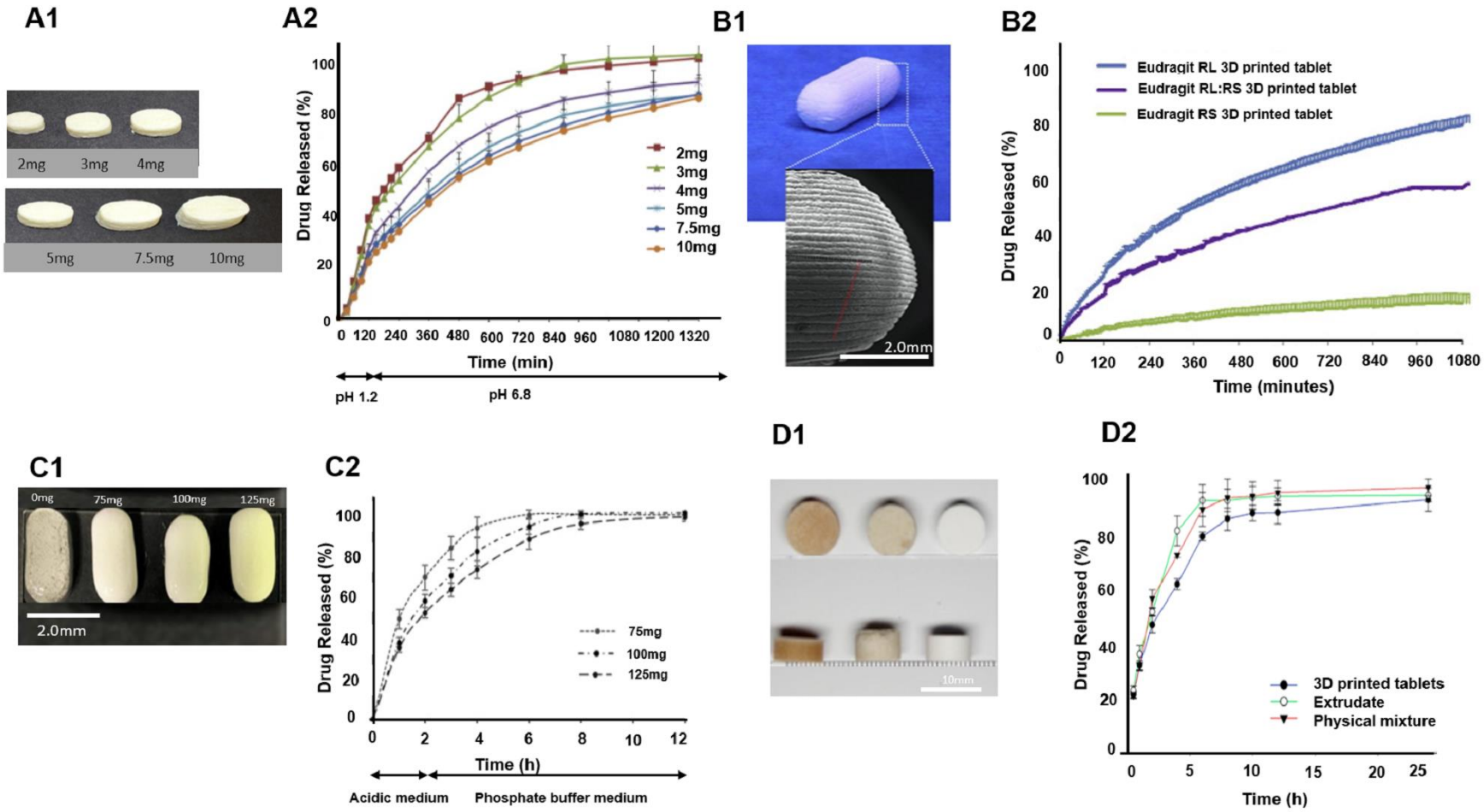

Fig 4. Examples of extended- release profiles from 3D printed dosage forms. A) Skowyra et al. fabrication of ER patient-tailored prednisolone tablets *via* FDM 3DP [75], B) Pietrzak et al. flexible-dose dispenser ER 3D printed tablets [76], C) Cheng et al. 3D printed ET tablets using hydroxypropyl methylcellulose hydrogels [78], D) Zhang et al. 3DP coupled with Hot-melt extrusion enhanced ER profiles.

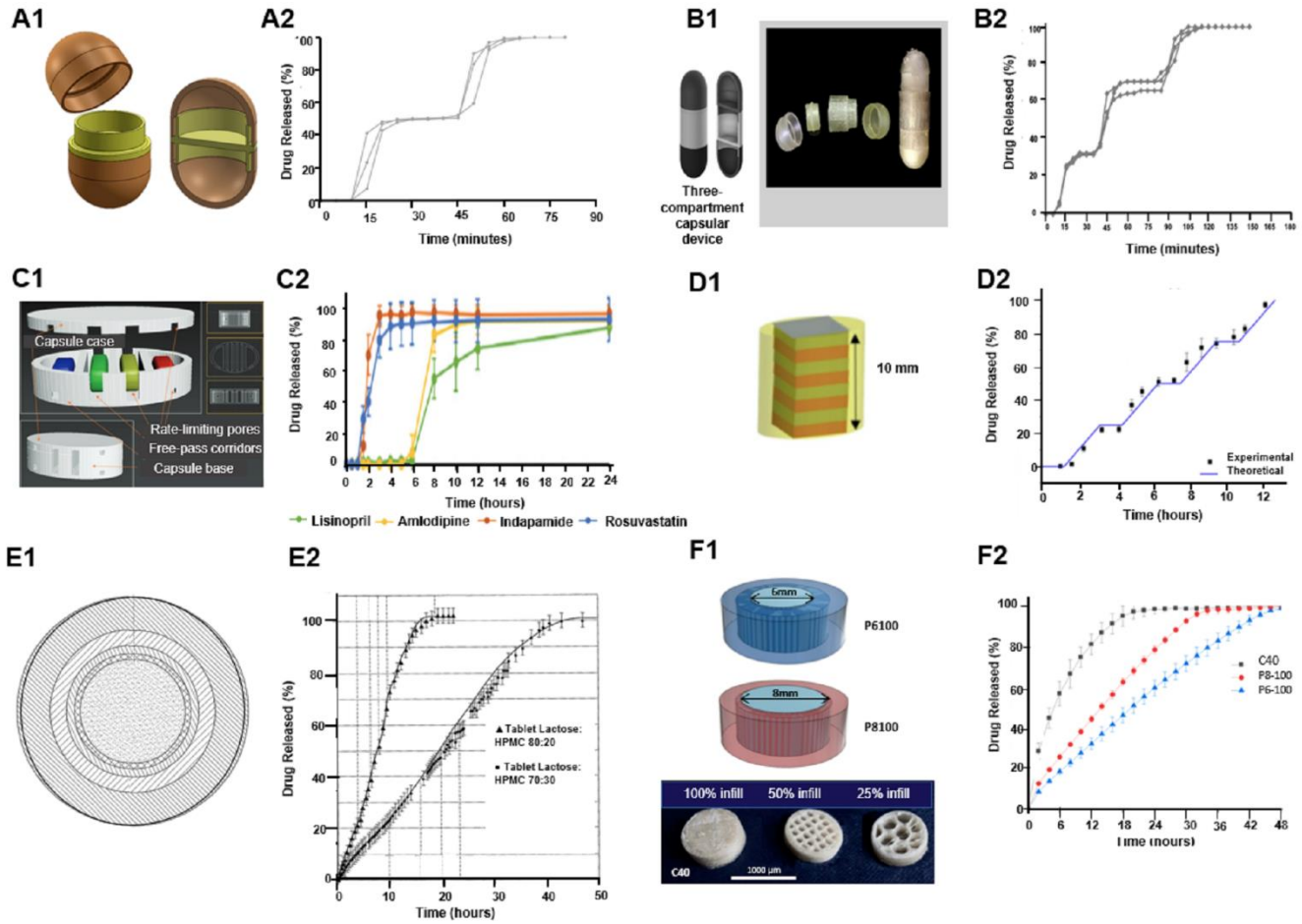

Fig. 5. Examples of pulsatile release profiles from 3D printed dosage forms. A1) Maroni et al. multi-compartment capsular device for two-pulse oral delivery [26], B1) Melocchi et al. lego-inspired capsular device [105], C1) Pereira et al. multicompartmental cardiovascular polypill capsule with four model drugs for bespoke drug release [27], D1) Sun et al. approach to obtain fully customizable release profiles for personalised medicine [7], E1) Patent zero-order drug release profile and F1) Goyanes et al. tunable zero-order release 3D printed tablets [143]. A2, B2, C2, D2, E2 and F2) In vitro release of the APIs from these structures in dissolution test.

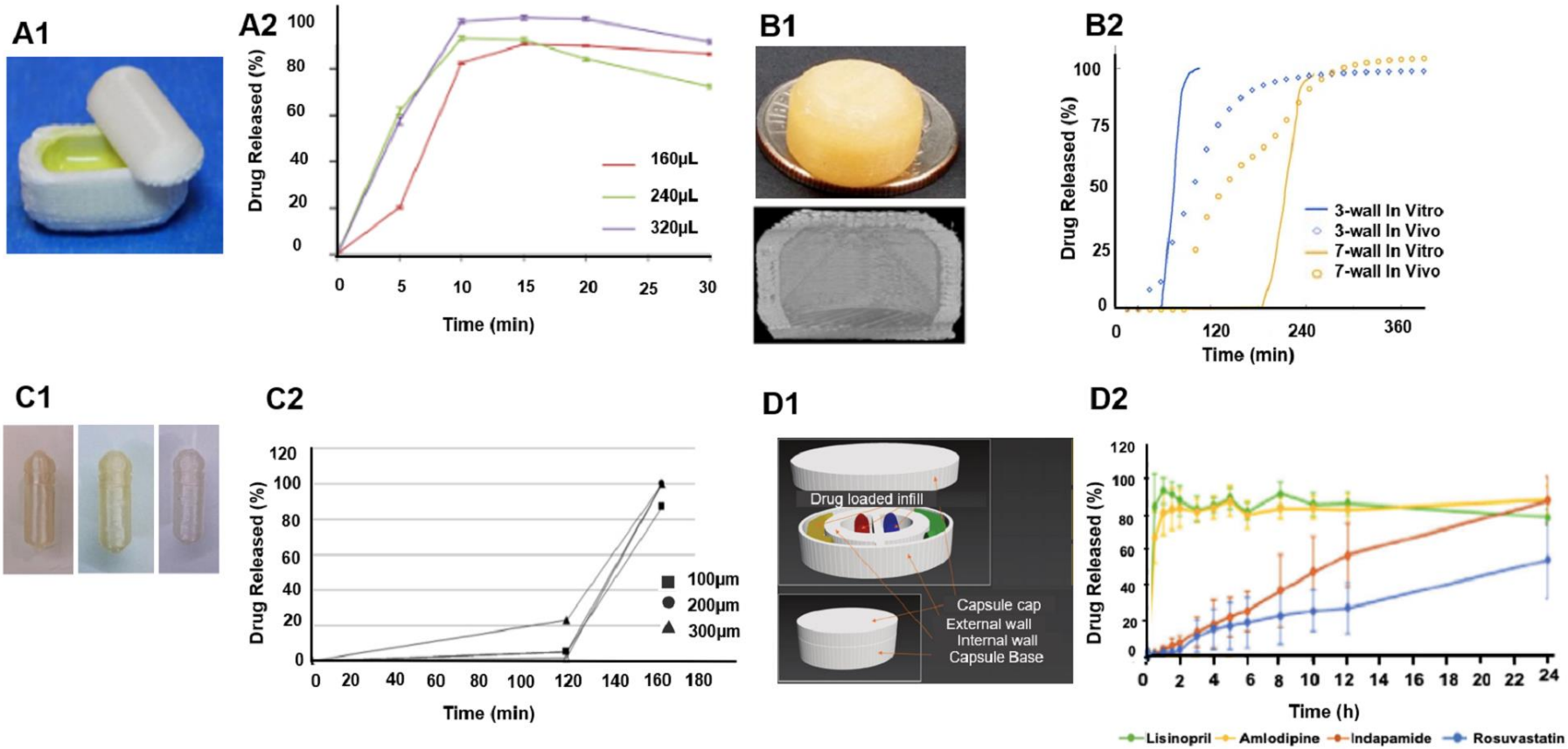

Fig 6. Visual representation of different examples of 3D printed capsules: A) Okwuosa et al. liquid capsule of different core volumes with Eudragit® EPO coating for immediate release [122] , B) Smith et al. PVA capsule shells of different wall thickness to delay API release [121], C) Nober et al. hermetic closure system of different polymers to obtain delayed release capsules [124] , D) Pereira et al. multicompartmental cardiovascular polypill capsule with four model drugs for bespoke drug release [27].

