3D printing by fused deposition modeling of single- and multi-compartment hollow systems for oral delivery - A review

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Abstract

Feasibility of fused deposition modeling in 3D printing of hollow systems intended to convey different formulations for oral administration has recently been investigated. A major advantage of such printed devices is represented by the possibility of separately undertaking the development of the inner core from that of the outer shell, which could also act as a release-controlling barrier. Systems either composed of parts to be filled and assembled after fabrication or fabricated and filled in a single manufacturing process represent the main focus of this review. Devices having relatively simple (*e.g.* single-compartment capsule-like) configuration were first proposed followed by systems entailing multiple inner compartments. The latter were meant to be filled with different formulations, left empty for ensuring floatation or achieve combined release kinetics. For each of the reviewed systems, design, formulation approaches, manufacturing as well as release performance obtained were critically described. Versatility of FDM, especially in terms of geometric freedom provided, was highlighted together with some limitations that still need to be addressed, as expected for a newly-adopted fabrication technique that holds potential for being implemented in the pharmaceutical field.

Contents:

Keywords: 3D printing, fused deposition modeling, oral drug delivery, hollow systems

List of abbreviation

3D, three-dimensional

ABS, acrylonitrile butadiene styrene

AM, additive manufacturing

CAD, computer-aided design

CAP, cellulose acetate phthalate

cGMPs, current Good Manufacturing Practices

DDSs, drug delivery systems

DSC, differential scanning calorimetry

EC, ethylcellulose

FDM, fused deposition modeling

FT-IR, fourier-transform infrared spectroscopy

GPC, gel permeation chromatography

HEC, hydroxyethyl cellulose

HME, hot melt extrusion

^{1}H-NMR, proton nuclear magnetic resonance

HPC, hydroxypropyl cellulose

HPMC, hydroxypropyl methylcellulose

HPMCAS, hydroxypropyl methylcellulose acetate succinate

HPMCP, hydroxypropyl methyl cellulose phthalate

IM, injection molding

IVF, injection volume filling

PCL, poly(ε-caprolactone)

PLA, polylactic acid

PEG, polyethylene glycol

PEO, polyethylene oxide

PVA, poly(vinyl alcohol)

PVP, polyvinylpyrrolidone

TEC, triethyl citrate

TGA, thermal gravimetric analysis

1. Introduction

3D printing indicates the fabrication of solid objects of almost whatever shape starting from their digital model and based on the addition of subsequent layers of materials, thus also being known as AM or solid freeform technology (Gibson et al., 2010; Pham and Gault, 1998; Zema et al., 2017). It encompasses a variety of techniques (*e.g.* binder jetting, selective laser sintering, digital beam melting, fused deposition modeling), which differ in the characteristics of the materials to be printed, deposition mode, mechanism involved in the formation of bonds between adjacent layers (*e.g.* photopolymerization, melting, solvent evaporation) and properties of the final product. Despite the initial enthusiasm about this technology demonstrated by the extensive use as a prototyping tool, its actual industrial application potential has only recently started to be in depth-investigated (Anton et al., 2014; Garmulewicz et al., 2018; Mir and Nakamura, 2017; Rehnberg and Ponte S., 2016; Tran, 2017). More into detail, in view of a few technological bottlenecks (*e.g.* production speed, cost and labor associated with pre- and post-printing operations), 3D printing is currently carving out a position as an effective method to complement the existing manufacturing processes, especially when its unique characteristics would be highly beneficial (*e.g.* on-demand and decentralized production, customization, increased design complexity).

In parallel with the increasing attention towards 3D printing in many different industrial areas, such a technology started to be implemented also in the healthcare field, particularly for the fabrication of personalized medical devices, mainly tissue scaffolds and prostheses (Gualdrón et al., 2019; Trenfield et al., 2019). Subsequently, also the community of pharmaceutical researchers, for which the exploitation of manufacturing processes belonging to other industrial environment represents one of the most interesting innovation tools, has started to be curious about it (Alhnan et al., 2016; Awad et al., 2018a; Goole and Amighi, 2016; Jamroz et al., 2018; Trenfield S. J., 2018a,b; Zhang et al., 2018). The main application considered for AM is that of a cost-effective alternative for moving from mass production of drug products (*i.e.* one-size-fits-all approach) to fabrication of small diversified batches meeting single patient's needs, thus supporting the development of personalized

medicine (Alomari et al., 2015; Kurzrock and Stewart 2015; Douroumis 2019; Sandler and Preis, 2016). In this respect, 3D printing techniques based on processes and materials that are common in the pharmaceutical field, such as primarily binder jetting and FDM, have drawn the widest interest (Aho et al., 2019; Aita et al, 2019). In a narrower and more advanced set of applications, 3D printing has also been investigated as a rapid prototyping tool for the design of DDSs before moving to mass-manufacturing and to streamline industrial development (Maroni et al, 2017; Melocchi et al. 2015; Shin et al., 2019).

3D printing was demonstrated to allow simple- (*e.g.* tablets, films, granules) and complex-geometry (*e.g.* coated and multilayered) products to be prepared using the same equipment, possibly in a single manufacturing process, thus also involving less unit operations (Chandekar et al., 2019; Prasad and Smyth, 2016). It would enable to personalize the typeand amount of the active ingredient(s) conveyed in a dosage form, modulate the release rate, customize the formulation (*e.g.* change flavors, avoid non-tolerated excipients) and the shape of the product to achieve challenging therapeutic targets (*e.g.* retentive DDSs fabricated *via* 4D printing) and improve patient compliance, only by developing different digital models and changing the printing materials and parameters (Alhnan et al., 2016; Goyanes et al., 2017a; Jonathan and Karim 2016; Lukin et al., 2019; Madla et al, 2018; Manizzurman, 2018; Melocchi et al, 2019a,b; Norman et al., 2017; Preis and Öblom, 2017; Zema et al, 2017). Moreover, the 3D printing technique based on extrusion of softened/molten materials is intrinsically endowed, if coupled with HME, with the ability to fulfill the needs of continuous manufacturing, which would take advantage of the limited room required for setting up a production facility (Cunha-Filho et al., 2017; Zhang et al., 2017).

What is really new and unique is the possibility of manufacturing by AM medicines on demand and at the point of care, fully responding to the request for customization and avoiding the need for long-term storage as well as stability studies (Araújo et al., 2019; Awad et al., 2018b; Baines et al., 2018; Rahman et al., 2018). The availability of customized drug products would not only decrease the healthcare system expenses associated with side effects and hospitalization but may be of

utmost importance in the case of people with special needs. These include subjects affected by rare diseases, children and elderly patients, poor and high metabolizers, individuals with illnesses at the expense of elimination organs and people taking multiple medicines that may interact with each other. Indeed, concomitant use of numerous prescription drugs (*i.e.* polypharmacy) has largely increased in the last years, for instance with 30% of elderly patients in the United States assuming five or more medicines *per* day (Gioumouxouzis et al., 2019; Sandler and Preis, 2016). This would mainly be due to the high rates of comorbidities, especially in seniors suffering by chronic diseases and to the tendency of physicians towards over prescription. Besides enhancing patient compliance, feasibility of combination products by 3D printing could extend patents and improve cost-effectiveness by creating a single product pipeline, thus reducing costs associated with packaging, prescribing and dispensing. In addition, all the aforementioned features make 3D printing a suitable tool for telemedicine, defined as remote delivery of healthcare services (*e.g.* consultation, diagnosis, advice, reminders, education, intervention, monitoring) by taking advantage of telecommunication technologies whenever physicians and patients are not physically close (Araújo, et al., 2019; Johnson and Brownlee, 2018; Wang and Kricka, 2018; Wen 2017). Telemedicine has the potential to bridge distances and ease healthcare in remote and rural areas where people struggle to receive appropriate treatments due to the lack of physicians. Moreover, it would ease the long-term monitoring of patients with chronic diseases, who could be directly checked at home. Indeed, 3D printing would be suitable for real-time manufacturing of medicines indicated in the virtual prescriptions sent from the doctor to the patient, by way of example whenever an adjustment in the maintenance therapy is needed. In this respect, 3D printing could advantageously be integrated with other technological advancements, such as smart health monitors, applications and cloud-based computing which would allow the physicians to evaluate patient health in real-time and collect any data about modifications of the *status quo*.

In spite of the great potential described for 3D printing for revolutionizing drug treatments, there is only one printed pharmaceutical product on the market based on powder jetting technique, *i.e.*

Spritam®, which turned out compatible with the existing approval path (Boudriau et al., 2016; https://www.spritam.com/#/patient/zipdose-technology/making-medicine-using-3d-printing). On the other hand, particularly when dealing with the idea of making personalization of drug products a reality, a lack of regulatory framework persists, especially related to quality control and assurance (Lamichhane et al., 2019; Mirza and Iqbal, 2018; Norman et al., 2017; Rahman et al., 2018). Unavailability on the market of 3D printers suitable for the standardization and validation of pharmaceutical processes is currently one of the main limitations to the development of this technology (Feuerbach et al., 2018). Only preliminary attempts to attain compliance with cGMPs regulations were recently described (Melocchi et al., 2018). Moreover, a thorough understanding of the interaction between critical process parameters and critical quality attributes of the finished products is an essential point and, by now, first steps have been undertaken in this respect (Carlier et al., 2019; Novák et al., 2018; Palekara et al., 2019).

2. FDM of drug products

2.1. Background

FDM was created in 1988 when Scott Crump tried to build a toy for his daughter. He used a simple glue gun in which he replaced the glue stick with a blend of polyethylene and candle wax and used it to form the toy layer-by-layer (Joo et al., 2019). An automated version was then developed by Crump and his wife who patented the technology with the trademark FDM™ and co-founded Stratasys, Ltd. to commercialize the equipment (US Patent 5121329, awarded on June 9, 1992). In the last 5 years, an outburst in the research activity and in the number of articles published regarding 3D printing has been highlighted, especially considering the scientific literature focused on the application of the FDM technique (Gioumouxouzis et al., 2019; Tan et al., 2018). This is an AM process entailing the deposition of successive layers of softened/molten materials in such a pattern to create the final object (Algahtani et al., 2017; Awad et al., 2018b; Joo et al., 2019; Long

et al., 2017; Zema et al., 2017). The starting materials are generally fed into the printer in the form of filaments with defined size and mechanical characteristics, fabricated by HME from a thermoplastic polymer. Preliminary attempts at modifying printer hardware have been very recently performed to enable to circumvent such an intermediate step (*e.g.* pellet and ram extrusion) (Goyanes et al, 2019; Musazzi et al., 2018).

2.2. Advantages and limitations

The broad interest in FDM was probably promoted by the relatively low cost of the equipment, which were also conceived to be as much user-friendly as possible if compared with other 3D printers. These features have made such a technology widely accessible for use in laboratory settings (Aho et al., 2019; Alhnan et al., 2016; Araújo et al., 2019; Zema et al., 2017). As for other hot-processing techniques, further advantages of FDM in the manufacturing of drug products would be associated with the lack of solvents, which would both reduce overall time and costs of the process and be beneficial to product stability. Moreover, the operating temperatures could limit microbial contamination and enhance bioavailability of the active substances conveyed by promoting drug-polymer interaction with the formation of solid dispersions. On the other hand, operating temperatures, which mainly depend on the rheological properties of the melt formulation, could impact on the stability of the drug and the excipient as well as on that of the finished items (*e.g.* presence of by-products, shrinkage and warpage phenomena). In this respect, the main formulation approach is represented by the identification of suitable plasticizers to lower the processing temperature, also including the possibility of using temporary plasticizers such as water (Baldi et al., 2017; Goyanes et al., 2017b, 2018; Okwuosa et al., 2018; Pereira et al., 2019). The resulting items are generally characterized by good mechanical resistance, except when very highly porous structures are sought. On the other hand, surface smoothness often needs to be enhanced, optionally considering post-processing operations, as the layer deposition pattern can frequently be

distinguished and might affect patient compliance. Resolution could also be an issue, particularly when the presence of details represents a critical parameter for the performance of the printed item. As already happened with the technological transfer of other hot-processes (*e.g.* HME and IM) to the drug delivery field, the real challenge for the FDM is currently related to the formulation step (Kallakunta et al., 2019; Sarabu et al., 2019; Zema et al., 2012). The starting materials would need to fulfill the strict quali-quantitative limitations required to ensure quality, efficacy and safety of drug products. However, the overall quality of the printed items (*e.g.* mechanical properties, release performance, stability) would also result from the impact of the thermo-mechanical properties of the materials (*e.g.* such as heat capacity, thermal conductivity, density, glass transition temperature) on the operating conditions. These parameters are much more numerous than the ones that could actually be set by the majority of the printers available on the market, which are conceived with closed software/hardware allowing just a limited number of changes to be introduced by the end-user. Among the others, useful parameters to be set would for example include flow rate, loading pressure, feed rate, temperatures and relevant control (of the heating chamber and build plate), nozzle diameter, deposition rate, layer height, infill percentage, number of shells, insulation of the printer from the external environment. In this respect, preliminary attempts at manufacturing of drug products were mainly feasibility studies, during which commercially available filaments were employed and standard operating conditions, already envisaged in the built-in software of the equipment, were set. Only very recently, studies aimed at evaluating the impact of FDM variables on the characteristics of the finished products have started to be carried out, also thanks to the exploitation of more advanced software enabling independent modification of single parameters (*e.g.* Simplify 3D, Slicer, Cura) (Aho et al., 2019; Feuerbach et al., 2018; Heras et al., 2018; Markl et al., 2017, 2018; Trenfield et al., 2018c).

3. Aim

During the first experiments with the application of FDM in the pharmaceutical field, feasibility of dosage forms with simple design (*i.e.* monolithic units, films) was evaluated. Systems with increasing complexity in both geometry and composition were then taken into account. Indeed, when a limited number of units has to be produced, FDM would be characterized by unique geometry versatility and cost-effectiveness with respect to other techniques providing a comparable degree of freedom. Multilayered, coated, hollow and pierced items as well as devices with gradient composition were thus proposed. Some of them were meant for either novel or uncommon therapeutic needs (*e.g.* microneedles for transdermal drug delivery, biodegradable prolonged-release projectiles for administration of contraceptive to wildlife), thus possibly proving the flexibility of FDM (Luzuriaga et al., 2018; Tagami et al., 2019). However, the majority of drug products described so far were intended for the oral route and for implantation, while other administration modes were subsequently considered to broaden the application range of such a technique (*e.g.* topical, vaginal, rectal and ear routes) (Agrahari et al., 2017; Lim et al., 2018; Long et al., 2018; Preis et al., 2015).

The number of articles published on FDM has started to grow exponentially, and the systematic description of all the relevant printed systems has already been covered (Hsiao et al., 2018; Lim et al., 2018). The aim of the present review is to discuss the use of FDM 3D printing to obtain systems for the manufacturing of which traditional technologies have shown limitations in terms of costs and time for development, or of sustainable scalability towards batches of reduced size. In this respect, the fabrication of hollow systems comprising one or more inner compartments and intended for oral delivery will be considered. Particularly, devices composed of either two or multiple parts to be filled and assembled after production were taken into account along with those entailing an outer shell and an inner core that were concomitantly manufactured. Referring to the fabrication of traditional dosage forms, the former kind of printed devices would resemble hard-gelatin capsules while the latter systems may recall softgels. In the case of hollow systems fabricated and filled in a single manufacturing process, the core could be a liquid, a semisolid or a solid formulation that

should only be loaded into the shell. When the solid core and the outer shell are concomitantly manufactured by FDM, which means that the deposition of the shell material alternates with that of the core in each layer, the resulting product is generally reported to be a coated system and will not be considered here. Indeed, in this case the shell and the core grow together and no filling step would be envisaged. On the other hand, devices for which the solid core was previously printed by FDM and then simply inserted into the shell during its fabrication were included among the systems reviewed. Only the primary scientific literature relevant to hollow systems to be orally administered was taken into account, while information reported in patents has purposely been left out. Indeed, the great majority of printed hollow systems proposed so far are intended for the oral route, except for a few examples meant for other administration modes, such as implants and suppositories (Tagami et al., 2019; Weisman et al., 2019).

4. Overview of hollow systems

4.1 Systems composed of parts to be assembled after fabrication

Basically, hollow systems composed of printed parts to be assembled after fabrication are devices resembling the design concept of hard-gelatin capsules, *i.e.* shells produced in the form of matching parts delimiting cavities (*i.e.* compartments) that may or may not be filled. In the present manuscript, all the research articles proposing such devices, including first attempts aimed at demonstrating the feasibility of these systems in their simplest configuration (*i.e.* two matching parts bordering a single inner cavity), and later ones focused on hollow structures with increased geometrical complexity (*e.g.* many matching parts and multiple internal compartments), were reviewed and described. Outlines of hollow systems analyzed in this review, aimed at highlighting the relevant peculiarities discussed by the authors, are depicted in Figure 1.

4.1.1 Systems with a single compartment

Starting from devices previously manufactured by IM, Melocchi and coauthors were first in exploring the potential of FDM for fabrication of capsular devices (Melocchi et al., 2014, 2015). In such devices, the polymeric layer of reservoir dosage forms was replaced by a release-controlling shell composed by a cap and a body to be filled after preparation (Gazzaniga et al., 2011; Briatico Vangosa et al., 2019; Casati et al., 2018; Zema et al., 2013a,b). This would provide benefits in terms of time-to-market and costs of the final delivery systems. In fact, the release performance was mainly determined by the composition and design features (*e.g.* morphology and thickness) of the shell, thus enabling independent development of the conveyed formulation and the capsule, also limiting relevant compatibility issues. Thanks to the experience gained with hydrophilic cellulose derivatives, feasibility of IM in the fabrication of capsular devices for pulsatile/colonic release was first approached using HPC, and the resulting system was registered under the name of Chronocap® (Foppoli et al., 2019; Gazzaniga et al., 2012; Maroni et al., 2016; Zema et al., 2007, 2013c). By developing CAD files from the technical drawings of the 600 µm thick Chronocap® mold and HPC-based filaments, as well as by adjusting the geometry features and the formulation several times, capsular devices with both technological characteristics and interaction behavior with aqueous fluids analogous to those produced by IM were obtained. This was one of the rare examples of application of FDM for real-time prototyping objectives.

Feasibility of enteric soluble capsules was then explored, approximately 5 years later, by Nober and colleagues, who identified a strong need for extemporaneous preparation of these systems within pharmacies and hospitals (Nober et al., 2019). In fact, when dealing with drugs to be protected inside the stomach environment, gastroresistant capsules are achieved through a time-consuming process, which entails dipping of hard-gelatin capsules into an organic solution of cellulose acetate phthalate. The use of organic solvents, however, is reported to be risky, as they are flammable, toxic, dangerous for the environment and the operators, and any possible residual traces within the product might be hazardous for patients (Foppoli et al., 2017). Moreover, the efficacy of this coating method may be erratic and lead to therapeutic failure. Three different sizes of shells,

231 resembling size 0, 00 and 000 hard-gelatin capsules, were designed with a nominal thickness of 400
232 μm. A challenging limitation encountered by the authors was that of the feasibility of working with
233 in house-made filaments. They identified as suitable a mixture composed of pieces of commercially
234 available PLA filament, Eudragit® L 100-55 and PEG 400 as the plasticizer. Being an insoluble
235 polymer with well-known printability, PLA was added to the formulation in the lowest possible
236 amount (10% w/w) to both reinforce the areas of the capsule known to be particularly weak (*i.e.*
237 domes and matching area between the cap and the body) and enable the FDM process, particularly
238 during deposition of the first layer. Overall, the process was quite time-consuming, requiring up to
239 48 min to print a size 000 capsule. Despite the setup work, systems filled with riboflavin-5′-
240 phosphate sodium and characterized by the most complex locking mechanism (*e.g.* the screw-type
241 one) were discarded due to resolution limits and failure in resistance to the acidic environment.
242 Only a simple capsule shape was demonstrated able to fulfill the Eur. Pharm. 9.8. criteria for oral
243 enteric products, *i.e.* < 10% release after 2 h in HCl 0.1 M.
244 The problem of the availability of filaments based on pharmaceutical-grade polymers and suitable
245 for 3D printing by FDM was first systematically approached by Melocchi and colleagues (Melocchi
246 et al., 2016). A variety of pharmaceutical-grade materials were tested, identifying suitable
247 formulation and processing conditions for both HME and FDM. Disk-shaped specimens having
248 thickness on the order of hundreds of microns were thus printed starting from filaments of polyvinyl
249 alcohol-polyethylene glycol graft copolymer (*i.e.* Kollicoat® IR), PEO, HPC, HPMC, PVA,
250 polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (*i.e.* Soluplus®), EC,
251 methacrylic acid copolymers (*i.e.* Eudragit® L 100-55 and Eudragit® RL), and HPMCAS. The
252 feasibility of fabricating multiple overlaid disks was also demonstrated. These screening items
253 proved advantageous to investigate both the processability of the polymeric filaments and the
254 potential for printing barriers, *i.e.* capsule shells and cosmetic or functional coating layers. In
255 addition, this work could represent a reference for a variety of further products, such as tablets and
256 matrices, that could be obtained by incorporating active ingredients into the filaments.