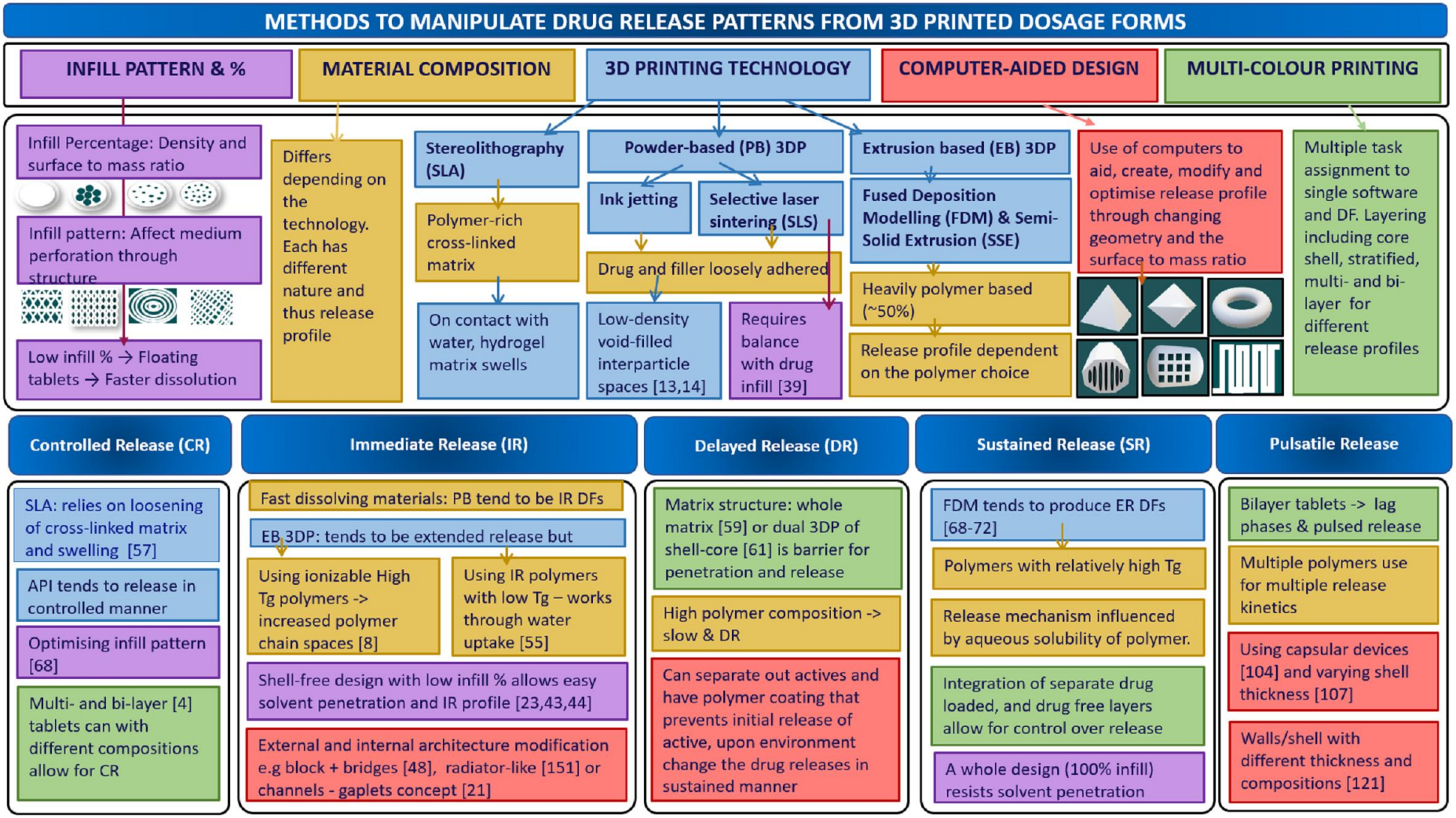

Fig. 7. A concept map that summarises the main exploitations to achieve different API release profiles (immediate, delayed, sustained, controlled, or pulsatile release) from 3D printed dosage forms.

Fig. 8. Different methods to design and optimise drug release patterns from 3D printed dosage forms: A) Manipulating the external structure using novel innovative design approaches such as the Gaplet [22], channel [21] and radiator-like [151] designs, B) Manipulating the internal structure using different infill patterns and percentages, C) Manipulating the size and structure of the dosage form.

.

References:

[1] S.L. Chan, X. Ang, L.L. Sani, H.Y. Ng, M.D. Winther, J.J. Liu, L.R. Brunham, A. Chan, Prevalence and characteristics of adverse drug reactions at admission to hospital: a prospective observational study, Br J Clin Pharmacol, 82 (2016) 1636-1646.

[2] J.C. Veeren, M. Weiss, Trends in emergency hospital admissions in England due to adverse drug reactions: 2008–2015, Journal of Pharmaceutical Health Services Research, 8 (2017) 5-11.

[3] J.U. Adams, Pharmacogenomics and personalized medicine, Nature Education, 1 (2008) 194.

[4] S.A. Khaled, J.C. Burley, M.R. Alexander, C.J. Roberts, Desktop 3D printing of controlled release pharmaceutical bilayer tablets, International journal of pharmaceutics, 461 (2014) 105-111.

[5] M. Pandey, H. Choudhury, J.L.C. Fern, A.T.K. Kee, J. Kou, J.L.J. Jing, H.C. Her, H.S. Yong, H.C. Ming, S.K. Bhattamisra, B. Gorain, 3D printing for oral drug delivery: a new tool to customize drug delivery, Drug Delivery and Translational Research, 10 (2020) 986-1001.

[6] M.S. Algahtani, A.A. Mohammed, J. Ahmad, E. Saleh, Development of a 3D Printed Coating Shell to Control the Drug Release of Encapsulated Immediate-Release Tablets, Polymers (Basel), 12 (2020).

[7] Y. Sun, S. Soh, Printing Tablets with Fully Customizable Release Profiles for Personalized Medicine, Adv Mater, 27 (2015) 7847-7853.

[8] M. Sadia, A. Sosnicka, B. Arafat, A. Isreb, W. Ahmed, A. Kelarakis, M.A. Alhnan, Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets, Int J Pharm, 513 (2016) 659-668.

[9] G. Kollamaram, D.M. Croker, G.M. Walker, A. Goyanes, A.W. Basit, S. Gaisford, Low temperature fused deposition modeling (FDM) 3D printing of thermolabile drugs, Int J Pharm, 545 (2018) 144-152.

[10] F. Fina, C.M. Madla, A. Goyanes, J. Zhang, S. Gaisford, A.W. Basit, Fabricating 3D printed orally disintegrating printlets using selective laser sintering, Int J Pharm, 541 (2018) 101-107.

[11] N. Allahham, F. Fina, C. Marcuta, L. Kraschew, W. Mohr, S. Gaisford, A.W. Basit, A. Goyanes, Selective Laser Sintering 3D Printing of Orally Disintegrating Printlets Containing Ondansetron, Pharmaceutics, 12 (2020).

[12] M.S. Cui, H. Pan, D.Y. Fang, S. Qiao, S. Wang, W.S. Pan, Fabrication of high drug loading levetiracetam tablets using semi-solid extrusion 3D printing, Journal of Drug Delivery Science and Technology, 57 (2020).

[13] E.A. Clark, M.R. Alexander, D.J. Irvine, C.J. Roberts, M.J. Wallace, J. Yoo, R.D. Wildman, Making tablets for delivery of poorly soluble drugs using photoinitiated 3D inkjet printing, International Journal of Pharmaceutics, 578 (2020).

[14] D.G. Yu, C. Branford-White, Y.C. Yang, L.M. Zhu, E.W. Welbeck, X.L. Yang, A novel fast disintegrating tablet fabricated by three-dimensional printing, Drug Dev Ind Pharm, 35 (2009) 1530-1536.

[15] J. Wang, A. Goyanes, S. Gaisford, A.W. Basit, Stereolithographic (SLA) 3D printing of oral modified-release dosage forms, Int J Pharm, 503 (2016) 207-212.

[16] A.V. Healy, E. Fuenmayor, P. Doran, L.M. Geever, C.L. Higginbotham, J.G. Lyons, Additive Manufacturing of Personalized Pharmaceutical Dosage Forms via Stereolithography, Pharmaceutics, 11 (2019).

[17] K. Shi, D.K. Tan, A. Nokhodchi, M. Maniruzzaman, Drop-On-Powder 3D Printing of Tablets with an Anti-Cancer Drug, 5-Fluorouracil, Pharmaceutics, 11 (2019).

[18] S.A. Khaled, M.R. Alexander, R.D. Wildman, M.J. Wallace, S. Sharpe, J. Yoo, C.J. Roberts, 3D extrusion printing of high drug loading immediate release paracetamol tablets, Int J Pharm, 538 (2018) 223-230.
[19] P. Li, H. Jia, S. Zhang, Y. Yang, H. Sun, H. Wang, W. Pan, F. Yin, X. Yang, Thermal Extrusion 3D Printing for the Fabrication of Puerarin Immediate-Release Tablets, AAPS PharmSciTech, 21 (2019) 20.
[20] F. Dores, M. Kuzminska, C. Soares, M. Bohus, A.S. L, R. Habashy, B.C. Pereira, M. Peak, A. Isreb, M.A. Alhnan, Temperature and solvent facilitated extrusion based 3D printing for pharmaceuticals, Eur J Pharm Sci, 152 (2020) 105430.
[21] M. Sadia, B. Arafat, W. Ahmed, R.T. Forbes, M.A. Alhnan, Channelled tablets: An innovative approach to accelerating drug release from 3D printed tablets, Journal of Controlled Release, 269 (2018) 355-363.
[22] B. Arafat, M. Wojsz, A. Isreb, R.T. Forbes, M. Isreb, W. Ahmed, T. Arafat, M.A. Alhnan, Tablet fragmentation without a disintegrant: A novel design approach for accelerating disintegration and drug release from 3D printed cellulosic tablets, European Journal of Pharmaceutical Sciences, 118 (2018) 191-199.
[23] M. Fanous, S. Gold, S. Hirsch, J. Ogorka, G. Imanidis, Development of immediate release (IR) 3D-printed oral dosage forms with focus on industrial relevance, European Journal of Pharmaceutical Sciences, 155 (2020) 105558.
[24] H. Wang, N. Dumpa, S. Bandari, T. Durig, M.A. Repka, Fabrication of Taste-Masked Donut-Shaped Tablets Via Fused Filament Fabrication 3D Printing Paired with Hot-Melt Extrusion Techniques, AAPS PharmSciTech, 21 (2020) 243.
[25] S.A. Khaled, J.C. Burley, M.R. Alexander, J. Yang, C.J. Roberts, 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles, J Control Release, 217 (2015) 308-314.
[26] A. Maroni, A. Melocchi, F. Parietti, A. Foppoli, L. Zema, A. Gazzaniga, 3D printed multi-compartment capsular devices for two-pulse oral drug delivery, J Control Release, 268 (2017) 10-18.
[27] B.C. Pereira, A. Isreb, M. Isreb, R.T. Forbes, E.F. Oga, M.A. Alhnan, Additive Manufacturing of a Point-of-Care "Polypill:" Fabrication of Concept Capsules of Complex Geometry with Bespoke Release against Cardiovascular Disease, Advanced Healthcare Materials, 9 (2020) 2000236.
[28] Marketsandmarkets. Drug delivery technology market. 15/10/ 2015. Available from: http://www.marketsandmarkets.com/ Market-Reports/drug-delivery-technologies-market-1085.html? gclid=CIXRuMT5osQCFe6WtAodmiUAZg.
[29] S. Corveleyn, J.P. Remon, Formulation and production of rapidly disintegrating tablets by lyophilisation using hydrochlorothiazide as a model drug, International Journal of Pharmaceutics, 152 (1997) 215-225.
[30] S.W. Hoag, Disintegrants in Tableting, Pharmaceutical Dosage Forms-Tablets, CRC Press2016, pp. 891-924.
[31] K. Verma, P.K. Sharma, R. Dudhe, S.K. Patro, FORMULATION, DESIGN AND DEVELOPMENT OF MIFEPRISTONE IMMEDIATE RELEASE TABLET.
[32] R. Natarajan, N. Patel, N.N. Rajendran, M. Rangapriya, Formulation and Evaluation of Immediate Release Bilayer Tablets of Telmisartan and Hydrochlorothiazide, International Journal of Pharmaceutical Sciences and Nanotechnology, 4 (2011).

[33] S. Jadhav, A.D. Mali, S.H. Rajeghadage, R. Bathe, Formulation and evaluation of immediate release tablets of Imipramine hydrochloride, International Journal of Biomedical and Advance Research, 5 (2014) 559-565.
[34] D. Markl, J.A. Zeitler, A Review of Disintegration Mechanisms and Measurement Techniques, Pharmaceutical research, 34 (2017) 890-917.
[35] D.G. Yu, X.X. Shen, C. Branford-White, L.M. Zhu, K. White, X.L. Yang, Novel oral fast-disintegrating drug delivery devices with predefined inner structure fabricated by Three-Dimensional Printing, J Pharm Pharmacol, 61 (2009) 323-329.
[36] W.E. Katstra, R.D. Palazzolo, C.W. Rowe, B. Giritlioglu, P. Teung, M.J. Cima, Oral dosage forms fabricated by three dimensional printing, J Control Release, 66 (2000) 1-9.
[37] C.W. Rowe, W.E. Katstra, R.D. Palazzolo, B. Giritlioglu, P. Teung, M.J. Cima, Multimechanism oral dosage forms fabricated by three dimensional printing, J Control Release, 66 (2000) 11-17.
[38] S.Y. Chin, V. Dikshit, B. Meera Priyadarshini, Y. Zhang, Powder-Based 3D Printing for the Fabrication of Device with Micro and Mesoscale Features, Micromachines, 11 (2020) 658.
[39] Aprecia ZipDose Technology 12/3/2015. Available from: https://aprecia.com/zipdose-platform/zipdose-technology.php.
[40] F. Fina, A. Goyanes, S. Gaisford, A.W. Basit, Selective laser sintering (SLS) 3D printing of medicines, Int J Pharm, 529 (2017) 285-293.
[41] A. Awad, F. Fina, A. Goyanes, S. Gaisford, A.W. Basit, 3D printing: Principles and pharmaceutical applications of selective laser sintering, Int J Pharm, 586 (2020) 119594.
[42] J.C. Carter, The Role of Disintegrants in Solid Oral Dosage Manufacturing, Carter Pharmaceutical Consulting, Inc., 2002-2006.
[43] D.S. Jones, FASTtrack: Pharmaceutics - Dosage Form and Design, Pharmaceutical Press, London, UNITED KINGDOM, 2016.
[44] W. Jamróz, J. Pyteraf, M. Kurek, J. Knapik-Kowalczuk, J. Szafraniec-Szczęsny, K. Jurkiewicz, B. Leszczyński, A. Wróbel, M. Paluch, R. Jachowicz, Multivariate Design of 3D Printed Immediate-Release Tablets with Liquid Crystal-Forming Drug-Itraconazole, Materials (Basel), 13 (2020).
[45] N.G. Solanki, M. Tahsin, A.V. Shah, A.T.M. Serajuddin, Formulation of 3D Printed Tablet for Rapid Drug Release by Fused Deposition Modeling: Screening Polymers for Drug Release, Drug-Polymer Miscibility and Printability, J Pharm Sci, 107 (2018) 390-401.
[46] H.E. Gültekin, S. Tort, F. Acartürk, An Effective Technology for the Development of Immediate Release Solid Dosage Forms Containing Low-Dose Drug: Fused Deposition Modeling 3D Printing, Pharm Res, 36 (2019) 128.
[47] M. Fanous, S. Gold, S. Muller, S. Hirsch, J. Ogorka, G. Imanidis, Simplification of fused deposition modeling 3D-printing paradigm: Feasibility of 1-step direct powder printing for immediate release dosage form production, Int J Pharm, 578 (2020) 119124.
[48] P.K. Nukala, S. Palekar, M. Patki, K. Patel, Abuse Deterrent Immediate Release Egg-Shaped Tablet (Egglets) Using 3D Printing Technology: Quality by Design to Optimize Drug Release and Extraction, AAPS PharmSciTech, 20 (2019) 80.
[49] W. Kempin, V. Domsta, G. Grathoff, I. Brecht, B. Semmling, S. Tillmann, W. Weitschies, A. Seidlitz, Immediate Release 3D-Printed Tablets Produced Via Fused Deposition Modeling of a Thermo-Sensitive Drug, Pharm Res, 35 (2018) 124.
[50] A. Goyanes, A.B. Buanz, A.W. Basit, S. Gaisford, Fused-filament 3D printing (3DP) for fabrication of tablets, Int J Pharm, 476 (2014) 88-92.

[51] G. Wu, W. Wu, Q. Zheng, J. Li, J. Zhou, Z. Hu, Experimental study of PLLA/INH slow release implant fabricated by three dimensional printing technique and drug release characteristics in vitro, BioMedical Engineering OnLine, 13 (2014) 97.
[52] I. Özgüney, D. Shuwisitkul, R. Bodmeier, Development and characterization of extended release Kollidon® SR mini-matrices prepared by hot-melt extrusion, European Journal of Pharmaceutics and Biopharmaceutics, 73 (2009) 140-145.
[53] H.K. Makadia, S.J. Siegel, Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier, Polymers, 3 (2011) 1377-1397.
[54] S.S. Gupta, N. Solanki, A.T. Serajuddin, Investigation of Thermal and Viscoelastic Properties of Polymers Relevant to Hot Melt Extrusion, IV: Affinisol HPMC HME Polymers, AAPS PharmSciTech, 17 (2016) 148-157.
[55] 3D Printing of Tablets - News | Merck KGaA, Darmstadt, Germany | Merck KGaA, Darmstadt, Germany, https://www.merckgroup.com/en/news/3d-printing-of-tablets-27-02-2020.html, 2020.
[56] I. El Aita, J. Breitkreutz, J. Quodbach, On-demand manufacturing of immediate release levetiracetam tablets using pressure-assisted microsyringe printing, Eur J Pharm Biopharm, 134 (2019) 29-36.
[57] T.C. Okwuosa, D. Stefaniak, B. Arafat, A. Isreb, K.W. Wan, M.A. Alhnan, A Lower Temperature FDM 3D Printing for the Manufacture of Patient-Specific Immediate Release Tablets, Pharm Res, 33 (2016) 2704-2712.
[58] S.Y. Chan, The development of PVP-based solid dispersions using hot melt extrusion for the preparation of immediate release formulations, University of East Anglia, 2013.
[59] I. Karakurt, A. Aydoğdu, S. Çıkrıkcı, J. Orozco, L. Lin, Stereolithography (SLA) 3D printing of ascorbic acid loaded hydrogels: A controlled release study, International Journal of Pharmaceutics, 584 (2020) 119428.
[60] P.R. Martinez, A. Goyanes, A.W. Basit, S. Gaisford, Fabrication of drug-loaded hydrogels with stereolithographic 3D printing, Int J Pharm, 532 (2017) 313-317.
[61] A. Goyanes, F. Fina, A. Martorana, D. Sedough, S. Gaisford, A.W. Basit, Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing, Int J Pharm, 527 (2017) 21-30.
[62] A. Goyanes, H. Chang, D. Sedough, G.B. Hatton, J. Wang, A. Buanz, S. Gaisford, A.W. Basit, Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing, Int J Pharm, 496 (2015) 414-420.
[63] T.C. Okwuosa, B.C. Pereira, B. Arafat, M. Cieszynska, A. Isreb, M.A. Alhnan, Fabricating a Shell-Core Delayed Release Tablet Using Dual FDM 3D Printing for Patient-Centred Therapy, Pharm Res, 34 (2017) 427-437.
[64] W. Kempin, V. Domsta, I. Brecht, B. Semmling, S. Tillmann, W. Weitschies, A. Seidlitz, Development of a dual extrusion printing technique for an acid- and thermo-labile drug, Eur J Pharm Sci, 123 (2018) 191-198.
[65] V. Linares, M. Casas, I. Caraballo, Printfills: 3D printed systems combining fused deposition modeling and injection volume filling. Application to colon-specific drug delivery, Eur J Pharm Biopharm, 134 (2019) 138-143.
[66] M.S. Algahtani, A.A. Mohammed, J. Ahmad, E. Saleh, Development of a 3D Printed Coating Shell to Control the Drug Release of Encapsulated Immediate-Release Tablets, Polymers, 12 (2020) 1395.

[67] J. Fu, H. Yin, X. Yu, C. Xie, H. Jiang, Y. Jin, F. Sheng, Combination of 3D printing technologies and compressed tablets for preparation of riboflavin floating tablet-in-device (TiD) systems, International Journal of Pharmaceutics, 549 (2018) 370-379.
[68] K. Huanbutta, T. Sangnim, Design and development of zero-order drug release gastroretentive floating tablets fabricated by 3D printing technology, Journal of Drug Delivery Science and Technology, 52 (2019) 831-837.
[69] S. Shin, T.H. Kim, S.W. Jeong, S.E. Chung, D.Y. Lee, D.-H. Kim, B.S. Shin, Development of a gastroretentive delivery system for acyclovir by 3D printing technology and its in vivo pharmacokinetic evaluation in Beagle dogs, PLoS One, 14 (2019) e0216875.
[70] D.Q.M. Craig, The mechanisms of drug release from solid dispersions in water-soluble polymers, International Journal of Pharmaceutics, 231 (2002) 131-144.
[71] R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N.A. Peppas, Mechanisms of solute release from porous hydrophilic polymers, 15 (1983) 25-35.
[72] N.A. Peppas, P. Bures, W. Leobandung, H. Ichikawa, Hydrogels in pharmaceutical formulations, European Journal of Pharmaceutics and Biopharmaceutics, 50 (2000) 27-46.
[73] E. Fuenmayor, M. Forde, A.V. Healy, D.M. Devine, J.G. Lyons, C. Mcconville, I. Major, Comparison of fused-filament fabrication to direct compression and injection molding in the manufacture of oral tablets, International Journal of Pharmaceutics, 558 (2019) 328-340.
[74] A. Goyanes, J. Wang, A. Buanz, R. Martinez-Pacheco, R. Telford, S. Gaisford, A.W. Basit, 3D Printing of Medicines: Engineering Novel Oral Devices with Unique Design and Drug Release Characteristics, Mol Pharm, 12 (2015) 4077-4084.
[75] K. Ilyés, N.K. Kovács, A. Balogh, E. Borbás, B. Farkas, T. Casian, G. Marosi, I. Tomuță, Z.K. Nagy, The applicability of pharmaceutical polymeric blends for the fused deposition modelling (FDM) 3D technique: Material considerations–printability–process modulation, with consecutive effects on in vitro release, stability and degradation, European Journal of Pharmaceutical Sciences, 129 (2019) 110-123.
[76] M. Saviano, R.P. Aquino, P. Del Gaudio, F. Sansone, P. Russo, Poly(vinyl alcohol) 3D printed tablets: The effect of polymer particle size on drug loading and process efficiency, International Journal of Pharmaceutics, 561 (2019) 1-8.
[77] Q. Li, H. Wen, D. Jia, X. Guan, H. Pan, Y. Yang, S. Yu, Z. Zhu, R. Xiang, W. Pan, Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing, International Journal of Pharmaceutics, 525 (2017) 5-11.
[78] C.I. Gioumouxouzis, O.L. Katsamenis, N. Bouropoulos, D.G. Fatouros, 3D printed oral solid dosage forms containing hydrochlorothiazide for controlled drug delivery, Journal of Drug Delivery Science and Technology, 40 (2017) 164-171.
[79] S.-I. Kimura, T. Ishikawa, Y. Iwao, S. Itai, H. Kondo, Fabrication of Zero-Order Sustained-Release Floating Tablets via Fused Depositing Modeling 3D Printer, Chemical and Pharmaceutical Bulletin, 67 (2019) 992-999.
[80] J. Skowyra, K. Pietrzak, M.A. Alhnan, Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing, Eur J Pharm Sci, 68 (2015) 11-17.
[81] K. Pietrzak, A. Isreb, M.A. Alhnan, A flexible-dose dispenser for immediate and extended release 3D printed tablets, Eur J Pharm Biopharm, 96 (2015) 380-387.
[82] J. Zhang, X. Feng, H. Patil, R.V. Tiwari, M.A. Repka, Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets, Int J Pharm, 519 (2017) 186-197.

[83] Y. Cheng, H. Qin, N.C. Acevedo, X. Jiang, X. Shi, 3D printing of extended-release tablets of theophylline using hydroxypropyl methylcellulose (HPMC) hydrogels, Int J Pharm, 591 (2020) 119983.
[84] J. Long, H. Gholizadeh, J. Lu, C. Bunt, A. Seyfoddin, Application of Fused Deposition Modelling (FDM) Method of 3D Printing in Drug Delivery, Curr Pharm Des, 23 (2017) 433-439.
[85] A. Goyanes, P. Robles Martinez, A. Buanz, A.W. Basit, S. Gaisford, Effect of geometry on drug release from 3D printed tablets, Int J Pharm, 494 (2015) 657-663.
[86] T.D. Reynolds, S.A. Mitchell, K.M. Balwinski, Investigation of the effect of tablet surface area/volume on drug release from hydroxypropylmethylcellulose controlled-release matrix tablets, Drug Dev Ind Pharm, 28 (2002) 457-466.
[87] S. Cailleaux, N.M. Sanchez-Ballester, Y.A. Gueche, B. Bataille, I. Soulairol, Fused Deposition Modeling (FDM), the new asset for the production of tailored medicines, Journal of Controlled Release, (2020).
[88] C.L. Li, L.G. Martini, J.L. Ford, M. Roberts, The use of hypromellose in oral drug delivery, J Pharm Pharmacol, 57 (2005) 533-546.
[89] A. Nokhodchi, S. Raja, P. Patel, K. Asare-Addo, The role of oral controlled release matrix tablets in drug delivery systems, Bioimpacts, 2 (2012) 175-187.
[90] H.M. Fadda, M. Khanna, J.C. Santos, D. Osman, S. Gaisford, A.W. Basit, The use of dynamic mechanical analysis (DMA) to evaluate plasticization of acrylic polymer films under simulated gastrointestinal conditions, European Journal of Pharmaceutics and Biopharmaceutics, 76 (2010) 493-497.
[91] A.A. Barba, M. d'Amore, S. Chirico, G. Lamberti, G. Titomanlio, Swelling of cellulose derivative (HPMC) matrix systems for drug delivery, Carbohydrate Polymers, 78 (2009) 469-474.
[92] V. Mazzanti, L. Malagutti, F. Mollica, FDM 3D Printing of Polymers Containing Natural Fillers: A Review of their Mechanical Properties, Polymers (Basel), 11 (2019).
[93] J.R.C. Dizon, A.H. Espera, Q. Chen, R.C. Advincula, Mechanical characterization of 3D-printed polymers, Additive Manufacturing, 20 (2018) 44-67.
[94] D.M. Smith, Y. Kapoor, G.R. Klinzing, A.T. Procopio, Pharmaceutical 3D printing: Design and qualification of a single step print and fill capsule, Int J Pharm, 544 (2018) 21-30.
[95] J. Boetker, J.J. Water, J. Aho, L. Arnfast, A. Bohr, J. Rantanen, Modifying release characteristics from 3D printed drug-eluting products, European Journal of Pharmaceutical Sciences, 90 (2016) 47-52.
[96] S. Thakral, N.K. Thakral, D.K. Majumdar, Eudragit: a technology evaluation, Expert Opin Drug Deliv, 10 (2013) 131-149.
[97] Evonik., Eudragit® Setting Benchmarks in Oral Solid Dosage Forms Since 1954. , Available online: https://healthcare.evonik.com/sites/lists/NC/DocumentsHC/Evonik-Eudragit_brochure.pdf .
[98] R. Wulff, C.S. Leopold, Coatings of Eudragit® RL and L-55 Blends: Investigations on the Drug Release Mechanism, AAPS PharmSciTech, 17 (2016) 493-503.
[99] N.B. Charbe, P.A. McCarron, M.E. Lane, M.M. Tambuwala, Application of three-dimensional printing for colon targeted drug delivery systems, Int J Pharm Investig, 7 (2017) 47-59.
[100] D. Sauer, J. McGinity, Properties of theophylline tablets dry powder coated with Eudragit((R)) E PO and Eudragit((R)) L 100-55, Pharm Dev Technol, (2009).