A further step in terms of design complexity of hollow systems was performed by few other research groups who undertook the fabrication of floating low-density gastroretentive capsules intended for the administration of drugs with an absorption window limited to the upper gastrointestinal tract or a therapeutic target within the stomach. Gastroretentive delivery systems were generally achieved by different strategies such as expansion, low-density floatation, high-density sedimentation as well as adhesion to the stomach walls, and are generally intended for the prolonged release of drugs (Altreuter et al., 2018; Kirtane et al., 2019; Liu et al., 2019; Maroni et al., 2020; Melocchi et al., 2019b). Charoenying and colleagues investigated the feasibility of a capsule-like floating device for local treatment of *Helicobacter pylori* resembling the design concept proposed in Melocchi et al., 2015, (Charoenying et al., 2020). The system was composed of matching cap and body parts designed for housing a commercially-available drug product containing amoxicillin (*i.e.* Sia-Mox® capsules). The closed printed capsules were conceived to be 2 mm longer and 2 mm wider than the Sia-Mox® ones they were intended to contain, thus leaving an empty space, possibly enabling buoyancy, between the inner 3D printed surface and the outer wall of the conveyed capsule. Cap and bodies were printed using a commercial PVA filament and then subjected to heat treatments (*i.e.* 20, 140 or 160 °C for 2 and 6 h) in order to promote crosslinking of the polymer. This would change its interaction properties with aqueous fluids, making the shell insoluble. After initial removal of water, the treatment progressively caused an increase in PVA crystallinity and changes in the arrangements of polymeric chains, as highlighted by TGA and FT-IR. By increasing the heating time and temperature, the device became progressively insoluble, with a concomitant reduction in water uptake capability. On the other hand, darkening of the shell was observed and attributed to thermal degradation of PVA. Buoyancy of the system was demonstrated, which could be attributed to the low density of the printed parts and might also depend on the presence of the empty space between the inner and the outer capsules. Notably, *in vitro* experiments pointed out no lag time before onset of buoyancy and total floating time ranging from 5 to 72 h, depending on the extent of crosslinking achieved. 10 h buoyancy was also obtained *in vivo* with

New Zealand rabbits. The performance of the PVA-based devices before crosslinking was characterized by a lag phase followed by slower release (*i.e.* approximately 90% of amoxicillin released in 90 min) than the immediate-release Sia-Mox® capsules. By complete crosslinking of the PVA shell, an insoluble non-releasing system was achieved, whereas only slow diffusion of the drug through the partially crosslinked wall was observed until small openings were formed. Indeed, these increased the rate of aqueous fluid penetration up to detachment of the cap from the body, which enabled release of the remaining amoxicillin.

4.1.2 Systems with multiple compartments

4.1.2.1 Partly empty systems

Following demonstration of feasibility of hollow systems having rather simple design, increasingly complex structures (*i.e.* multi-compartment systems) drew the researchers' attention. In this respect, research groups working on gastric retention proposed the idea of decoupling the compartment for drug loading and release control from the void space that would be responsible for floatation, thus leading to devices with multiple inner cavities to be left partly empty.

Huanbutta and Sangnim developed a gastroretentive floating device for the treatment of peptic ulcers associated with the presence of *Helicobacter pylori* (Huanbutta and Sangnim, 2019). It was envisaged in the form of a shell comprising a body in which a metronidazole-based immediate release tablet was housed, and a matching cap comprising the buoyancy-responsible void space. A single orifice enabling drug release was placed on the bottom of the body. The feasibility of the cap and body parts was only proved with commercial PVA and ABS filaments, leading to assembled systems with cylindrical, conical and spherical shapes. Only the cylindrical system proved worthy of development. The influence of shell thickness, composition and dimension as well as that of the opening size on drug release, overall floating time and lag-time before floating was evaluated.

Shin and coauthors developed quite an original hollow system composed of two separated semi-cylindrical parts, a body and a cap, to be assembled on their longitudinal axis, leading to the

formation of three internal compartments: two closed empty compartments operating as air pockets at each end of the capsular device, and a central compartment allowing conveyance of a drug-containing dosage form (Shin et al., 2019). As the shell was composed of an insoluble polymer, purposely-designed openings were envisaged in the wall of the central compartment to enable drug release. Once again, the identification of materials approved for oral use was postponed by manufacturing the system from a commercially available PLA filament. An acyclovir-containing prolonged-release matrix was conveyed in the shell, and different number, shape and size of the openings were tested to fine-tune the release kinetics. The final design of the device (*i.e.* 5 rectangular windows representing 60% of the overall area) was characterized by opening sizes suitable for slowing down drug release while retaining the inner core until exhausted. The system obtained was proved able to float for more than 24 h *in vitro* and the time corresponding to 80% release of the active ingredient from the inner matrix was approximately 2.5 h. It was also evaluated *in vivo* following oral administration to Beagle dogs and, by floating for more than 12 h, the device allowed the attainment of prolonged acyclovir plasma concentration profiles over about 20 h.

An analogous floating system fabricated starting from a commercially available PLA filament was developed by Fu and coworkers (Fu et al., 2018). It was obtained by assembly of two matching parts able to define two inner closed compartments. The former was supposed to remained empty to ensure buoyancy, while the latter was intended to contain an immediate-release dosage form and exhibited different surface openings (*i.e.* mesh net). The system was developed for the administration of riboflavin and was named by the authors as "tablet in device". Notably, the authors came up with this design after they unsuccessfully tried to directly fabricate by FDM, starting from PLA/PCL filaments containing riboflavin, prolonged-release floating devices. While these were demonstrated able to float, no release was observed. One of the key points during the subsequent design phase was to have enough void volume to ensure floating while keeping the overall device dimensions suitable for easy swallowing. Both single- and double-net devices were proposed, entailing a closure system (*i.e.* two holes in the body matching bulges on the cap). In the

single-net configuration, the capsule body enclosed a sealed air-filled chamber and an open chamber, in which a soluble non-disintegrating tablet would be placed before closing with the matching cap provided with a mesh structure. In the double-net design, the body exhibited two different compartments: the former chamber was purposely devised for housing the tablet, and therefore its bottom was closed with a net, and the second chamber was devised to remain empty. In this configuration, the cap exhibited a net area, perfectly matching the body chamber for tablet holding, and an internal septum to ensure sealing of the air containing compartment. As expected, based on the increase in the tablet area exposed to aqueous fluids, during *in vitro* studies single-net systems exhibited slower drug release than double-net ones, and both of them were characterized by long-lasting floating. Prolonged *in vivo* gastric floating (> 72 h) in rabbit model was demonstrated by performing computerized tomography. Notably, further improvement in terms of duration of release could be achieved by working on the tablet formulation, thus making it a prolonged-release matrix itself.

4.1.2.2 Filled systems

The main goal addressed with hollow systems with multiple compartments to be filled, which would justify their more elaborate configuration, was an enhanced versatility, for instance allowing conveyance of different active molecules and achieving multiple release kinetics upon administration of a single product. Moreover, modified release could be obtained from such devices for instance by changing the relevant geometry or combining different parts rather than using a variety of formulation adjuvants that would be typical of DDSs manufactured by other techniques.

Maroni and coworkers improved the versatility and flexibility of the first proposed capsular devices by conceiving shells comprising multiple inner compartments (Maroni et al., 2017). This was achieved by combining three modular parts: two hollow halves differing in thickness and composition and a middle part acting as a joint and a partition. The selected thicknesses were 600 and 1200 µm, thus involving two CAD files for the hollow parts and three for the joints so as to

361 enable assembly of halves having same or different thickness. Such a device could be filled with
362 various drugs, also incompatible, or with different doses/formulations of the same one. Filaments
363 employed for printing the capsule halves were prepared by HME based on promptly-soluble,
364 soluble/swellable and soluble at specific pH values pharmaceutical-grade polymers, such as
365 Kollicoat® IR, HPMC, and HPMCAS. Because only the composition and shell thickness were
366 responsible for the release performance of each compartment, systems showing different two-pulse
367 release kinetics were attained by combining compartments having different characteristics. The
368 possibility of manufacturing such capsular devices *via* IM was also investigated as this process
369 would better fit larger production volumes that may be advantageously used for the development of
370 customized dietary supplements. In this respect, the delivery platform was further improved to
371 comprise 3 inner compartments of different volume and to be housed, once assembled, in a
372 gastroresistant capsule shell (Melocchi et al., 2019c). Moreover, a capsular device entailing 400 and
373 800 µm thick compartments, both based on HPC (Klucel™ LF), was considered for the industrial
374 development of customized dietary supplements (Melocchi et al., 2018). Notably, FDM would need
375 further studies before being reliably used for manufacturing of products intended for safe human
376 consumption. Indeed, only preliminary administration trials were carried out so far on human
377 volunteers, for instance to qualitatively evaluate taste masking properties of the drug products
378 obtained (Scoutaris et al., 2018). In this respect, the compliance of the entire production process,
379 including extrusion of the polymeric filament and capsule printing, with the cGMPs for dietary
380 supplements was faced by Melocchi and colleagues. Relevant pilot plants were set up and studies
381 aimed at demonstrating the stability of the starting material after two subsequent hot-processing
382 steps were undertaken. Critical process variables and parameters that would serve as indices of both
383 intermediate and final product quality were identified. Data collected from thermal analyses (DSC
384 and TGA), FT-IR and ^{1}H-NMR, along with GPC and viscosity studies supported the quality and
385 safety of HPC after processing by HME and FDM. Moreover, an evaluation protocol was provided
386 that could be applied to other polymeric materials. Compliance of filament and printed parts with

USP monographs regarding elemental and microbiological contaminants in dietary supplements was finally assessed.

Genina and colleagues focused on the design of a dual-compartmental dosage unit, relying on the use of commercially available PLA and PVA filaments (Genina et al., 2017). The device was meant for ensuring physical separation of active ingredients widely employed together, as an anti-tuberculosis drug combo (*i.e.* rifampicin and isoniazid), and concomitantly enabling modulation of the relevant release profiles. Indeed, rifampicin and isoniazid are mainly absorbed from the stomach and in the intestinal environment, respectively. Moreover, stability and bioavailability of the former drug in the acidic medium was demonstrated to be impaired in the presence of dissolved isoniazid. These are the reasons why physical separation and pulsatile release would be of utmost importance for this drug combination. Such goals were achieved thanks to the design freedom typical of AM. The device was indeed conceived in the form of an insoluble PLA cylindrical container with a separation wall in the middle, perpendicular to its main axis, which was aimed at creating two separate compartments of 5 μL in volume for independent drug filling. The miniaturization of the system was required to enable administration to rats through their esophagus using a flexible cannula. As only the opposed ends of the cylinder were open, unidirectional release was allowed. Prolonged release of the conveyed drugs was obtained due to the formulation of the drugs in the form of PEO-based extruded products and their reduced area of interaction with aqueous fluids. Cylinders cut from the drug-containing extruded rods were loaded into the system compartments in order to avoid a second heating step. By closing one of the open ends of the cylinder with a PVA cap, the release of one drug could be deferred for the time necessary for the erosion/dissolution of the plug. The performance of the system was confirmed *in vitro* but some limitations were shown *in vivo*, probably due to resolution limits and printing imperfections, the impact of which may have been highlighted by hydrodynamic conditions encountered upon administration.