[101] J. Krause, M. Bogdahn, F. Schneider, M. Koziolek, W. Weitschies, Design and characterization of a novel 3D printed pressure-controlled drug delivery system, European Journal of Pharmaceutical Sciences, 140 (2019) 105060.
[102] A. Ceballos, M. Cirri, F. Maestrelli, G. Corti, P. Mura, Influence of formulation and process variables on in vitro release of theophylline from directly-compressed Eudragit matrix tablets, Farmaco, 60 (2005) 913-918.
[103] N. Follonier, E. Doelker, E.T. Cole, Evaluation of hot-melt extrusion as a new technique for the production of polymer-based pellets for sustained release capsules containing high loadings of freely soluble drugs, Drug Development and Industrial Pharmacy, 20 (1994) 1323-1339.
[104] A. Awad, F. Fina, S.J. Trenfield, P. Patel, A. Goyanes, S. Gaisford, A.W. Basit, 3D Printed Pellets (Miniprintlets): A Novel, Multi-Drug, Controlled Release Platform Technology, Pharmaceutics, 11 (2019).
[105] E.L. McConnell, H.M. Fadda, A.W. Basit, Gut instincts: Explorations in intestinal physiology and drug delivery, International Journal of Pharmaceutics, 364 (2008) 213-226.
[106] F.J.O. Varum, H.A. Merchant, A.W. Basit, Oral modified-release formulations in motion: The relationship between gastrointestinal transit and drug absorption, International Journal of Pharmaceutics, 395 (2010) 26-36.
[107] B. Abrahamsson, M. Alpsten, U.E. Jonsson, P. Lundberg, A. Sandberg, M. Sundgren, A. Svenheden, J. Tölli, Gastro-intestinal transit of a multiple-unit formulation (metoprolol CR/ZOK) and a non-disintegrating tablet with the emphasis on colon, International journal of pharmaceutics, 140 (1996) 229-235.
[108] E. Haus, F. Halberg, L.E. Scheving, J.E. Pauly, S. Cardoso, J.F. Kühl, R.B. Sothern, R.N. Shiotsuka, D.S. Hwang, Increased tolerance of leukemic mice to arabinosyl cytosine with schedule adjusted to circadian system, Science, 177 (1972) 80-82.
[109] F. Levi, U. Schibler, Circadian rhythms: mechanisms and therapeutic implications, Annu Rev Pharmacol Toxicol, 47 (2007) 593-628.
[110] I. Krögel, R. Bodmeier, Evaluation of an enzyme-containing capsular shaped pulsatile drug delivery system, Pharmaceutical research, 16 (1999) 1424-1429.
[111] I. Krögel, R. Bodmeier, Floating or pulsatile drug delivery systems based on coated effervescent cores, International Journal of Pharmaceutics, 187 (1999) 175-184.
[112] I. Krögel, R. Bodmeier, Pulsatile drug release from an insoluble capsule body controlled by an erodible plug, Pharmaceutical research, 15 (1998) 474-481.
[113] A. Melocchi, F. Parietti, G. Loreti, A. Maroni, A. Gazzaniga, L. Zema, 3D printing by fused deposition modeling (FDM) of a swellable/erodible capsular device for oral pulsatile release of drugs, Journal of Drug Delivery Science and Technology, 30 (2015) 360-367.
[114] A. Melocchi, M. Uboldi, F. Parietti, M. Cerea, A. Foppoli, L. Palugan, A. Gazzaniga, A. Maroni, L. Zema, Lego-Inspired Capsular Devices for the Development of Personalized Dietary Supplements: Proof of Concept With Multimodal Release of Caffeine, J Pharm Sci, 109 (2020) 1990-1999.
[115] Y.J.N. Tan, W.P. Yong, J.S. Kochhar, J. Khanolkar, X. Yao, Y. Sun, C.K. Ao, S. Soh, On-demand fully customizable drug tablets via 3D printing technology for personalized medicine, J Control Release, 322 (2020) 42-52.
[116] N. Reddy Dumpa, S. Bandari, A.R. M, Novel Gastroretentive Floating Pulsatile Drug Delivery System Produced via Hot-Melt Extrusion and Fused Deposition Modeling 3D Printing, Pharmaceutics, 12 (2020).

[117] S.A. Khaled, J.C. Burley, M.R. Alexander, J. Yang, C.J. Roberts, 3D printing of tablets containing multiple drugs with defined release profiles, Int J Pharm, 494 (2015) 643-650.
[118] A.N. de Cates, M.R. Farr, N. Wright, M.C. Jarvis, K. Rees, S. Ebrahim, M.D. Huffman, Fixed-dose combination therapy for the prevention of cardiovascular disease, Cochrane Database of Systematic Reviews, (2014).
[119] WHO, Secondary prevention of non-communicable diseases in low- and middle-income countries through community-based and health service,, http://apps.who.int/iris/bitstream/10665/42567/1/WHO_MPN_CVD_2002.01.pdf, , (30/12/2020); 2002.
[120] J.M. Castellano, G. Sanz, J.L. Peñalvo, S. Bansilal, A. Fernández-Ortiz, L. Alvarez, L. Guzmán, J.C. Linares, F. García, F. D'Aniello, J.A. Arnáiz, S. Varea, F. Martínez, A. Lorenzatti, I. Imaz, L.M. Sánchez-Gómez, M.C. Roncaglioni, M. Baviera, S.C. Smith, K. Taubert, S. Pocock, C. Brotons, M.E. Farkouh, V. Fuster, A Polypill Strategy to Improve Adherence, Journal of the American College of Cardiology, 64 (2014) 2071-2082.
[121] V. Becerra, A. Gracia, K. Desai, S. Abogunrin, S. Brand, R. Chapman, F. García Alonso, V. Fuster, G. Sanz, Cost-effectiveness and public health benefit of secondary cardiovascular disease prevention from improved adherence using a polypill in the UK, BMJ Open, 5 (2015) e007111.
[122] S. Bangalore, A. Shahane, S. Parkar, F.H. Messerli, Compliance and fixed-dose combination therapy, Current hypertension reports, 9 (2007) 184-189.
[123] C.I. Hsu, F.Y. Hsiao, F.L. Wu, L.J. Shen, Adherence and medication utilisation patterns of fixed-dose and free combination of angiotensin receptor blocker/thiazide diuretics among newly diagnosed hypertensive patients: a population-based cohort study, Int J Clin Pract, 69 (2015) 729-737.
[124] C. Schiller, C.P. Fröhlich, T. Giessmann, W. Siegmund, H. Mönnikes, N. Hosten, W. Weitschies, Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging, Aliment Pharmacol Ther, 22 (2005) 971-979.
[125] B.C. Pereira, A. Isreb, R.T. Forbes, F. Dores, R. Habashy, J.B. Petit, M.A. Alhnan, E.F. Oga, 'Temporary Plasticiser': A novel solution to fabricate 3D printed patient-centred cardiovascular 'Polypill' architectures, Eur J Pharm Biopharm, 135 (2019) 94-103.
[126] P. Robles-Martinez, X. Xu, S.J. Trenfield, A. Awad, A. Goyanes, R. Telford, A.W. Basit, S. Gaisford, 3D Printing of a Multi-Layered Polypill Containing Six Drugs Using a Novel Stereolithographic Method, Pharmaceutics, 11 (2019).
[127] G. Reich, Formulation and physical properties of soft capsules, Pharmaceutical Capsules, (2004).
[128] A. Prakash, H. Soni, A. Mishra, P. Sarma, Are your capsules vegetarian or nonvegetarian: An ethical and scientific justification, Indian J Pharmacol, 49 (2017) 401-404.
[129] R.P. Gullapalli, C.L. Mazzitelli, Gelatin and Non-Gelatin Capsule Dosage Forms, J Pharm Sci, 106 (2017) 1453-1465.
[130] M.K. Gupta, F. Meng, B.N. Johnson, Y.L. Kong, L. Tian, Y.W. Yeh, N. Masters, S. Singamaneni, M.C. McAlpine, 3D Printed Programmable Release Capsules, Nano Lett, 15 (2015) 5321-5329.
[131] D. Smith, Y. Kapoor, A. Hermans, R. Nofsinger, F. Kesisoglou, T.P. Gustafson, A. Procopio, 3D printed capsules for quantitative regional absorption studies in the GI tract, International Journal of Pharmaceutics, 550 (2018) 418-428.

[132] T.C. Okwuosa, C. Soares, V. Gollwitzer, R. Habashy, P. Timmins, M.A. Alhnan, On demand manufacturing of patient-specific liquid capsules via co-ordinated 3D printing and liquid dispensing, Eur J Pharm Sci, 118 (2018) 134-143.
[133] A.J. Capel, R.P. Rimington, M.P. Lewis, S.D.R. Christie, 3D printing for chemical, pharmaceutical and biological applications, Nature Reviews Chemistry, 2 (2018) 422-436.
[134] C. Nober, G. Manini, E. Carlier, J.-M. Raquez, S. Benali, P. Dubois, K. Amighi, J. Goole, Feasibility study into the potential use of fused-deposition modeling to manufacture 3D-printed enteric capsules in compounding pharmacies, International Journal of Pharmaceutics, 569 (2019) 118581.
[135] 4 - Main mechanisms to control the drug release, in: M.L. Bruschi (Ed.) Strategies to Modify the Drug Release from Pharmaceutical Systems, Woodhead Publishing2015, pp. 37-62.
[136] S. Wang, R. Liu, Y. Fu, W.J. Kao, Release mechanisms and applications of drug delivery systems for extended-release, Expert Opinion on Drug Delivery, 17 (2020) 1289-1304.
[137] N.A. Peppas, B. Narasimhan, Mathematical models in drug delivery: How modeling has shaped the way we design new drug delivery systems, Journal of Controlled Release, 190 (2014) 75-81.
[138] J. Siepmann, N.A. Peppas, Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC), Advanced Drug Delivery Reviews, 64 (2012) 163-174.
[139] H.Y. Karasulu, G. Ertan, Different geometric shaped hydrogel theophylline tablets: statistical approach for estimating drug release, Farmaco, 57 (2002) 939-945.
[140] J.W. Skoug, M.T. Borin, J.C. Fleishaker, A.M. Cooper, In vitro and in vivo evaluation of whole and half tablets of sustained-release adinazolam mesylate, Pharm Res, 8 (1991) 1482-1488.
[141] E.H. Gökçe, M. Ozyazici, G. Ertan, The effect of geometric shape on the release properties of metronidazole from lipid matrix tablets, J Biomed Nanotechnol, 5 (2009) 421-427.
[142] J. Parojčić, Z. Đurić, M. Jovanović, S. Ibrić, An Investigation into the Factors Influencing Drug Release from Hydrophilic Matrix Tablets Based on Novel Carbomer Polymers, Drug Delivery, 11 (2004) 59-65.
[143] M.A. Bayomi, Geometric approach for zero-order release of drugs dispersed in an inert matrix, Pharmaceutical research, 11 (1994) 914-916.
[144] H. Öblom, J. Zhang, M. Pimparade, I. Speer, M. Preis, M. Repka, N. Sandler, 3D-Printed Isoniazid Tablets for the Treatment and Prevention of Tuberculosis-Personalized Dosing and Drug Release, AAPS PharmSciTech, 20 (2019) 52.
[145] X. Xu, J. Zhao, M. Wang, L. Wang, J. Yang, 3D Printed Polyvinyl Alcohol Tablets with Multiple Release Profiles, Sci Rep, 9 (2019) 12487.
[146] K. Rycerz, K.A. Stepien, M. Czapiewska, B.T. Arafat, R. Habashy, A. Isreb, M. Peak, M.A. Alhnan, Embedded 3D Printing of Novel Bespoke Soft Dosage Form Concept for Pediatrics, Pharmaceutics, 11 (2019).
[147] M. Cui, Y. Li, S. Wang, Y. Chai, J. Lou, F. Chen, Q. Li, W. Pan, P. Ding, Exploration and Preparation of a Dose-Flexible Regulation System for Levetiracetam Tablets via Novel Semi-Solid Extrusion Three-Dimensional Printing, J Pharm Sci, 108 (2019) 977-986.
[148] Y. Yang, H. Wang, H. Li, Z. Ou, G. Yang, 3D printed tablets with internal scaffold structure using ethyl cellulose to achieve sustained ibuprofen release, European Journal of Pharmaceutical Sciences, 115 (2018) 11-18.

[149] B.R. Giri, E.S. Song, J. Kwon, J.H. Lee, J.B. Park, D.W. Kim, Fabrication of Intragastric Floating, Controlled Release 3D Printed Theophylline Tablets Using Hot-Melt Extrusion and Fused Deposition Modeling, Pharmaceutics, 12 (2020).
[150] C. Wei, N.G. Solanki, J.M. Vasoya, A.V. Shah, A.T.M. Serajuddin, Development of 3D Printed Tablets by Fused Deposition Modeling Using Polyvinyl Alcohol as Polymeric Matrix for Rapid Drug Release, J Pharm Sci, 109 (2020) 1558-1572.
[151] H. Kadry, T.A. Al-Hilal, A. Keshavarz, F. Alam, C. Xu, A. Joy, F. Ahsan, Multi-purposable filaments of HPMC for 3D printing of medications with tailored drug release and timed-absorption, Int J Pharm, 544 (2018) 285-296.
[152] G. Verstraete, A. Samaro, W. Grymonpre, V. Vanhoorne, B. Van Snick, M.N. Boone, T. Hellemans, L. Van Hoorebeke, J.P. Remon, C. Vervaet, 3D printing of high drug loaded dosage forms using thermoplastic polyurethanes, Int J Pharm, 536 (2018) 318-325.
[153] F. Fina, A. Goyanes, M. Rowland, S. Gaisford, W.B. A, 3D Printing of Tunable Zero-Order Release Printlets, Polymers (Basel), 12 (2020).
[154] S. Lamichhane, J.B. Park, D.H. Sohn, S. Lee, Customized Novel Design of 3D Printed Pregabalin Tablets for Intra-Gastric Floating and Controlled Release Using Fused Deposition Modeling, Pharmaceutics, 11 (2019).
[155] Q. Li, X. Guan, M. Cui, Z. Zhu, K. Chen, H. Wen, D. Jia, J. Hou, W. Xu, X. Yang, W. Pan, Preparation and investigation of novel gastro-floating tablets with 3D extrusion-based printing, Int J Pharm, 535 (2018) 325-332.
[156] A. Goyanes, A.B. Buanz, G.B. Hatton, S. Gaisford, A.W. Basit, 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets, Eur J Pharm Biopharm, 89 (2015) 157-162.
[157] T. Tagami, K. Fukushige, E. Ogawa, N. Hayashi, T. Ozeki, 3D Printing Factors Important for the Fabrication of Polyvinylalcohol Filament-Based Tablets, Biol Pharm Bull, 40 (2017) 357-364.
[158] E. Fuenmayor, C. O'Donnell, N. Gately, P. Doran, D.M. Devine, J.G. Lyons, C. McConville, I. Major, Mass-customization of oral tablets via the combination of 3D printing and injection molding, Int J Pharm, 569 (2019) 118611.
[159] R. Thakkar, A.R. Pillai, J. Zhang, Y. Zhang, V. Kulkarni, M. Maniruzzaman, Novel On-Demand 3-Dimensional (3-D) Printed Tablets Using Fill Density as an Effective Release-Controlling Tool, Polymers (Basel), 12 (2020).
[160] A. Ajmal, A. Meskarzadeh, N. Genina, C. Hirschberg, J.P. Boetker, J. Rantanen, The Use of 3D Printed Molds to Cast Tablets with a Designed Disintegration Profile, AAPS PharmSciTech, 20 (2019) 127.
[161] A. Isreb, K. Baj, M. Wojsz, M. Isreb, M. Peak, M.A. Alhnan, 3D printed oral theophylline doses with innovative 'radiator-like' design: Impact of polyethylene oxide (PEO) molecular weight, Int J Pharm, 564 (2019) 98-105.
[162] X. Chai, H. Chai, X. Wang, J. Yang, J. Li, Y. Zhao, W. Cai, T. Tao, X. Xiang, Fused deposition modeling (FDM) 3D printed tablets for intragastric floating delivery of domperidone, Scientific reports, 7 (2017) 1-9.
[163] P.R. Martinez, A. Goyanes, A.W. Basit, S. Gaisford, Influence of Geometry on the Drug Release Profiles of Stereolithographic (SLA) 3D-Printed Tablets, AAPS PharmSciTech, 19 (2018) 3355-3361.
[164] M. Ibrahim, M. Barnes, R. McMillin, D.W. Cook, S. Smith, M. Halquist, D. Wijesinghe, T.D. Roper, 3D Printing of Metformin HCl PVA Tablets by Fused Deposition Modeling: Drug Loading, Tablet Design, and Dissolution Studies, AAPS PharmSciTech, 20 (2019) 195.

[165] L. Viidik, J. Vesala, R. Laitinen, O. Korhonen, J. Ketolainen, J. Aruväli, K. Kirsimäe, K. Kogermann, J. Heinämäki, I. Laidmäe, T. Ervasti, Preparation and characterization of hot-melt extruded polycaprolactone-based filaments intended for 3D-printing of tablets, Eur J Pharm Sci, (2020) 105619.
[166] R.C.R. Beck, P.S. Chaves, A. Goyanes, B. Vukosavljevic, A. Buanz, M. Windbergs, A.W. Basit, S. Gaisford, 3D printed tablets loaded with polymeric nanocapsules: An innovative approach to produce customized drug delivery systems, Int J Pharm, 528 (2017) 268-279.
[167] H. Wen, B. He, H. Wang, F. Chen, P. Li, M. Cui, Q. Li, W. Pan, X. Yang, Structure-Based Gastro-Retentive and Controlled-Release Drug Delivery with Novel 3D Printing, AAPS PharmSciTech, 20 (2019) 68.
[168] W. Jamróz, M. Kurek, J. Szafraniec-Szczęsny, A. Czech, K. Gawlak, J. Knapik-Kowalczuk, B. Leszczyński, A. Wróbel, M. Paluch, R. Jachowicz, Speed it up, slow it down…An issue of bicalutamide release from 3D printed tablets, Eur J Pharm Sci, 143 (2020) 105169.
[169] D. Moldenhauer, D.C.Y. Nguyen, L. Jescheck, F. Hack, D. Fischer, A. Schneeberger, 3D screen printing - An innovative technology for large-scale manufacturing of pharmaceutical dosage forms, Int J Pharm, (2020) 120096.
[170] S.Y. Chang, S.W. Li, K. Kowsari, A. Shetty, L. Sorrells, K. Sen, K. Nagapudi, B. Chaudhuri, A.W.K. Ma, Binder-Jet 3D Printing of Indomethacin-laden Pharmaceutical Dosage Forms, J Pharm Sci, 109 (2020) 3054-3063.
[171] C. Korte, J. Quodbach, 3D-Printed Network Structures as Controlled-Release Drug Delivery Systems: Dose Adjustment, API Release Analysis and Prediction, AAPS PharmSciTech, 19 (2018) 3333-3342.
[172] A. Samaro, P. Janssens, V. Vanhoorne, J. Van Renterghem, M. Eeckhout, L. Cardon, T. De Beer, C. Vervaet, Screening of pharmaceutical polymers for extrusion-Based Additive Manufacturing of patient-tailored tablets, Int J Pharm, 586 (2020) 119591.
[173] J.P. Real, M.E. Barberis, N.M. Camacho, S. Sánchez Bruni, S.D. Palma, Design of novel oral ricobendazole formulation applying melting solidification printing process (MESO-PP): An innovative solvent-free alternative method for 3D printing using a simplified concept and low temperature, Int J Pharm, 587 (2020) 119653.
[174] A. Ghanizadeh Tabriz, U. Nandi, A.P. Hurt, H.W. Hui, S. Karki, Y. Gong, S. Kumar, D. Douroumis, 3D printed bilayer tablet with dual controlled drug release for tuberculosis treatment, Int J Pharm, 593 (2020) 120147.
[175] G. Gorkem Buyukgoz, D. Soffer, J. Defendre, G.M. Pizzano, R.N. Davé, Exploring tablet design options for tailoring drug release and dose via fused deposition modeling (FDM) 3D printing, Int J Pharm, 591 (2020) 119987.
[176] D. Horst, 3D Printing of Pharmaceutical Drug Delivery Systems, Archives of Organic and Inorganic Chemical Sciences, 1 (2018) 1-5.
[177] T. Campbell, C. Williams, O. Ivanova, B. Garrett, Could 3D printing change the world, Technologies, Potential, and Implications of Additive Manufacturing, Atlantic Council, Washington, DC, 3 (2011).
[178] C.Y. Liaw, M. Guvendiren, Current and emerging applications of 3D printing in medicine, Biofabrication, 9 (2017) 024102.
[179] S. Jacob, A.B. Nair, V. Patel, J. Shah, 3D Printing Technologies: Recent Development and Emerging Applications in Various Drug Delivery Systems, AAPS PharmSciTech, 21 (2020).
[180] M.A. Azad, D. Olawuni, G. Kimbell, A.Z.M. Badruddoza, M.S. Hossain, T. Sultana, Polymers for Extrusion-Based 3D Printing of Pharmaceuticals: A Holistic Materials-Process Perspective, Pharmaceutics, 12 (2020).

[181] S.J. Trenfield, A. Awad, A. Goyanes, S. Gaisford, A.W. Basit, 3D Printing Pharmaceuticals: Drug Development to Frontline Care, Trends Pharmacol Sci, 39 (2018) 440-451.
[182] M. Palo, J. Holländer, J. Suominen, J. Yliruusi, N. Sandler, 3D printed drug delivery devices: perspectives and technical challenges, Expert Rev Med Devices, 14 (2017) 685-696.
[183] A.A. Konta, M. García-Piña, D.R. Serrano, Personalised 3D Printed Medicines: Which Techniques and Polymers Are More Successful?, Bioengineering (Basel), 4 (2017).
[184] M. Preis, H. Oblom, 3D-Printed Drugs for Children-Are We Ready Yet?, AAPS PharmSciTech, 18 (2017) 303-308.
[185] E.M. Agency, Guideline on Real Time Release Testing (formerly Guideline on Parametric Release), https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-real-time-release-testing-formerly-guideline-parametric-release-revision-1_en.pdf, EMA/CHMP/QWP/811210/2009-Rev1
Committee for Medicinal Products for Human Use (CHMP) (29 March 2012
).
[186] J. Norman, R.D. Madurawe, C.M. Moore, M.A. Khan, A. Khairuzzaman, A new chapter in pharmaceutical manufacturing: 3D-printed drug products, Adv Drug Deliv Rev, 108 (2017) 39-50.
[187] Evonik., EVONIK LAUNCHES RESOMER® FILAMENTS FOR THE 3D PRINTING OF BIORESORBABLE MEDICAL IMPLANTS, https://corporate.evonik.com/en/evonik-launches-resomer-filaments-for-the-3d-printing-of-bioresorbable-medical-implants-114379.html, (2020).
[188] Y. Li, J. Bøtker, J. Rantanen, M. Yang, A. Bohr, In silico design and 3D printing of microfluidic chips for the preparation of size-controllable siRNA nanocomplexes, Int J Pharm, 583 (2020) 119388.
[189] T.B. Martonen, J.D. Schroeter, J.S. Fleming, 3D in silico modeling of the human respiratory system for inhaled drug delivery and imaging analysis, J Pharm Sci, 96 (2007) 603-617.
[190] J.M. Jayaraj, G. Krishnasamy, J.K. Lee, K. Muthusamy, In silico identification and screening of CYP24A1 inhibitors: 3D QSAR pharmacophore mapping and molecular dynamics analysis, J Biomol Struct Dyn, 37 (2019) 1700-1714.
[191] Q. He, C. Han, G. Li, H. Guo, Y. Wang, Y. Hu, Z. Lin, Y. Wang, In silico design novel (5-imidazol-2-yl-4-phenylpyrimidin-2-yl)[2-(2-pyridylamino)ethyl]amine derivatives as inhibitors for glycogen synthase kinase 3 based on 3D-QSAR, molecular docking and molecular dynamics simulation, Comput Biol Chem, 88 (2020) 107328.
[192] Q. He, H. Chu, Y. Wang, H. Guo, Y. Wang, S. Wang, Z. Feng, X.Q. Xie, Y. Hu, H. Liu, Z. Lin, In silico design novel vibsanin B derivatives as inhibitor for heat shock protein 90 based on 3D-QSAR, molecular docking and molecular dynamics simulation, J Biomol Struct Dyn, 38 (2020) 4313-4324.
[193] R. Jerez-Mesa, J.A. Travieso-Rodriguez, X. Corbella, R. Busqué, G. Gomez-Gras, Finite element analysis of the thermal behavior of a RepRap 3D printer liquefier, Mechatronics, 36 (2016) 119-126.
[194] Y. Zhang, K. Chou, A parametric study of part distortions in fused deposition modelling using three-dimensional finite element analysis, Proceedings of the Institution of Mechanical Engineers, Part B: Journal of Engineering Manufacture, 222 (2008) 959-968.
[195] A. Bellini, S. Güçeri, Mechanical characterization of parts fabricated using fused deposition modeling, Rapid Prototyping Journal, 9 (2003) 252-264.