A commercially available PVA filament was also employed by Matijašić and colleagues to prove the feasibility of printing a concentrically compartmental can-capsule and a modular super-H

capsule, having walls with different thicknesses (Matijašić et al., 2019). As the dual-compartment dosage unit described before, these systems were intended for either administration of drugs that would benefit from release at different time points or for the delivery of incompatible active ingredients. More into detail, the can-capsule was obtained upon assembly of a cylindrical cap with a cylindrical body. The latter was composed of two concentric cylinders, thus resulting in a double wall and two concentric compartments with approximately the same volume. Particularly, the overlapping area between the cap and the body was characterized by halved thickness to ensure an outer shell with the same thickness along all its length. The inner side of the cap was also designed to perfectly match and close the inner cylinder of the body. The system pointed out a two-pulse release profile. Overall, the release performance was modulated by changing the wall thickness of each compartment. On the other hand, the super-H capsule was obtained upon combination of three different parts, *i.e.* an internal cylindrical H-structure with a central 1.5 mm thick septum, and two cylindrical caps for insertion onto each of the open ends of the H-shaped body. The closed end of the caps, *i.e.* the bases of the two open cylinders, were designed with different thicknesses (*i.e.* 0.2, 0.3, 0.4 or 0.5 mm). Because such bases constituted the least thick portions of the shell, they were responsible for defining the drug release profile. By combining the central H structure with caps having different base thicknesses, several release combinations were achieved. However, the base was also found to be the most challenging area to be printed due to the limited resolution of the equipment. By performing *in vitro* studies at different pHs and in biorelevant fluids, the authors demonstrated the ability of the system proposed to fine tune the release of model drugs (*i.e.* dronedarone hydrochloride and ascorbic acid). Printing problems (*i.e.* poor adhesion and presence of holes) turned out evident in the caps, particularly the area of junction between the release controlling base and the cylinder walls, which led to poor reproducibility of the release performance among different samples.

4.2. Systems fabricated and filled in a single manufacturing process

Hollow systems belonging to this category entail an inner core and an outer shell fabricated in a single manufacturing process. During FDM of the shell, the core was either filled with drug-containing formulations or left empty for enabling flotation. The former approach involved in some cases coupling of the FDM technique with other automatic or manual processes enabling, for instance, dispensing of liquid or powder preparations. This would not only improve the versatility of the systems proposed, but also broaden their applicability to active ingredients not stable under the FDM operating temperatures. Hollow systems here reviewed would resemble softgels for the presence of an external single-piece shell, in principle hermetically sealed. However, their mechanical characteristics would be more similar to those of hard-gelatin capsules. Outlines of the systems reviewed are depicted in Figure 2.

4.2.1 Systems with single/multiple compartments

4.2.1.1 Filled systems

First attempts at printing hollow systems in a single manufacturing process involved the use of standard printers with a single arm, although with the intention of applying a dual FDM extrusion for achieving the core and the shell. Kempin and colleagues initially evaluated the possibility of manufacturing an empty part by single extrusion, filling it with a previously printed drug formulation and finally getting back to the FDM process to complete the top part of the shell, with no need for closing the body with a separately printed matching cap (Kempin et al., 2018). In particular, the authors focused on the manufacturing of gastroresistant shells in which pantoprazole sodium-containing cores were conveyed. This is a challenging drug that is neither stable at acidic pH-values nor at high temperatures. Enteric soluble filaments were obtained by extrusion starting from various polymers, *i.e.* CAP, Eudragit® L 100-55 and HPMCP. On the other hand, drug-containing filaments based on PCL and PEG 6000 were used to build monolithic cores in view of the lower processing temperatures such polymers require. To attain the final system, fabrication of the shell was paused, the core was inserted into the hollow device obtained and FDM was restarted

to close the system with four additional layers. However, any minimal overhang of the core represented an obstacle to print the top layers that were also characterized by low mechanical stability. Even when the printing of the covering layers was successful, the systems showed a very poor mechanical resistance leading to breakup during removal from the build plate or handling.

Dealing with different formulations of the core (*e.g.* liquid, semisolid or particulate ones), the problem of drug filling was faced with that of integrity and mechanical resistance of the shell. The research activity carried out by Smith and coworkers was aimed at producing high-quality liquid-filled capsules (Smith et al., 2018a). Custom hardware and software were developed to attain, in a single manufacturing process, capsules containing water-based drug preparations. A feasibility study, with a strong engineering edit, was initially carried out using commercially available PLA/PVA filaments and printers. Afterwards, the equipment was in-house modified to develop a three-stage manufacturing process involving: *i)* fabrication of an open 400 µm thick shell, *ii)* relevant filling and *iii)* printing of the top layers leading to a fully sealed item. Indeed, the optimal configuration of the final system would exhibit a comparable thickness in all the areas of the shell, also after filling, and would provide enough support for printing the top part of the capsule, thus allowing effective closure. Printing was faced by splitting the shell into portions characterized by specific geometric features (*i.e.* zoning process). For each area a dedicated G-code was developed entailing specific operating parameters. The printing conditions were systematically modified for improving the overall product quality, decreasing the print-to-print variability and reducing the process time. Multiple adjustments of the electronic model were also required to define the best shell geometry, which turned out similar to that of a tablet with rounded edges. The equipment was provided with a 30 mL syringe for capsule filling. Unlike softgels, which mainly contain non aqueous fillings, these hollow systems were intended to convey a water-based formulation. However, swelling of the PVA layers and relevant delamination (*i.e.* detachment of two adjacent layers) occurred. Because the latter would be critical for mechanical properties and performance, a finite element analysis of tensile stresses generated during swelling was carried out. The study also

491 involved X-ray microcomputed tomography to highlight spatial uniformity and morphology of the
492 printed parts. As regards the formulation conveyed, PVA and HEC-based gels containing 15 % w/w
493 of metformin HCl were employed to identify a threshold value of viscosity above which continuous
494 filling could be attained. A G-code was purposely written to enable retraction of the syringe head to
495 minimize dripping and reduce the risk of water evaporation due to the high operating temperature
496 (206 °C) involved in the FDM process. The PVA-based hollow system obtained was proved able to
497 defer the release of its content as a function of the wall thickness. As a further development, it was
498 proposed as a platform to investigate regional absorption of drugs during pre-clinical studies, with
499 the final aim to identify the best release mode for new active molecules (Smith et al., 2018b).
500 Indeed, research and development stages of innovative DDSs are particularly time-consuming and
501 expensive and, currently, there is no straightforward and simple method for providing regional
502 absorption information. Double- or triple-lumen catheter systems are generally used, which are
503 based on the use of a tube to be inserted into the intestinal tract allowing to inflate balloons that
504 would be responsible for isolating a portion of the intestine during the experiments. However, these
505 are invasive procedures and would not be feasible as routine tests. As a step forward, IntelliCap®, a
506 quite expensive oral delivery system capable of investigating regional absorption, was proposed by
507 Medimetrics (Becker et al., 2014; Söderlind et al., 2015). In this respect, Smith and coworkers
508 evaluated the potential of FDM to prototype hollow systems with a range of wall thicknesses (400
509 µm - 2 mm), which would be able to provide programmable lag times before release and allow to
510 adjust the amount of drug to be conveyed without needing to retool manufacturing. Liquid and solid
511 formulations of two different drugs (*i.e.* lamivudine and a Merck's proprietary compound) were
512 considered. While liquid dosing was automated to ensure FDM of the shell and filling in a single
513 process following proper G-code instructions, solid granules or powder were conveyed by pausing
514 the printing and performing hand filling. Hollow systems, fabricated following the zoning process
515 above described, were manufactured with an increasing number of outer shells (*e.g.* 1, 3 and 5) to
516 attain different wall thicknesses while keeping the internal cavity volume equal to 300 µL. Notably,

it was necessary to develop an appropriate method, entailing in-house 3D printed baskets, for assessing the release performance of the system accounting for layer orientation in the printed shell, thus avoiding premature delamination phenomena. The data collected confirmed the possibility of exploiting the system proposed as an inexpensive and non-invasive tool for evaluating regional absorption in pre-clinical studies.

A similar approach was followed by Goyanes and coauthors, who focused on evaluating printed hollow items as a platform for pre-clinical trials (Goyanes et al., 2018). They carried out a pilot *in vivo* study demonstrating the potential of FDM in the preparation of hollow systems of small dimensions (*i.e.* analogous to size 9 hard-gelatin capsules) suitable for pre-clinical testing of drugs in animal models such as rodents. Small-sized capsular devices with shell thickness of 0.5 mm were conceived, able to overcome typical contractions of the gastrointestinal tract without damage, thus ensuring a reproducible drug release performance in different regions. Prototypes were fabricated by FDM starting from filaments based on Kollicoat® IR, HPC, EC and HPMCAS prepared by single-screw extrusion, also adding plasticizers (*i.e.* methylparaben, mannitol) and lubricants (*i.e.* talc, magnesium stearate) to the polymeric formulations. These devices were in principle provided with different release performance, depending on the mechanism of interaction with biological fluids of the relevant main component. A capsule shell with further reduced dimensions was manufactured using HPMCAS, in order to determine the cutoff size of gastric emptying in rats. The systems were fabricated using a commercially available printer, following adjustment of the printing temperature based on the filament used. X-ray micro computed tomography was employed to assess the quality of the printed devices. Capsules were manually cut, filled with a radiotracer (*i.e.* fluorodeoxyglucose) and reassembled, to avoid contamination of the printer with a filament loaded with the radiolabeled compound. However, the limited half-life of the latter and the small dimensions of the empty cavity of the capsules would be especially critical when moving to the preparation of these systems in a single process. Upon oral intake, transit and possible opening of the devices were tracked *via* small animal positron emission tomography and computed

tomography. The results obtained highlighted that all systems, also the HPMCAS-based ones with reduced size, were retained in the stomach without passing into the small intestine. Therefore, further studies with smaller capsules would be necessary in order to determine the cutoff size of gastric emptying in rats. Opening of Kollicoat® IR- and HPC-based devices occurred after 60 and 120 min upon oral administration, respectively. On the other hand, EC-based system did not release the radiotracer for 11 h. The HPMCAS-based device broke up after more than 420 min, which was attributed to its prolonged gastric residence. Indeed, the use of integrated information from the employed techniques would allow to collect data not only regarding radiopharmaceutical release but also about the anatomical position of the systems at different times with no need for invasive procedures, thus reducing the number of animals used for each analysis while increasing the number of measurements taken.

Markl et al. followed an engineering approach analogous to the previously described zoning process for the development of single-compartment and multi-compartment cylindrical shells containing different drug preparations (Markl et al., 2017). They first employed both commercially-available PLA and PVA filaments and filled the systems with carbamazepine powder. On the other hand, devices to be filled with self-nanoemulsifying formulations containing different drugs (*i.e.* saquinavir, halofantrine) were printed using a PVA filament only. The two-compartment systems entailed two cylinders one within the other, delimiting two concentric inner cavities. In all cases, the printing process was stopped to enable manual filling of the shells and then started again to close the structure. The authors specially focused on identifying methods to evaluate the quality of the printed units, *i.e.* quality control tests to be performed in a fast, non-destructive and efficient way. X-ray computed microtomography and terahertz pulsed imaging were compared as tools to study the microstructure of the printed parts (bulk porosity, pore volume and pore length), which is related to the printing resolution. Although X-ray computed microtomography provided very detailed information and would be beneficial in highlighting defects in the 3D printed structures, it involved long acquisition and reconstruction times (>1 hour). On the other hand, terahertz pulsed

imaging could represent an alternative quality control tool for fast acquisition of depth profiles (< 1 s), thus enabling the check of a higher number of samples. It was confirmed that the stop of the process negatively affected the product quality. For instance, the cylinder diameter slightly shrank and the pore structure turned out to be less consistent. Based on the polymer employed for manufacturing, the system exhibited different lag phases prior to drug release from each compartment. Release from the inner compartment started later, after approximately 240 min, when about 80% of the drug was released from the outer compartment.