[196] J. Zhang, W. Yang, A.Q. Vo, X. Feng, X. Ye, D.W. Kim, M.A. Repka, Hydroxypropyl methylcellulose-based controlled release dosage by melt extrusion and 3D printing: Structure and drug release correlation, Carbohydr Polym, 177 (2017) 49-57.
[197] M. Novák, T. Boleslavská, Z. Grof, A. Waněk, A. Zadražil, J. Beránek, P. Kovačík, F. Štěpánek, Virtual Prototyping and Parametric Design of 3D-Printed Tablets Based on the Solution of Inverse Problem, AAPS PharmSciTech, 19 (2018) 3414-3424.
[198] B. Robnik, B. Likozar, B.F. Wang, T.S. Ljubin, Z. Casar, Understanding and Kinetic Modeling of Complex Degradation Pathways in the Solid Dosage Form: The Case of Saxagliptin, Pharmaceutics, 11 (2019).
[199] B. Zhang, B. Seong, V. Nguyen, D. Byun, 3D printing of high-resolution PLA-based structures by hybrid electrohydrodynamic and fused deposition modeling techniques, Journal of Micromechanics and Microengineering, 26 (2016) 025015.
[200] S.E. Moulton, G.G. Wallace, 3-dimensional (3D) fabricated polymer based drug delivery systems, J Control Release, 193 (2014) 27-34.
[201] A. Muzaffar, M.B. Ahamed, K. Deshmukh, T. Kovářík, T. Křenek, S.K.K. Pasha, Chapter 4 - 3D and 4D printing of pH-responsive and functional polymers and their composites, in: K.K. Sadasivuni, K. Deshmukh, M.A. Almaadeed (Eds.) 3D and 4D Printing of Polymer Nanocomposite Materials, Elsevier2020, pp. 85-117.
[202] K.H. Low, K.F. Leong, C.K. Chua, Z.H. Du, C.M. Cheah, Characterization of SLS parts for drug delivery devices, Rapid Prototyping Journal, 7 (2001) 262-268.
[203] C. Huang, Extrusion-based 3D Printing and Characterization of Edible Materials, 2018.
[204] M. Algahtani, A. Mohammed, J. Ahmad, Extrusion-Based 3D Printing for Pharmaceuticals: Contemporary Research and Applications, Current Pharmaceutical Design, 25 (2019).
[205] C.-J. Bae, A.B. Diggs, A. Ramachandran, 6 - Quantification and certification of additive manufacturing materials and processes, in: J. Zhang, Y.-G. Jung (Eds.) Additive Manufacturing, Butterworth-Heinemann2018, pp. 181-213.
[206] W. Wu, Q. Zheng, X. Guo, J. Sun, Y. Liu, A programmed release multi-drug implant fabricated by three-dimensional printing technology for bone tuberculosis therapy, Biomed Mater, 4 (2009) 065005.
[207] D.G. Yu, X.L. Yang, W.D. Huang, J. Liu, Y.G. Wang, H. Xu, Tablets with material gradients fabricated by three-dimensional printing, J Pharm Sci, 96 (2007) 2446-2456.
[208] S. Lamichhane, S. Bashyal, T. Keum, G. Noh, J.E. Seo, R. Bastola, J. Choi, D.H. Sohn, S. Lee, Complex formulations, simple techniques: Can 3D printing technology be the Midas touch in pharmaceutical industry?, Asian Journal of Pharmaceutical Sciences, 14 (2019) 465-479.
[209] T. Higuchi, Mechanism of Sustained-Action Medication. Theoretical Analysis of Rate of Release of Solid Drugs Dispersed in Solid Matrices, J Pharm Sci, 52 (1963) 1145-1149.
[210] H. Hopfenberg, Controlled release from erodible slabs, cylinders, and spheres, ACS Publications1976.
[211] T. Salsa, F. Veiga, M.E. Pina, Oral Controlled-Release Dosage Forms. I. Cellulose Ether Polymers in Hydrophilic Matrices, Drug Development and Industrial Pharmacy, 23 (1997) 929-938.
[212] A.W. Hixson, J.H. Crowell, Dependence of Reaction Velocity upon surface and Agitation, Industrial & Engineering Chemistry, 23 (1931) 923-931.
[213] A.A. Noyes, W.R. Whitney, THE RATE OF SOLUTION OF SOLID SUBSTANCES IN THEIR OWN SOLUTIONS, Journal of the American Chemical Society, 19 (1897) 930-934.

[214] R.K. Mamidala, V. Ramana, G. Sandeep, M. Lingam, R. Gannu, M.R. Yamsani, Review Article Factors Influencing the Design and Performance of Oral Sustained/Controlled Release Dosage Forms, 2009.
[215] B.S. Sudha, B.K. Sridhar, A. Srinatha, Modulation of tramadol release from a hydrophobic matrix: implications of formulations and processing variables, AAPS PharmSciTech, 11 (2010) 433-440.
[216] E.A. Clark, M.R. Alexander, D.J. Irvine, C.J. Roberts, M.J. Wallace, S. Sharpe, J. Yoo, R.J.M. Hague, C.J. Tuck, R.D. Wildman, 3D printing of tablets using inkjet with UV photoinitiation, Int J Pharm, 529 (2017) 523-530.
[217] R. Zarzycki, Z. Modrzejewska, K. Nawrotek, U. Leków, Z. Hydrożeli, Drug release from hydrogel matrices, Ecological Chemistry and Engineering S, 17 (2010).
[218] C.C. Lin, A.T. Metters, Hydrogels in controlled release formulations: network design and mathematical modeling, Adv Drug Deliv Rev, 58 (2006) 1379-1408.
[219] R.W. Korsmeyer, S.R. Lustig, N.A. Peppas, Solute and penetrant diffusion in swellable polymers. I. Mathematical modeling, Journal of Polymer Science Part B: Polymer Physics, 24 (1986) 395-408.
[220] Y.H. Wu, H.B. Park, T. Kai, B.D. Freeman, D.S. Kalika, Water uptake, transport and structure characterization in poly(ethylene glycol) diacrylate hydrogels, J. Membr. Sci., 347 (2010) 197-208.
[221] H.N. Chia, B.M. Wu, Recent advances in 3D printing of biomaterials, Journal of biological engineering, 9 (2015) 1-14.
[222] X. Wang, M. Jiang, Z. Zhou, J. Gou, D. Hui, 3D printing of polymer matrix composites: A review and prospective, Composites Part B: Engineering, 110 (2017) 442-458.
[223] S.C. Ligon, R. Liska, J. Stampfl, M. Gurr, R. Mülhaupt, Polymers for 3D Printing and Customized Additive Manufacturing, Chemical Reviews, 117 (2017) 10212-10290.
[224] H. Wickstrom, M. Palo, K. Rijckaert, R. Kolakovic, J.O. Nyman, A. Maattanen, P. Ihalainen, J. Peltonen, N. Genina, T. de Beer, K. Lobmann, T. Rades, N. Sandler, Improvement of dissolution rate of indomethacin by inkjet printing, Eur J Pharm Sci, 75 (2015) 91-100.