Okwuosa et al. worked on printed hollow systems filled with liquid formulations to enhance the bioavailability of poorly soluble drugs. They focused on the achievement of shells able to reduce the incidence of drug migration and, by decreasing moisture and oxygen permeation, to improve the relevant stability with respect to softgels (Okwuosa et al., 2018). The characteristics of the printed shell could also provide better taste and odor masking. The authors fully automated and synchronized FDM with liquid dispensing, identifying as the main challenges effective sealing of successive capsule layers and filling with small volumes of liquid formulations (a model solution and suspension). A commercially available printer was modified by replacing one of the extruder heads with a home-made liquid dispenser entailing syringes of different capacity. For the shell fabrication filaments based on Eudragit® E (soluble at pH ≤ 5) or Eudragit® RL (insoluble and permeable), were used employing TEC as the plasticizer and talc as the reinforcement. A dipyridamole suspension (1.5% w/v) and a theophylline solution, both aqueous, were used as model filling preparations. 1.6 mm turned out the minimum shell thickness able to prevent leakage of the liquid during the printing process and storage. A cubic core was designed in order to simplify the calculations associated with the volume to be filled, setting it to be equal to 80, 160, 240 or 320 μL, and to limit the movement of the dispenser head within the space of the cavity. Both single-stage (entailing polymer deposition and liquid dispensation alternated for each layer) and multi-stages (entailing sequentially printing of the shell bottom, liquid filling and sealing of the shell) printing processes were tested, but only the latter turned out feasible. Filling accuracy in dispensing the

595 desired volume of liquid preparations was achieved with a 2 mL syringe. Only the system based on
596 Eudragit® E filled with the dypiridamole formulation pointed out a dissolution performance that met
597 the USP requirements for immediate-release products. On the other hand, extended release of drug
598 tracers, at a rate that could be modulated depending on the shell thickness, was obtained with the
599 capsules based on Eudragit® RL.
600 The hollow system proposed by Krause and coworkers was a pressure-controlled DDS based on
601 Eudragit® RS, chosen as the starting material in view of its water insolubility, pH independent
602 swelling properties, low permeability and brittleness (Krause et al., 2019). The idea came from data
603 published by Wilde and colleagues regarding small volumes of a highly concentrated drug solutions
604 released by a system triggered by the high pressure that is established in the antropyloric region
605 (Wilde et al., 2014). Such a pressure can reach 500 mbar concurrently with gastric emptying, so that
606 the release would occur in the small intestine. One of the major drawbacks of this delivery system
607 was the complexity of the production process, leading to poor reproducibility of the performance. A
608 capsule-like shell was designed and the G-code for its printing was purposely written. More than 35
609 adjustments were necessary to achieve a completely closed device. Each layer was oriented in
610 parallel with the circular cross section of the capsule, which was also fabricated as a single-walled
611 item without any support structure. Shells of different thickness, in the 250 - 550 µm rage, were
612 manually filled with a powder formulation containing acetaminophen by interrupting the printing
613 process. A specific procedure for the evaluation of mechanical resistance was developed based on
614 progressive inflation with pressurized air of a balloon inserted into empty capsules. As expected,
615 pressure values ranging from 200 to 900 mbar leading to breakup of the shell correlated with its
616 wall thickness. Drug release from the resulting prototypes was studied under biorelevant conditions
617 with the aid of a modified dissolution/stress test device. Initially, no release occurred, while the
618 entire dose was released within a short time when a pressure was exerted, confirming the expected
619 working mechanism of the system.

Zhao and colleagues proposed a modified-release system undergoing a change of geometry during interaction with aqueous fluids thus leading to a convex drug release profile (Zhao et al., 2018). Starting from a commercially available PVA filament, a spherical shell of 12 mm in diameter circumscribing an inner regular tetrahedron (pyramid) cavity was printed. Such an inner cavity was filled with an acetaminophen-containing PVA gel by drilling a 0.7 mm hole in the thinnest portion of the shell. This procedure was made necessary by the poor stability of the drug at the PVA processing temperature. However, it represented a first attempt. Indeed, in a further development of the system, the outer shell and the inner core would be printed together by two switchable nozzles. The progressive dissolution of the shell in aqueous fluids brought about a change in the surface area available for drug release with a consequent increase in the relevant rate. Accordingly, acetaminophen concentration was maintained until 300 min of testing and then quickly increased, finally reaching a peak value after 450 min.

4.2.1.2 Empty systems

Another type of hollow system was proposed, in which the inner cavity was supposed to remain empty to attain low-density and buoyancy needed for the development of gastroretentive DDSs. Chai and coworkers investigated the feasibility of a floating prolonged-release system containing domperidone (Chai et al., 2017). This was conceived as an empty cylinder having the external wall loaded with the active molecule and an inner low-density region, created by reducing the number of shells and the infill percentage, ensuring buoyancy. HPC-based filaments either containing the active ingredient (10% w/w) alone or with $BaSO_4$ (10% w/w) were produced by HME and used for printing shells with different dimensions and density of the inner cavity. $BaSO_4$ was added for enabling *in vivo* testing by X-ray images in an animal model (New Zealand rabbit). By way of example, when the internal area of the system was printed with 2 shells and 0% infill, density turned out 0.77 g/cm^3 and the system was demonstrated able to float *in vitro* for more than 10 h. $BaSO_4$-labeled devices turned out able to remain in the rabbit stomach for 8 h. The *in vivo* release

performance of the drug-loaded system was compared with that obtained following administration of a commercially available tablet containing domperidone. The data collected indicated that the printed device exhibited longer-lasting levels consistent with *in vitro* floating results, thus improving the oral bioavailability of the molecule in the animal model selected.

A similar approach to the development of a floating prolonged-release system was followed by Lamichhane and coworkers (Lamichhane et al., 2019). Starting from different polymers (*i.e.* HPMCAS, PVA, HPMC of different grades and types), formulations containing PEG 400 (0-10%) as the plasticizer and pregabalin (25-50%) as the active ingredient were in-house extruded. Pregabalin was selected as the drug candidate in view of its high melting temperature, the relatively short half-life and because it is known for being mainly absorbed into the stomach. Only the filament composed of HPMCAS, pregabalin and PEG 400 in the 50:40:10 *ratio* turned out suitable for being fed into the FDM printer. Cylindrical devices were printed, progressively reducing the infill percentage till 25% and also removing top and bottom layers to decrease the overall density. All the open systems sank immediately, whereas the closed ones showed excellent floating properties for more than 24 h. As expected, a faster drug release was found from closed devices printed with lower infill percentages. Such an effect was less marked in the case of the open devices due to the greater area already available for contact with biological fluids. Moreover, DSC studies demonstrated that pregabalin remained partly crystalline in the final system, while TGA data showed a 5% mass loss, which was associated with possible decomposition of the main polymeric component due to the double heating process undergone. The configuration envisaging 25% infill, a closed bottom layer and a partially opened top layer showed floating ability comparable with that of closed systems of analogous structure, and zero-order drug release kinetics. The prolonged-release performance was attributed to the maintenance of the polymeric structure based on HPMCAS in acidic environment and the limited diffusion of fluids (*i.e.* gastric fluid and drug solution) through the top opening of the system. However, the *in vivo* drawback of an insoluble floating system would be the elimination from the stomach.

Very recently, the same strategy for attaining low-density gastroretentive systems was also pursued by Chen and coworkers (Chen et al., 2020). They printed ellipsoid-shaped devices with different porosity (25% and 15% of infill) starting from in-house extruded filaments composed of PVA and glycerol as the plasticizer, and containing propranolol hydrochloride. The latter was identified as a suitable model drug in view of its already proven suitability for hot-processing and stability as well as enhanced solubility in the acidic environment, associated with half-life issues. Besides being easy to swallow, ellipsoid-shaped systems would be characterized by less close printed inner grids, which would ensure enough void volume for floatation. However, with infill percentages lower than 15% it was not possible to avoid collapse of the structure when the top layers were printed. By adjusting other process parameters (*e.g.* flow rate, printing and build plate temperature, printing speed while extruding and moving) prototypes with satisfactory characteristics in terms of weight, drug content, density, hardness, floating and release rate were obtained. In particular, relative standard deviation of the weight < 5%, drug content in the 95-105% range, density of 0.674 g/cm^3 and 0.877 g/cm^3 for items printed with 15% and 25% infill percentages, respectively, were attained. Floating in HCl 0.1 M was observed for all the prototypes immediately after starting the *in vitro* test and lasted for approximately 2 h only, which was associated with the dissolution rate of the low molecular weight PVA employed. For the same reason, the systems pointed out a prolonged release pattern limited to 4 h overall. As expected, different infill percentages resulted in diverse drug content and release rate.

Kimura and coauthors modified the floating system described by Chai et al., in order to achieve a zero-order release (Kimura et al., 2019). Their approach was based on a dimensional change of the device during interaction with aqueous fluids, which would lead to a progressive increase of the area available for drug release. A hollow cylindrical structure with a greater number of overlapped shells on the lateral walls than on the bases was printed. As the lateral walls were expected to dissolve/erode faster, the device entailed them in the 0.5 - 1.5 mm range and upper and bottom surfaces in the 0.3 - 0.5 mm range. Itraconazole was selected as the model drug and, for

manufacturing of filaments, PVP was added to HPC because of its ability to form a solid dispersion with the poorly water-soluble drug. The active molecule was found completely amorphous only in the printed samples probably due to the use of a higher temperature with respect to HME (> of the melting point of crystalline itraconazole). Depending on the number of shells on the side walls, and therefore on the overall density of the system, the items floated for different times (from a few min to 540 min) in gastric fluid. A nearly zero-order *in vitro* drug release was achieved by adjusting the thickness characteristics of the shells.

4.2.2 Complex systems

In the field of hollow systems fabricated and filled in a single manufacturing process, more complex devices were also proposed. Gioumouxouzis and colleagues developed a colonic delivery system based on the use of polymers with pH-dependent solubility (Gioumouxouzis et al., 2018). The system was filled with uncoated and chitosan-coated alginate beads containing 5-fluorouracil. Such a drug, which is toxic against small-intestine mucosa, is slowly absorbed from the large intestine, which may also decrease the risk of myelosuppression induced by relevant high concentrations in the blood. Moreover, the printed device would allow the need for customized doses to be addressed. A cylindrical hollow structure with smoothed edges was conceived, comprising insoluble parts (*i.e.* wall and top base) and a bottom thin base (200 µm) with pH-dependent solubility. The system would be able to attain one-directional release following the thin base dissolution. The insoluble structure was printed with a commercial PLA filament, while for the thinner part a filament based on Eudragit® L100-55 and Eudragit® S100, soluble at pH > 5.5 and 7.0, respectively, was prepared by HME. A double-nozzle equipment was employed. Infill was set to 30% and three outer shells were conceived to ensure lateral impermeability of the system. Due to these printing parameters, and in particular to the infill value, the system was not completely void but entailed an inner grid. The top base was 1.2 mm thick to ensure sinking by increasing the weight of the device. Either chitosan-coated or uncoated drug-containing beads were loaded by pausing the FDM process before

completion for manual filling and restarting printing afterwards. The integrity of the hollow structure in increasing pH media (from 1.2 to 7.4) was assessed by means of time-lapsed microfocus computed tomography. The system was shown able to resist *in vitro* in pH 1.2 medium, and release about 40% of drug content in the first 2 h of testing at pH 7.4. The rate of release after dissolution of the thin base of the shell was dependent on the presence of the chitosan-based coating on the beads.