Figure 1

Click here to access/download;Figure;Shriya-Fig1.tif

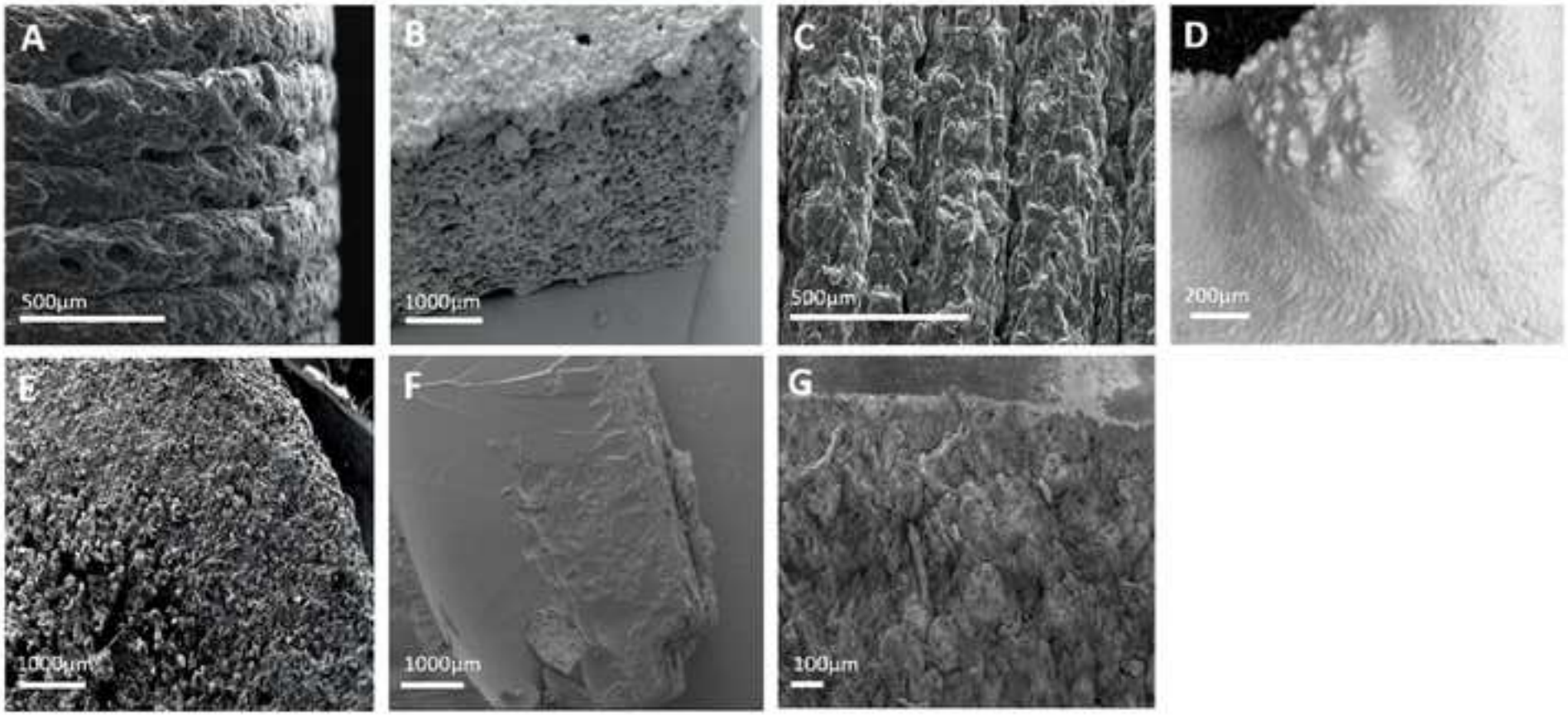

Figure 2

Click here to access/download;Figure;Shriya-Fig2.tif

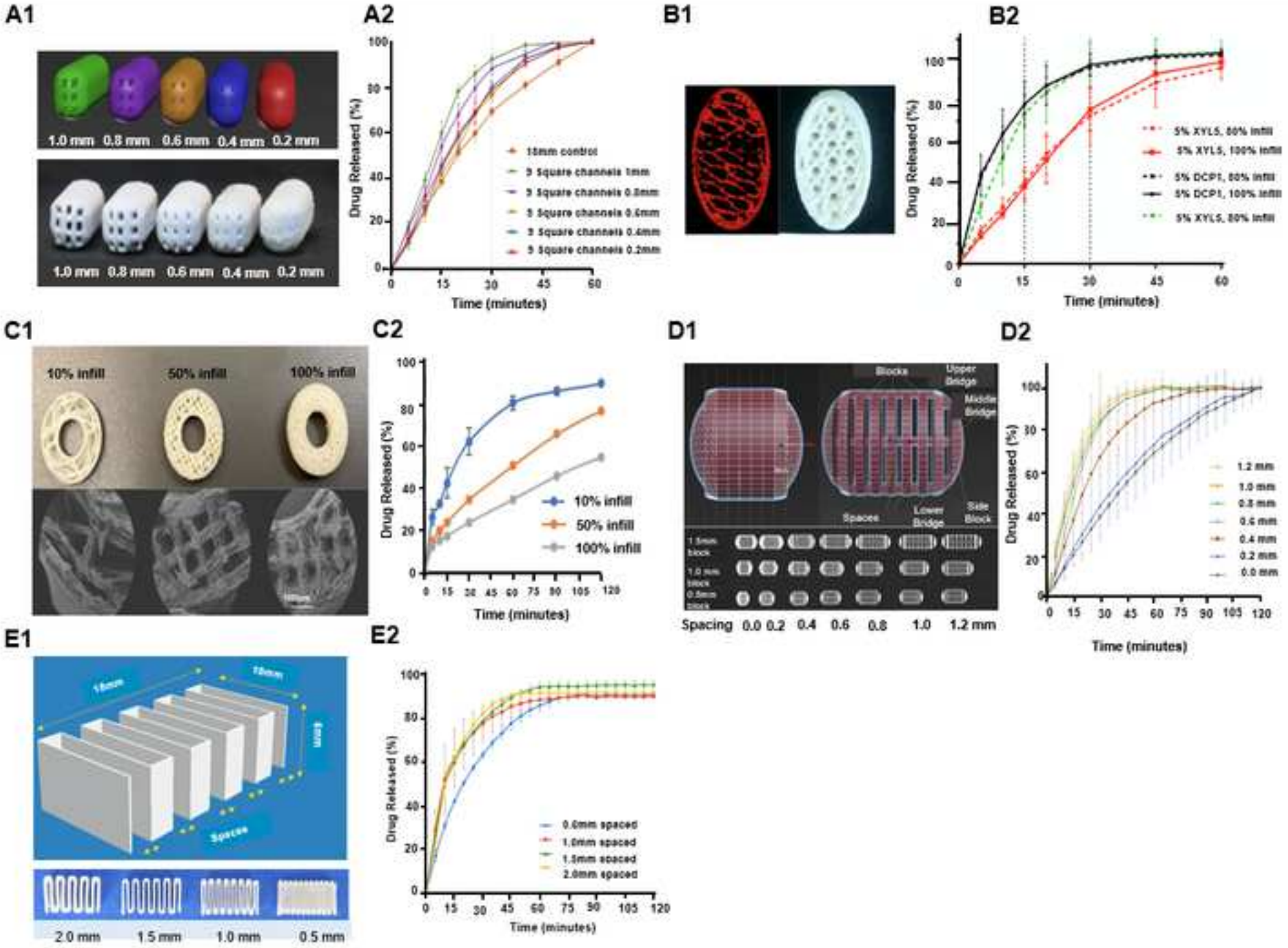

Figure 3

Click here to access/download;Figure;Shriya-Fig3.tif

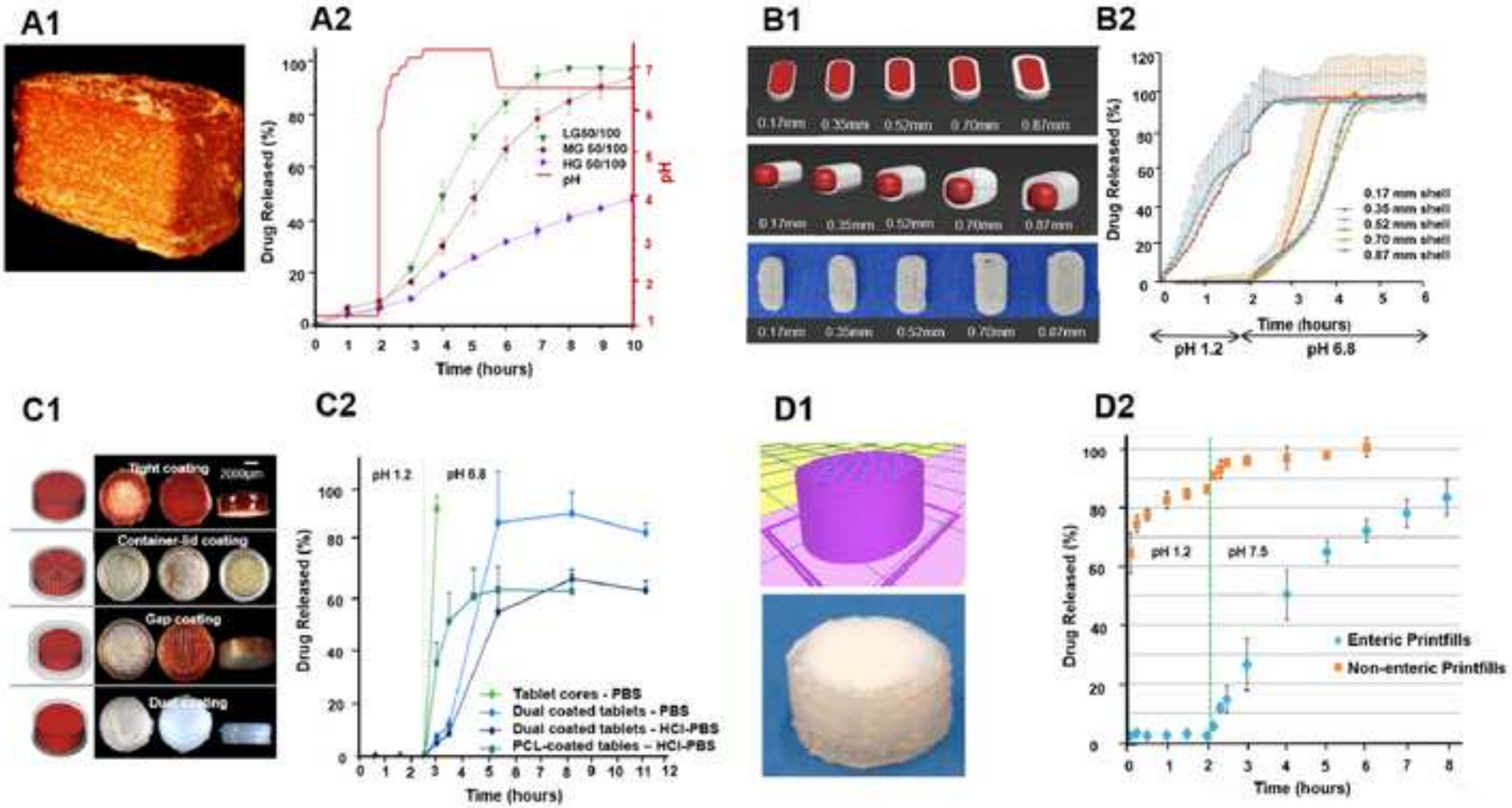

Figure 4

Click here to access/download;Figure;Shriya-Fig4.tif

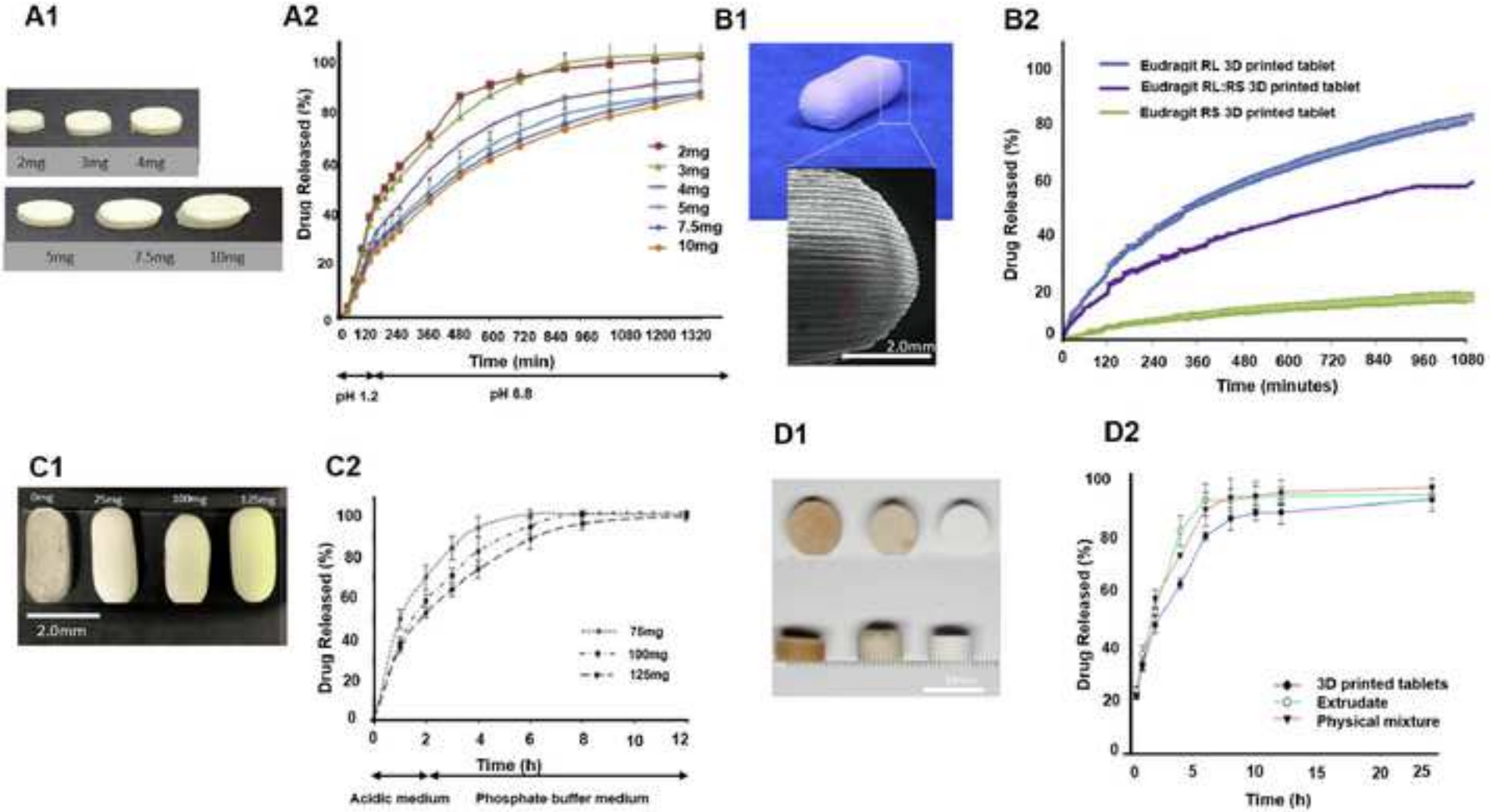

Figure 5

Click here to access/download;Figure;Shriya-Fig5.tif

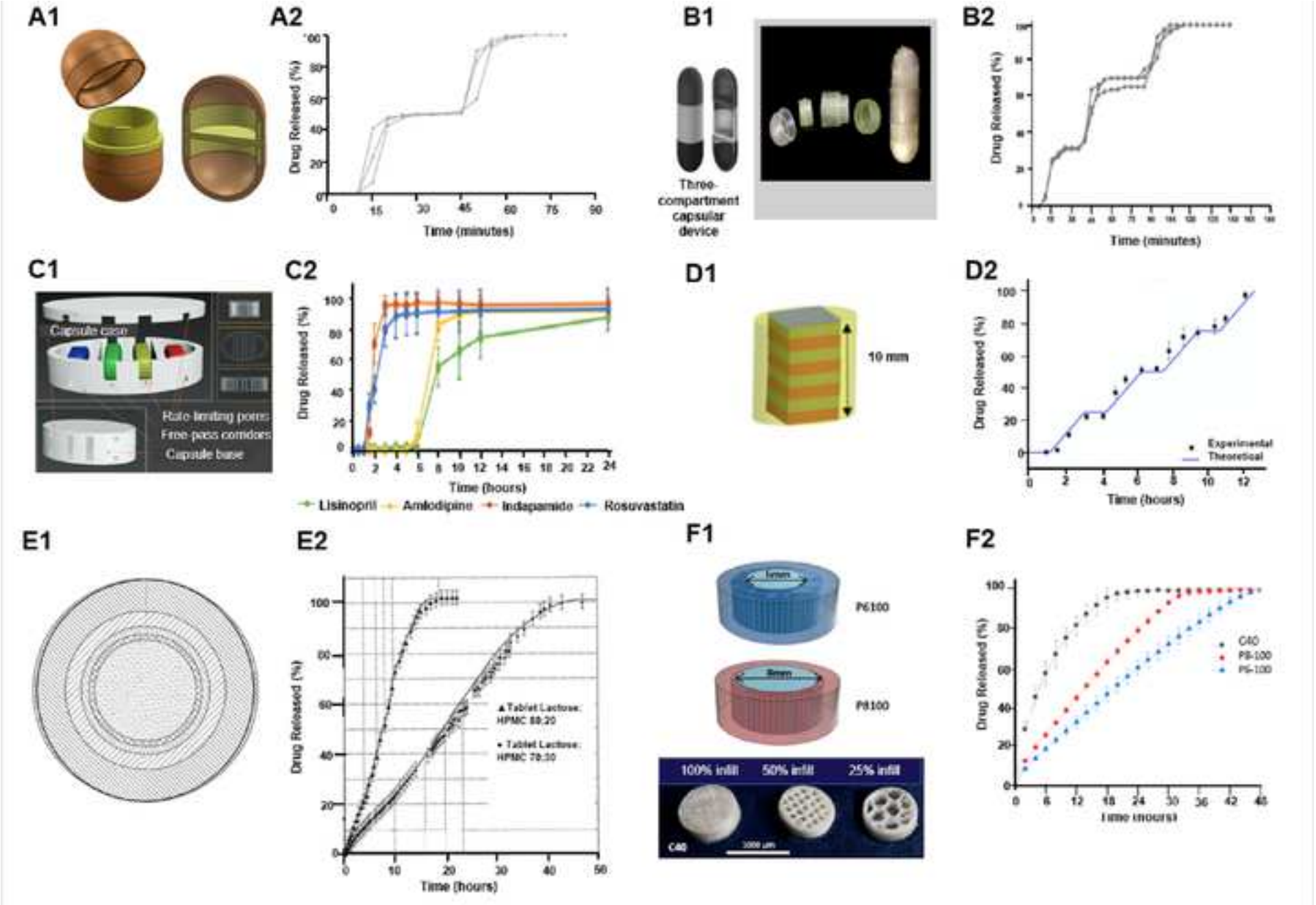

Figure 6

Click here to access/download;Figure;ShriyaFig6.tif

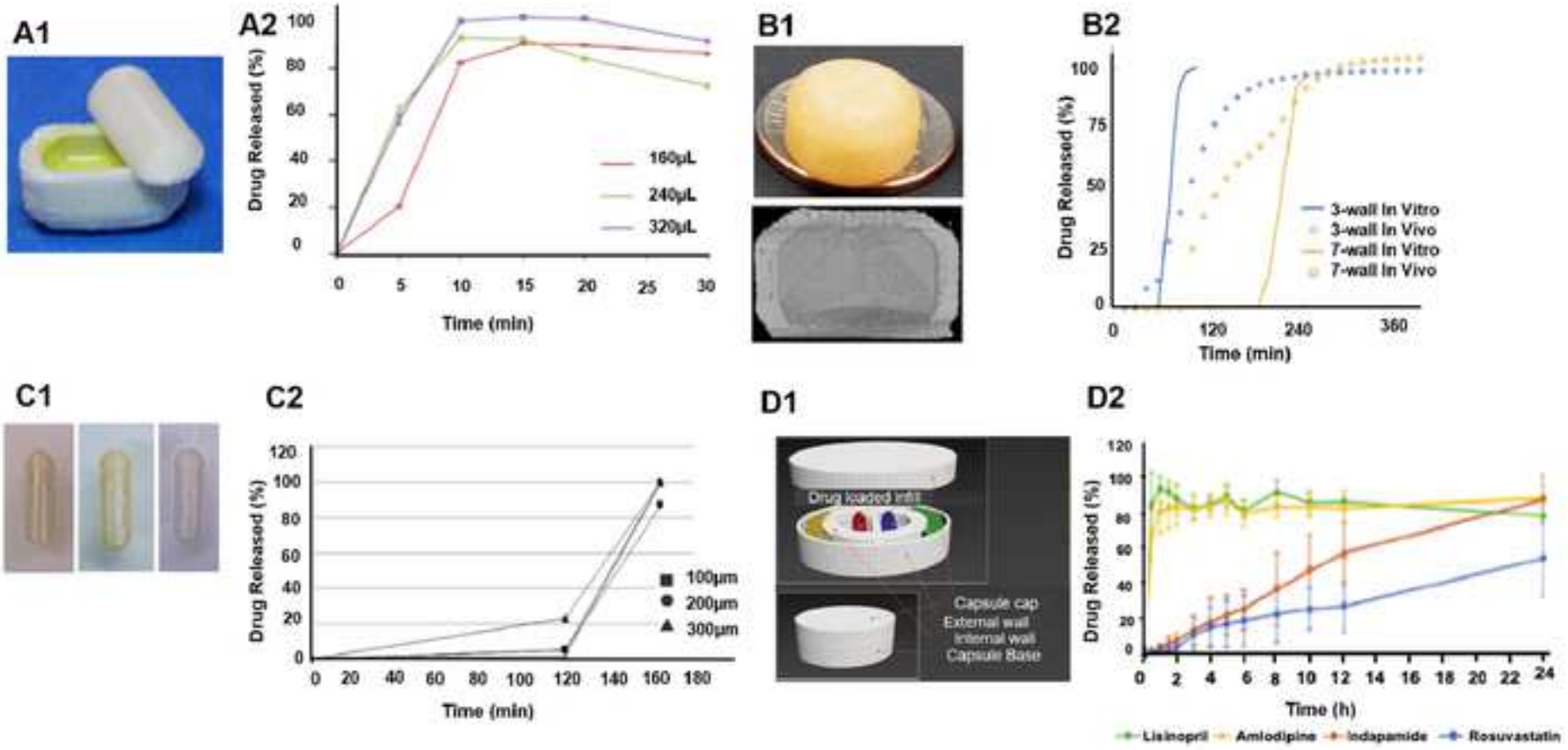

Figure 7

Click here to access/download;Figure;ShriyaFig7.tif

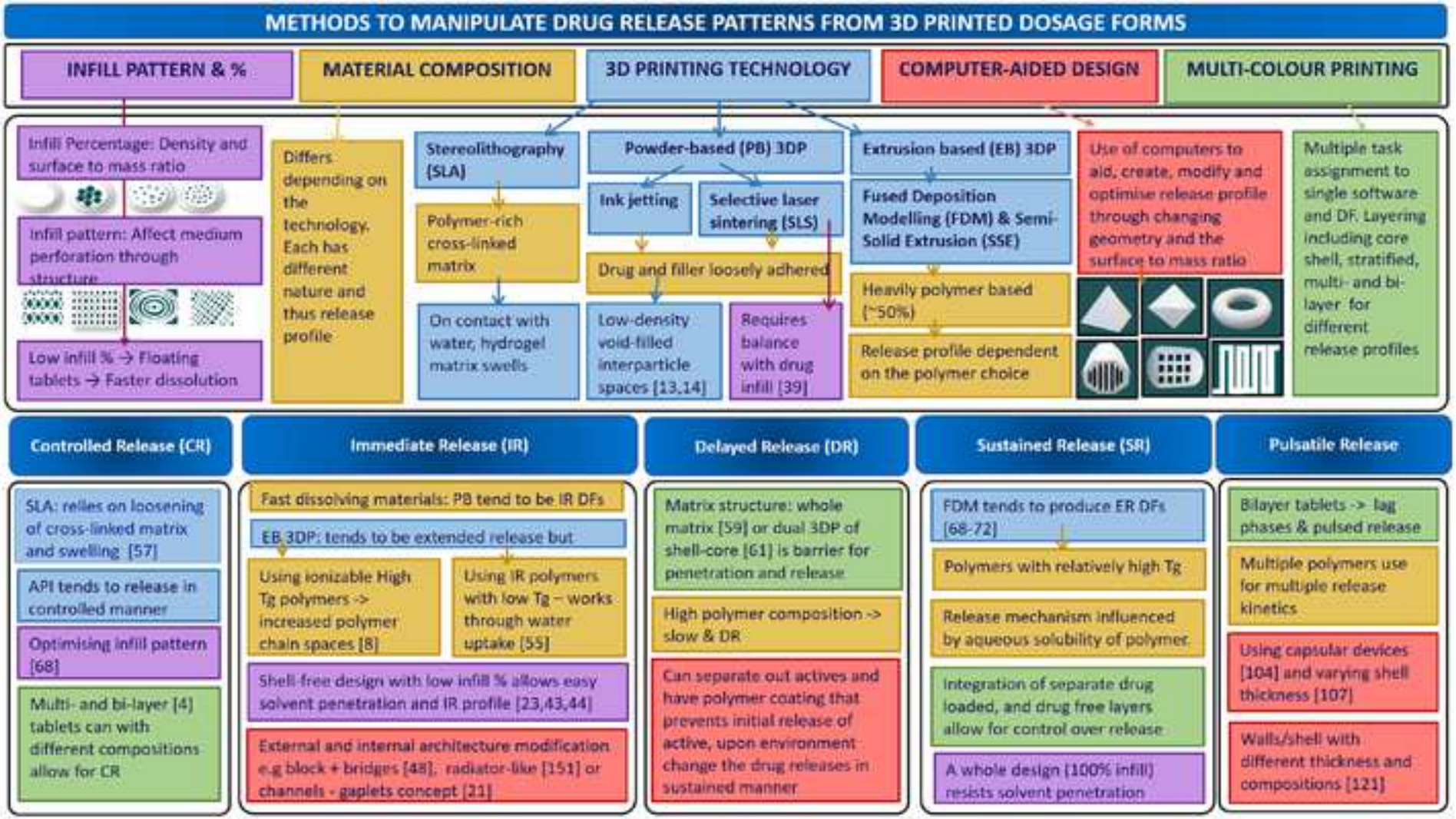

Figure 8

Click here to access/download;Figure;ShriyaFig8.tif

Click here to access/download;Table;Shriya Tables R1.docx

Table 1. Summary of the different 3DP technologies: formation mechanism, composition, nature and resolution of form DF.

3D printing technology	Typical Matrix Composition	Concept	Nature of Matrix formed	Typical Resolution	References
Fused Deposition Modelling (FDM)	Active pharmaceutical ingredient (API), polymer, filler, lubricant and stabilizer.	Polymer-rich filament is melt-extruded through a hot nozzle in a controlled layer-by-layer manner.	Polymer-rich structure (~50%) of relatively high glass transition temperature (Tg) polymer species.	80-200µm [199]	[9, 50, 80, 156, 200]
Selective Laser Sintering (SLS)	API, thermoplastic polymer (powder form), light absorbing agent (salt, metal, or lake dye), and a filler (optional).	Powder-based technology – laser fuses thermoplastic polymer resin, drawing layer-b-layer a specific pre-configured pattern on the surface of a powder bed.	Loosely packed powder bed yields significant voids following particle fusion. Highly porous, void-filled matrix.	20-150µm, depending on particle size [201]	[10, 40, 202]
Semi-Solid Extrusion (SSE)	API, polymer/matrix, filler, evaporable or non-evaporable solvent (optional), plasticiser/solvent and a lubricant (optional).	Rotating screw gear or pressurised air extrudes semi-solids (e.g. homogenous paste) through a nozzle over moveable stage in a layer-by-layer fashion.	Dense and rigid matrix. Depends on solvent nature: evaporable - dense matrix forms; non-evaporable - solid, rigid structure forms.	100-500µm, depending on size of the nozzle tip [203]	[4, 12, 25, 117, 204]
Binder Jet/Powder Based (PB)	API, carrier fluids, binder, surface tension and viscosity modifiers.	The ink (binder(s) and/or API(s) binder solution) sprayed over a powder bed in a layer-by-layer fashion until 3D DF is printed.	Void-filled, porous printed matrix forms.	~100µm [205]	[37, 206, 207]
Stereolithography (SLA)	API, oligomer, liquid polymer, photo-initiator.	Curing of a photosensitive oligomer-based resin by scanning a focused ultraviolet laser in a layer-by-layer fashion.	Dense, void-less, polymer rich, cross-linked structure. Hydrogel forms for aqueous polymer solutions.	16-100µm [208]	[15, 60, 126]

Table 2. A summary of the predicted/ typical release profile and mechanism from DF produced by the different 3DP technologies, and the challenges presenting utilising these technologies.

Technology	Material Composition/ Substrates	Predicted/ Typical Release mechanism	Applicable mathematical models and factors affecting drug release	Challenges
Fused Deposition Modelling (FDM)	Soluble polymer based	Matrix erosion: API is dispersed within a polymeric matrix. API release is controlled by the polymer intrinsic properties. In dissolution medium, polymer surface erosion leads to API release, mainly governed by the kinetic of degradation [135].	Higuchi's model [209] (water soluble and low soluble APIs) Hopfenbergs model (surface-erosion) [210]. API release controlled by polymer properties, e.g. composition, molecular mass, matrix thickness.	• Difficulty to achieve immediate release [52, 57]. • Limited number of polymers available to produce compatible filaments [50, 80].
	Insoluble polymer based, e.g. ethyl acetate	Diffusion-based: API molecules diffuse through the pores of the polymeric matrix. Release rate decreases as a function of time as API in the	Korsmeyer-Peppas [71] (if mechanism is unknown or more than one involved). Other mechanisms: Fickian Zero-order model and Non-Fickian models, e.g. first-order release, Hixon and	• Limited loading capacity (≤50%) [62, 156]. • Limited number of polymers available to produce compatible filaments [45].

	and Eudragit® RL + RS	central domains travels a longer diffusion path [211].	Cromwell [212] were suggested (when release is dependent on particle surface area).	
Selective Laser Sintering (SLS)	Polymer-based	Erosion and dissolution: API released by the polymeric erosion providing controlled release. API release governed by thickness and dissolution rate of polymer.	Noyes-Whitney relationship [213]. Factors such as penetration rate of the dissolution medium into the matrix, degree of porosity, wettability of system and surface topography of particles control the rate of API release [214].	• Limited to polymer of certain glass transition temperature [40, 51]. • Requires API compatibility with photoabsorbent material
Semi-Solid Extrusion (SSE)	Soluble polymer matrix	Erosion and diffusion based: Upon contact with the dissolution medium the polymer surface erodes, and the active agent is released by diffusion.	Higuchi [209] (water soluble and low soluble drugs incorporated into semi-solid and/or solid matrices). Fickian Zero-order model and Non-Fickian models, e.g. first-order release, Hixon and Cromwell [212].	• Residual solvent can affect release profile. • Requires disintegrant at a much higher percentage than conventionally required which can impact the obtained release profile.
	Insoluble polymer matrix	Diffusion based: API molecules diffuse through the pores of insoluble polymeric matrix.	Fickian zero-order, non-Fickian models, e.g. first-order release - Hixon and Cromwell [212].	• Residual solvent/drying can affect the obtained release profile

Binder /Material Jetting (BJ/ MJ)	Wax based jetting	Dissolution and diffusion: API diffuses out the matrix, with the process moving towards the interior. Release rate can be altered by increasing the amount of API or the wax concentration, and/or incorporation of hydrophilic polymer [215].	API release related to the square root of time accounting for the volume and length of the openings of the porous matrix. The release of drug from a homogenous matrix system can be controlled by varying the initial concentration of drug matrix porosity and tortuosity, the type and solubility of polymer-forming the matrix.	• Compatible materials are wax based that may hinder drug release [216].
	Powder -based jetting	Disintegration and dissolution: powder-based jetting produces porous, void-filled structures with inter-particulate spaces. Upon contact with dissolution medium, water penetrates the matrix resulting in rapid disintegration and IR.	Mathematical model applicable shows correlation between API release and the square root of time which accounts for the volume and lengths of openings in the porous matrix.	• Reproducibility of drug release from dosage forms depends on drying.

Stereolithography (SLA)	Liquid polymer	Swelling and diffusion: drug diffusion through the hydrogel swollen matrix. On contact with water the hydrogel matrix swells, the cross-linked network loosens, and API is released in a controlled manner. API release depends on the swelling rate and extent of the hydrogel.	API diffusivity in hydrogels [217] can be modelled using Lusting and Peppas' relationship (drug diffusivity and hydrogel network structure) [218] and Korsmeyer and Peppas' correlation [219] (moving boundary phenomena with hydrogel swelling). Decreasing cross-linkable polymers and/or increasing non-cross linkable components and water in the initial resin can modulate the hydrogel characteristics such as water uptake, pore size and therefore release profile [220].	• Hydrogels shrink and thus can change the observed release profile [15, 59]. • Regulatory concerns for using photo initiators. • Compatibility is required between API and initiator. • Slow drug release makes its more suitable for implant rather than oral dosage forms [15, 221].

Table 3. A summary of challenges, future trends and potential and opportunity of 3DP for producing controlled-release DF.

3DP challenges	Impact of challenge on release profile	Future trends	Opportunity upon overcoming limitation	References
Limited number of compatible, commercially available approved polymers.	Limited range of 3D printed DF.	Testing a wider range of existing polymers for their use in 3DP technologies. Development of new grades of approved pharmaceutical excipients specially optimised for 3DP.	Achievement of reproducible release patterns, especially for immediate release. Shortened development time and approval.	[45, 176]
Requiring high concentration of polymer.	Release profile heavily impacted by the high concentration of polymers required in the 3DP technologies, producing a low drug loading.	Development of new polymers with behavioural characteristics that suit the wide range of release kinetics or that can be used in lower concentrations.	Agility at controlling the release profile without having to factor in the polymer concentration.	[222, 223]
Limited knowledge on stability of pre-product (pharmaceutical ink) and final product of 3DP.	The stability of pre-product (filaments, inkjets, substrates and cartridges) is to be established.	Better understanding of the stability of initial and final products and the link to process parameters and selected materials.	Stable pre-product will generate a reproducible drug release. Ideally, paired with *in silico* simulation for prediction and pre-design of release profile as desired.	[181, 224]
Release profile reproducibility.	Reproducibility of drug release is not established.	Better understanding of the variability of initial and final product and its link to process parameters and selected materials.	Dialling the release profile as desired would open the door for an infinite number of geometries and freedom of design for the production team.	[177, 178]
Low resolution of 3D printed dosage forms	Currently 3D printers are designed for larger objects than solid DF.	The technology and materials need development to allow 3DP at greater resolution.	High resolution 3D printed dosage form with better aesthetics. New opportunities for drug release controlled by design and multiple drug release starting from the same materials.	[63, 180]
Quality control (QC) and	No clear regulatory route for QC and QA specific for the release of	Better understanding of quality challenges affecting drug release.	Rapid release of small batch production.	[181-184]

quality assurance (QA)	3D printed dosage forms. QC for end-product involves time-consuming *in vitro* dissolution test.	QA means replacing QC of end product. Fast QC means for dissolution testing.