Another example of pH-sensitive colonic delivery system, named "printfill", was fabricated by Linares and colleagues using a particular bioprinter that incorporates a second technology, *i.e.* IVF (Linares et al., 2019). The combination of FDM with IVF enables handling of starting materials with very different characteristics and, in the biomedical field, was employed for the fabrication of scaffolds layer-by-layer filled with living cells. The authors used such an equipment, provided with one FDM head and two IVF syringes, for the manufacturing of a device entailing a backbone structure with an internal quadrilateral mesh (1.2 × 1.2 mm), printed with a commercially available PLA filament. Two different formulations were injected into the backbone in pre-determined 3D positions (at the18th and 22nd layer of the PLA scaffold): a hydro-alcoholic HPMC gel containing theophylline as a model drug and a Eudragit® FS30D dispersion, respectively. The cylindrical PLA framework had only a support function and for this reason its continuity was verified by SEM analysis. In order to avoid too early drug release, the base of the PLA cylinder was printed by overlapping 2 layers and the external walls entailed 4 shells. First, 200 µL of the hydroalcoholic gel were injected into 4 different points, digitally defined to ensure uniform drug distribution inside the scaffold, and then 350 µL of Eudragit® FS30D dispersion was added to close the structure. Once the device was completely built, it was let dry at room temperature for 24 h, to allow solvent evaporation and creation of a continuous Eudragit® film above the theophylline-containing reservoir. The release would occur from the upper side of the system only, following dissolution of the pH-sensitive film, which was approximately 150 µm thick. Indeed, in pH 1.2 the system released just 2.3% of the drug conveyed, while in pH 7.5 aqueous medium the amount of drug

released suddenly increased, reaching 80% in 8 h. Systems having an analogous structure and composition but printed without Eudragit® FS30D released about 60% of the model drug in the first 5 min of testing. The main drawback associated with the infilling technology is the limited drug load achieved so far (0.36%).

5. Conclusions

In the last five years, a great interest was raised by FDM for the manufacturing of drug products. This was attributed to the limited costs of equipment commercially available, most of which would easily be hackable by the users thus resulting interesting for lab settings, and to the possibility, in principle, of using thermoplastic polymers of pharmaceutical grade as starting materials. In the present work, only hollow systems intended for oral delivery of active molecules have been reviewed. Such devices have been distinguished into two main categories based on the manufacturing approach: *i)* systems composed of parts to be filled and assembled after printing and *ii)* items in which the outer shell and the inner core were manufactured in a single process. According to the geometry complexity of the systems considered, their key formulation, manufacturing and performance characteristics are summarized in Table 1.

Table 1: Hollow systems reviewed and relevant characteristics; grey and white backgrounds refer to devices composed of parts to be assembled after fabrication and fabricated/filled in a single manufacturing process, respectively.

		STARTING MATERIALS	PERFORMANCE	EQUIPMENT	REFERENCES

SYSTEMS WITH A SINGLE COMPARTMENT	FILLED	**SHELL**
		- commercially available PVA filament
		- in-house made filaments based on
		  - HPC, PEG 1500
		  - pieces of commercially available PLA filament, Eudragit® L100-55, CAP, PEG 400, diethyl phthalate
		
		DRUG-CONTAINING CORE
		- powder formulations (*e.g.* dyes, acetaminophen, riboflavin-5′-phosphate sodium)
			Gastric resistance and pulsatile release	**EXTRUDER**
				- conical twin-screw extruder (HAAKE™ MiniLab II, Thermo Fisher Scientific)
				- parallel twin-screw extruder (Process 11, Thermo Fisher Scientific)
				
				PRINTER
				- MakerBot Replicator 2 (Makerbot Industries)
				- purposely-modified MakerBot Replicator 2 (Makerbot Industries)
					Melocchi et al., 2015; Nober et al., 2019.

		SHELL
		- commercially available PLA and PVA filaments
		- in-house made filaments based on
		  - CAP
		  - Eudragit® L 100-55
		  - Eudragit® L and TEC
		  - HPMCP
		  - PCL
		  - Kollicoat® IR, methylparaben, mannitol, talc and magnesium stearate
		  - HPC, mannitol and magnesium stearate
		  - EC, methylparaben and magnesium stearate
		  - HPMCAS, methylparaben, talc and magnesium stearate
		  - Eudragit® EPO, TEC and talc
		  - Eudragit® RL, TEC and talc
		  - Eudragit® RS 100
			Gastric resistance; immediate, prolonged and pulsatile release; pressure-controlled and convex release	**EXTRUDER**
				- conical twin-screw extruder (HAAKE™ Mini CTW hot melt compounder, Thermo Fisher Scientific)
				- single-screw filament extruder (Noztec Pro hot melt extruder, Noztec)
				- Three-Tec ZE 12 twin-screw extruder (Three-Tec GmbH)
				- in-house built single- and twin-screw extruders
				
				PRINTER
				- Creator Pro (FlashForge)
				- dual extrusion Multirap M420 (Multec GmbH)
				- MakerBot Replicator 2x (Makerbot Industries)
				- Mendel Max 2.5 (German RepRap GmbH)
				- Ultimaker 2+ (Geldermalsen)
				- purposely-modified MakerBot Replicator 2x (Makerbot Industries)
				- purposely-modified Hyrel 3D System 30M printer (GA)
					Goyanes et al., 2018; Kempin et al., 2018; Krause et al., 2019; Markl et al., 2017; Okwuosa et al., 2018; Smith et al., 2018a, b; Zhao et al., 2018

		DRUG-CONTAINING CORE - FDM units based on in-house made filaments (*e.g.* pantoprazole sodium sesquihydrate) - gel formulations (*e.g.* metformin, proprietary Merck's compound) - powder formulations (*e.g.* dyes, carbamazepine, lamivudine, acetaminophen and mannitol) - solutions and dispersions (*e.g.* dipyridamole, theophylline)			
	PARTLY EMPTY	**SHELL** - commercially available PVA filament **DRUG-CONTAINING CORE** - commercially available capsule (*e.g.* amoxicillin)	Gastric retention by floating and prolonged release	**PRINTER** - Prusa i3 MK3 (Prusa Research)	Charoenying et al., 2020
	EMPTY	**DRUG-CONTAINING SHELL** - in-house made filaments based on - HPC, $BaSO_4$, domperidone - HPC, PVP, itraconazole - HPMC, HPMCAS, PEG 400, pregabalin - HPMC, PEG 400, pregabalin - PVA, glycerol, propranolol hydrochloride	Gastric retention by floating and prolonged release	**EXTRUDER** - conical twin-screw extruder (HAAKE™ Mini CTW hot melt compounder, Thermo Fisher Scientific) - parallel twin-screw extruder (Process 11, Thermo Fisher Scientific) - single screw extruder (Original EX2 and FOV1, Filabot®) **PRINTER** - 4025-MP FDM printer (3D Korea, Yongsin-ri) - MakerBot Replicator 2x (Makerbot Industries) - MF2200-D (Mutoh industries)	Chen et al, 2020; Chai et al., 2017; Kimura et al., 2019; Lamichhane et al., 2019
SYSTEMS WITH MULTIPLE COMPARTMENTS	**FILLED**	**SHELL** - commercially available PLA and PVA filaments - in-house made filaments based on - HPC - HPC and PEG 1500 - HPMC and PEG 400 - HPMCAS and PEG 8000	Combinations of differing release kinetics (*i.e.* gastric resistance, immediate, pulsatile, prolonged)	**EXTRUDER** - conical twin-screw extruder (HAAKE™ MiniLab II, Thermo Fisher Scientific) - twin-screw compounder (DSM, ®XPLORE) - purposely-developed single-screw extruder (Gimac) **PRINTER**	Genina et al., 2017; Maroni et al., 2017; Matijašić et al., 2019; Melocchi et al., 2018, 2019c.

		- Kollicoat® IR and glycerol - PVA and glycerol **DRUG-CONTAINING CORE** - extruded rods (*e.g.* isoniazid) - powder formulations (*e.g.* dyes, acetaminophen, caffeine)		- Kloner3D 240® Twin (Kloner3D) - Inventor I printer (Flashforge) - Ultimaker 3 extended printer (Geldermalsen) - purposely-modified MakerBot Replicator 2 (Makerbot Industries) - purposely-modified Type A printer (Type A Machines)	
		SHELL - commercially available PLA and PVA filaments **DRUG-CONTAINING CORE** - self-nanoemulsions (*e.g.* saquinavir)	Pulsatile release	**PRINTER** MakerBot Replicator 2 (Makerbot Industries)	Markl et al., 2017
	PARTLY EMPTY	**SHELL** - commercially available ABS, PLA and PVA filaments **DRUG-CONTAINING CORE** - immediate-release tablets (*e.g.* metronidazole) - prolonged-release matrices (*e.g.* riboflavin)	Gastric retention by floating and prolonged release	**PRINTER** - F-12410B (Manli Technology Group) - Raise3D N2 (Raise3D, Inc.) - UP mini2 (Tiertime)	Fu et al., 2018; Huanbutta and Sangnim, 2019; Shin et al., 2019.

COMPLEX SYSTEMS		**SHELL**
		- commercially available PLA filament + in-house made filaments based on
		  - Eudragit® L100-55 and TEC
		  - Eudragit® S100 and TEC
		  - Eudragit® L100-55, Eudragit® S100 and TEC
		- commercially available PLA filament + Eudragit® FS30D suspension
		
		DRUG-CONTAINING CORE
		- beads (*e.g.* 5-fluorouracil)
		- gel formulations (*e.g.* theophylline)
			Delayed release and pH-dependent colon delivery	**EXTRUDER**
				- single-screw extruder (Original EX2, Filabot®)
				
				PRINTER
				- MakerBot Replicator 2x (Makerbot Industries)
				- Regemat 3D V1 printer (Regemat 3D)
					Gioumouxouzis et al., 2018; Linares et al., 2019

739 Independent of the fabrication mode (*i.e.* printing of the parts and relevant assembling after
740 production, or printing and filling of the systems in a single manufacturing process), hollow items
741 progressed from resembling the well-known design concept of hard- and soft-gelatin capsules
742 towards more complex configurations, entailing multiple inner compartments and combined release
743 kinetics. Such an evolution highlights the greater versatility of FDM with respect to other traditional
744 manufacturing processes, especially in terms of geometric freedom. However, the feasibility of a
745 large number of the hollow systems proposed was only evaluated with commercially available
746 filaments purposely developed for FDM, which were not of pharmaceutical grade. Consequently,
747 the resulting prototypes might not be representative of the final systems in terms of both physico-
748 technological characteristics and performance. By way of example, micrometric details responsible
749 for appropriate functioning of the system (*e.g.* openings for release, overlapping portions for correct
750 part matching) were shown to require high reproducibility and printing resolution, which would
751 have to be reproduced also with the final formulation composed of materials already approved for
752 oral administration. In this respect, filaments with measurable and comparable printability
753 characteristics as those already available on the market would be worth developing. While such a
754 topic has been approached with regard to monolithic drug products (*i.e.* not entailing cavities), it
755 still needs to be deepened in the field of hollow systems for which 3D printing feasibility was
756 demonstrated to be particularly challenging. At the same time, only preliminary attempts were made
757 to better understand the printing process itself, the impact of item design and operating conditions
758 on features identified as critical quality attributes for the final system and how to fine-tune the
759 printing parameters for the achievement of the desired characteristics. Even though separating the
760 fabrication of the outer shell from that of the conveyed formulation could ease the development of
761 the final device, stability and quality of both these elements may benefit from further investigation.
762 Coupling FDM with other automatic processes for the dispensing of mainly liquid and semisolid
763 formulations was adopted to broaden the range of active ingredients that may be conveyed in
764 hollow systems, also including thermosensitive ones. However, during dosing, an increase in the

765 temperature of the drug preparation may occur due to contact of the filling with the item under
766 fabrication, which needs to be maintained at the proper temperature to ensure correct bonding and
767 integrity of the external shell. Only the use of systems composed of parts to be assembled after
768 production would overcome such an issue.
769 Overall, an upgrade from research works focused on feasibility to engineering studies investigating
770 any critical process and product aspects would need to be undertaken. In the prospect of
771 pharmaceutical development of printed products and use of FDM for actual manufacturing, safety
772 and quality issues should be addressed. This would involve the evaluation of products in terms of
773 reproducibility of each printing process, presence of microbial and elemental contaminants and
774 stability of the drug conveyed as well as of the polymeric components used, especially when
775 undergoing multiple hot-processing steps. However, this new phase of FDM application to the
776 pharmaceutical field cannot be implemented until dedicated and compliant 3D printers are
777 available. Only then, case studies involving the development of specific printed products could be
778 undertaken and become the benchmark for approaching FDM 3D printing as an actual
779 manufacturing process with inherent production standards and means to ensure process/product
780 quality. From the regulatory point of view, this could also take advantage of co-working and
781 discussion with the newly founded emerging technology team of the Food and Drug
782 Administration.
783

784 ## 6. References

785 Agrahari V., Agrahari V., Mitra A. K., 2017, Inner ear targeted drug delivery: what does the future
786 hold?, Ther. Deliv., 8: 179-184.

787 Aho J., Bøtker J. P., GeninaN., Edinger M., Arnfast L., Rantanen J., 2019, Roadmap to 3D-printed
788 oral pharmaceutical dosage forms: feedstock filament properties and characterization for fused
789 deposition modeling, J. Pharm. Sci., 108: 26-35.

790 Aita I. E., Ponsar A., Quodbach J., 2018, A Critical Review on 3D-printed dosage forms, Curr.
791 Pharm. Des., 24: 4957-4978.

792 Alhnan M. A., Okwuosa T. C., Sadia M., Wan K. W., Ahmed W., Arafat B., 2016, Emergence of
793 3D printed dosage forms: opportunities and challenges, Pharm. Res., 33: 1817-1832.

794 Algahtani M.S., Mohammed A. A, Ahmad J., 2018, Extrusion-based 3D printing for
795 pharmaceuticals: contemporary research and applications, Curr. Pharm. Des., 24: 4991-5008.

796 Alomari M., Mohamed F. H., Basit A. W., Gaisford S., 2015, Personalised dosing: printing a dose
797 of one's own medicine, Int. J. Pharm., 494: 568-577.

798 Altreuter D. H., Kirtane A. R., Grant T., Kruger C., Traverso G., Bellinger A. M., 2018, Changing
799 the pill: developments toward the promise of an ultra-long-acting gastroretentive dosage form,
800 Expert Opin. Drug Deliv., 15: 1189-1198.

801 Anton G., Schoot Uiterkamp A. J. M., Visser C., 2014, A global sustainability perspective on 3D
802 printing technologies, Energy Policy, 74: 158-167.

803 Araújo M. R. P., Sa-Barreto L. L., Gratieri T., Gelfuso G. M., Cunha-Filho M., 2019, The digital
804 pharmacies era: how 3D printing technology using fused deposition modeling can become a reality,
805 Pharmaceutics, 11: 128.

806 Awad A., Trenfield S.J., Goyanes A., Gaisford S., Basit A.W., 2018a, Reshaping drug development
807 using 3D printing, Drug Discov. Today, 23: 1547-1555.

808 Awad A., Trenfield S.J., Goyanes A., Gaisford S., Basit A.W., 2018b, 3D printed medicines: A new
809 branch of digital healthcare, Int. J. Pharm., 548: 586-596.

810 Baines D., Nørgaard L. S., Babarc Z.-U.-D., Rossing C., 2019, The fourth industrial revolution: will
811 it change pharmacy practice?, Res. Social Adm. Pharm.,
812 https://doi.org/10.1016/j.sapharm.2019.04.003.

Baldi F., Ragnoli J., Zinesi D., Bignotti F., Briatico-Vangosa F., Casati F., Loreti G., Melocchi A., Zema L., 2017, Rheological characterization of ethylcellulose-based melts for pharmaceutical applications, AAPS PharmSciTech., 18: 855-866.

Becker D., Zhang J., Heimbach T., Penland R.C., Wanke C., Shimizu J., Kulmatycki K., 2014, Novel orally swallowable IntelliCap (®) device to quantify regional drug absorption in human GI tract using diltiazem as model drug, AAPS PharmSciTech., 5: 1490-1497.

Boudriau S., Hanzel C., Massicotte J., Sayegh L., Wang J., Lefebvre M., 2016, Randomized comparative bioavailability of a novel three-dimensional printed fast-melt formulation of levetiracetam following the administration of a single 1000-mg dose to healthy human volunteers under fasting and fed conditions, Drugs R. D., 16: 229-238.

Briatico-Vangosa F., Melocchi A., Uboldi M., Gazzaniga A., Zema L., Maroni A., 2019m Effect of polyethylene glycol content and molar mass on injection molding of hydroxypropyl methylcellulose acetate succinate-based gastroresistant capsular devices for oral drug delivery, Polymers, 11: 517.

Carlier E., Marquette S., Peerboom C., Denis L., Benali S., Raquezc J.-M., Amighia K., Goole J., 2019, Investigation of the parameters used in fused deposition modeling of poly(lactic acid) to optimize 3D printing sessions, Int. J. Pharm., 565: 367-377.

Casati F., Briatico-Vangosa F., Baldi F., Melocchi A., Maroni A., Gazzaniga A., Zema L., 2018, Assessment of hot-processability and performance of ethylcellulose-based materials for injection-molded prolonged-release systems: an investigational approach, Int. J. Pharm., 548: 400-407.

Chai X., Chai H., Wang X., Yang J., Li, J., Zhao Y., Cai W., Tao T., Xiang X., 2017, Fused deposition modeling (FDM) 3D printed tablets for intragastric floating delivery of domperidone, Sci. Rep., 7: 2829.

Chandekar A., Mishra D. K., Sharma S., Saraogi G. K., Gupta U., Gupta G., 2019, 3D printing technology: A new milestone in the development of pharmaceuticals, Current Pharm. Design 25: 937-945.

Charoenying T., Patrojanasophon P., Ngawhirunpat T., Rojanarata T., Akkaramongkolporn P., Opanasopit P., 2020, Fabrication of floating capsule - in- 3D - printed devices as gastro-retentive delivery systems of amoxicillin, J. Drug Deliv. Sci. Tech., 55: 101393.

Chen D., Xu X .- Y., Li R., Zang G. - A., Zhang Y., Wang M. - R., Xiong M. - F., Xu J. - R., Wang T., Fu H., Hu Q., Wu B., Yan G.-R., Fan T. - Y., 2020, Preparation and *in vitro* evaluation of FDM 3D-printed ellipsoid-shaped gastric floating tablets with low infill percentages, AAPS PharmSciTech., 21: 6.

Cunha-Filho M., Araújo M. R. P., Gelfuso G.M., Gratieri T., 2017, FDM 3D printing of modified drug-delivery systems using hot melt extrusion: a new approach for individualized therapy, Ther. Deliv., 8: 957-966.

Douroumis D., 2019, 3D Printing of pharmaceutical and medical applications: a new era, Pharm. Res., 36: 42.

Feuerbach T., Kock S., Thommes M., 2018, Characterisation of fused deposition modeling 3D printers for pharmaceutical and medical applications, Pharm. Dev. Technol., 23: 1136-1145.

Foppoli A., Maroni A., Cerea M., Zema L., Gazzaniga A., 2017, Dry coating of solid dosage forms: an overview of processes and applications, Drug Dev. Ind. Pharm., 43: 1919-1931.

Foppoli A., Maroni A., Moutaharrik S., Melocchi A., Zema L., Palugan L., Cerea M., Gazzaniga A., 2019, In vitro and human pharmacoscintigraphic evaluation of an oral 5-ASA delivery system for colonic release, Int. J. Pharm., 572: 118723.

857 Fu J., Yin H., Yu X., Xie C., Jiang H., Jin Y., Sheng F., 2018, Combination of 3D printing
858 technologies and compressed tablets for preparation of riboflavin floating tablet-in-device (TiD)
859 systems, Int. J. Pharm., 549: 370-379.

860 Garmulewicz A., Holweg M., Veldhuis H., Yang A., 2018, Disruptive technology as an enabler of
861 the circular economy: what potential does 3D printing hold? Calif. Manage. Rev., 60: 112-132.

862 Gazzaniga A., Cerea M., Cozzi A., Foppoli A., Maroni A., Zema L., 2011, A novel injection-
863 molded capsular device for oral pulsatile delivery based on swellable/erodible polymers, AAPS
864 PharmSciTech., 12: 295-303.

865 Melocchi A., Parietti F., Loreti G., Maroni A., Zem L., Gazzaniga A., 3D-printing: application
866 potential for the manufacturing of drug delivery systems in the form of capsular devices,
867 Transactions of the annual workshop of the Controlled Release Society - Italy chapter, Florence,
868 November 6-8, 2014

869 Genina N., Boetker J.P., Colombo S., Harmankaya N., Rantanen J., Bohr A., 2017, Anti-
870 tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage
871 forms: from drug product design to in vivo testing, J. Control. Release, 268: 40-48.

872 Gibson I., Rosen D. W., Stucker B., Additive manufacturing technologies: rapid prototyping to
873 direct digital manufacturing, 2nd ed. New York: Springer; 2010.

874 Gioumouxouzis C. I., Chatzitaki A. - T., Karavasili C., Katsamenis O. L., Tzetzis D., Mystiridou E.,
875 Bouropoulos N., Fatouros D. G., 2018, Controlled Release of 5-Fluorouracil from alginate beads
876 encapsulated in 3d printed ph-responsive solid dosage forms, AAPS PharmSciTech., 19: 3362-
877 3375.

878 Gioumouxouzis C.I., Karavasili C., Fatouro D. G., 2019, Recent advances in pharmaceutical dosage
879 forms and devices using additive manufacturing technologies, Drug Discov. Today, 24: 636-643.

880 Goole J., Amighi K., 2016, 3D printing in pharmaceutics: a new tool for designing customized drug
881 delivery systems, Int. J. Pharm., 499: 376-394.

882 Goyanes A., Scarpa M., Kamlow M., Gaisford S., Basit A. W., Orlu M., 2017a, Patient
883 acceptability of 3D printed medicines, Int. J. Pharm., 530: 71-78.

884 Goyanes A., Fina F., Martorana A., Sedough D., Gaisford S., Basit A. W., 2017b, Development of
885 modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive
886 manufacturing, Int. J. Pharm., 527: 21-30.

887 Goyanes A., Fernández-Ferreiro A., Majeed A., Gomez-Lado N., Awad A., Luaces-Rodríguez A.,
888 Gaisford S., Aguiar P., Basit A.W., 2018, PET/CT imaging of 3D printed devices in the
889 gastrointestinal tract of rodents, Int. J. Pharm., 536: 158-164.

890 Goyanes A., Allahham N., Trenfield S. J., Stoyanov E., Gaisford S., Basit A. W., 2019, Direct
891 powder extrusion 3D printing: fabrication of drug products using a novel single-step process, Int. J.
892 Pharm., 567: 118471.

893 Gualdrón C. - I. L., Ibarra E. - R. B., Bohórquez A. - P. M., Bohórquez I. G., 2019, Present and
894 future for technologies to develop patient-specific medical devices: a systematic review approach,
895 Med. Devices (Auckl), 12: 253-273.

896 Heras E. S., Haro F. B., de Agustín del Burgo J. M., Marcos M. I., D'Amato R., 2018, Filament
897 advance detection sensor for fused deposition modelling 3D printers, Sensors, 18: 1495.

898 Hsiao W.K., Lorber B., Reitsamer H., Khinast J., 2018, 3D printing of oral drugs: A new reality or
899 hype? Expert Opin. Drug Deliv., 15: 1-4.

900 https://www.spritam.com/#/patient/zipdose-technology/making-medicine-using-3d-printing, last
901 access on November 18, 2019.

902 Huanbutta K., Sangnim T., 2019, Design and development of zero-order drug release
903 gastroretentive floating tablets fabricated by 3D printing technology, J. Drug Deliv. Sci. Technol.,
904 52: 831-837.

905 Jamróz W., Szafraniec J., Kurek M., Jachowicz R., 2018, 3D Printing in pharmaceutical and
906 medical applications - recent achievements and challenges, Pharm. Res., 35: 176.

907 Jonathan G., Karim A., 2016, 3D printing in pharmaceutics: a new tool for designing customized
908 drug delivery systems, Int. J. Pharm., 499: 376-394.

909 Johnson T. J., Brownlee M. J., 2018, Development and innovation of system resources to optimize
910 patient care, Am. J. Health Syst. Pharm., 75: 465-472.

911 Joo Y., Shin I., Ham G., Md Abuzar S., Hyun S.-M., Hwan S.-J., Hwang, 2019, The advent of a
912 novel manufacturing technology in pharmaceutics: superiority of fused deposition modeling 3D
913 printer, J. Pharm. Investig., https://doi.org/10.1007/s40005-019-00451-1.

914 Kallakunta V. R., Sarabu S., Bandari S., Tiwari R., Patil H., Repka M. A., 2019, An update on the
915 contribution of hot-melt extrusion technology to novel drug delivery in the twenty-first century: part
916 I, Expert Opin. Drug Deliv., 16: 539-550.

917 Kempin W., Domsta V., Brecht I., Semmling B., Tillmann S., Weitschies W., Seidlitz A., 2018,
918 Development of a dual extrusion printing technique for an acid- and thermolabile drug, Eur. J.
919 Pharm. Sci., 123: 191-198.

920 Kimura S., Ishikawa T., Iwao Y., Itai S., Kondo H., 2019, Fabrication of zero-order sustained-
921 release floating tablets *via* fused depositing modeling 3D printer, Chem. Pharm. Bull., 67: 992-999.

922 Kirtane A. R., Hua T., Hayward A., Bajpayee A., Wahane A., Lopes A., Bensel T., Ma L., Stanczyk
923 F. Z., Brooks S., Gwynne D., Wainer J., Collins J., Tamang S. M., Langer R., Traverso G., 2019, A
924 once-a-month oral contraceptive, Sci. Trans. Med., 11: eaay2602.

925 Krause J., Bogdahn M., Schneider F., Koziolek M., Weitschies W., 2019, Design and
926 characterization of a novel 3D printed pressure-controlled drug delivery system, Eur. J. Pharm. Sci.,
927 140: 105060.

928 Kurzrock R., Stewart D. J., 2015, Click chemistry, 3D-printing, and omics: the future of drug
929 development, Oncotarget., 7: 2155-2158.

930 Lamichhane S., Bashyal S., Keum T., Noh G., Seo J. E., Bastola R., Choi J., Sohn D. H., Lee S.,
931 2019, Complex formulations, simple techniques: can 3D printing technology be the Midas touch in
932 pharmaceutical industry?, Asian J. Pharm. Sci., 14: 465-479.

933 Lamichhane S., Park J.-B., Sohn D. H., Lee S., 2019, Customized novel design of 3D printed
934 pregabalin tablets for intra-gastric floating and controlled release using fused deposition modeling,
935 Pharmaceutics, 11: 564.

936 Lim S. H., Kathuria H., Tan J. J. Y., Kang L., 2018, 3D printed drug delivery and testing systems -
937 A passing fad or the future?, Adv. Drug Deliv. Rev., 132: 139-168.

938 Linares V., Casas M., Caraballo I., 2019, Printfills: 3D printed systems combining fused deposition
939 modeling and injection volume filling. application to colon-specific drug delivery, Eur. J. Pharm.
940 and Biopharm., 134: 138-143.

941 Liu X., Steiger C., Lin S., Parada G.A., Liu J., Chan H. F., Yuk H., Phan N. V., Collins J., Tamang
942 S., Traverso G., Zhao X., 2019, Ingestible hydrogel device, Nat. Commun., 10: 493.

943 Long J., Gholizadeh H., Lu J., Bunt C., Seyfoddin A., 2017, Application of fused deposition
944 modelling (FDM) method of 3D printing in drug delivery, Curr. Pharm. Des., 23: 433-439.

945 Long J., Nand A. V, Ray S., Mayhew S., White D., Bunt C. R., Seyfoddina A., 2018, Development
946 of customised 3D printed biodegradable projectile for administrating extended-release contraceptive
947 to wildlife, Int. J. Pharm., 548: 349-356.

948 Lukin I., Musquiz S., Erezuma I., Al-Tel T. H., Golafshan N., Dolatshahi-Pirouz A., Orive G.,
949 2019, Can 4D bioprinting revolutionize drug development?, Expert Opin. Drug Discov., 14: 953-
950 956.

951 Luzuriaga M. A., Berry D. R., Reagan J. C., Smaldone R. A., Gassensmith J. J., 2018,
952 Biodegradable 3D printed polymer microneedles for transdermal drug delivery, Lab. Chip, 18:
953 1223-1230.

954 Madla C. M., Trenfield S. J., Goyanes A., Gaisford S., Basit A.W., 3D printing technologies,
955 implementation and regulation: An overview. In 3D Printing of Pharmaceuticals, 1st ed.; Basit, A.,
956 Gaisford, S., Eds.; Springer: London, UK, 2018; Volume 31, pp. 21-40.

957 Maniruzzamann M. (Ed.), 3D and 4D printing in biomedical applications: 784 process engineering
958 and additive manufacturing, Weinheim: Wiley VCH; 2018.

959 Markl D., Zeitler J.A., Rasch C., Michaelsen M. H., Müllertz A., Rantanen J., Rades T., Bøtker J.,
960 2017, Analysis of 3D prints by x-ray computed microtomography and terahertz pulsed imaging,
961 Pharm. Res., 34: 1037-1052.

962 Markl D., Zeitler A., Rades T., Rantanen J., Bøtker J., 2018, Toward quality assessment of 3D
963 printed oral dosage forms, J. 3D Print. Med., 2: 27-33.

964 Maroni A., Del Curto M. D., Salmaso S., Zema L., Melocchi A., Caliceti P., Gazzaniga A., 2016, *In*
965 *vitro* and *in vivo* evaluation of an oral multiple-unit formulation for colonic delivery of insulin, Eur.
966 J. Pharm. Biopharm., 108: 76-82.

967 Maroni A., Melocchi A., Parietti F., Foppoli A., Zema L., Gazzaniga A., 2017, 3D printed multi-
968 compartment capsular devices for two-pulse oral drug delivery, J. Control. Release, 268: 10-18.

969 Maroni A., Melocchi A., Zema L, Foppoli A., Gazzaniga A., 2020, Retentive drug delivery systems
970 based on shape memory materials, J. Appl. Polym. Sci., https://doi.org/10.1002/app.48798.

971 Matijašić G., Gretić M., Vinčić J., Poropat A., Cuculić L., Rahelić T., 2019, Design and 3D printing
972 of multi-compartmental PVA capsules for drug delivery, J Drug Deliv. Sci. Technol., 52: 677-686.

973 Melocchi A., Parietti F., Loreti G., Maroni A., Gazzaniga A., Zema, L., 2015, 3D printing by fused
974 deposition modeling (FDM) of a swellable/erodible capsular device for oral pulsatile release of
975 drugs. J. Drug. Deliv. Sci. Technol., 30: 360-367.

976 Melocchi A., Parietti F., Maroni A., Foppoli A., Gazzaniga A., Zema, L., 2016, Hot-melt extruded
977 filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling,
978 Int. J. Pharm., 509: 255-263.

979 Melocchi A., Parietti F., Maccagnan S., Ortenzi M.A., Antenucci S., Briatico-Vangosa F., Maroni
980 A., Gazzaniga A., Zema L., 2018, Industrial Development of a 3D-printed nutraceutical delivery
981 platform in the form of a multicompartment HPC capsule, AAPS PharmSciTech., 19: 3343-3354.

982 Melocchi A., Inverardi N., Uboldi M., Baldi F., Maroni A., Pandini S., Briatico-Vangosa F., Zema
983 L., Gazzaniga A., 2019a, Retentive device for intravesical drug delivery based on water-induced
984 shape memory response of poly(vinyl alcohol): design concept and 4D printing feasibility, Int. J.
985 Pharm., 559: 299-311.

986 Melocchi A., Uboldi M., Inverardi N., Briatico-Vangosa F., Baldi F., Pandini S., Scalet G.,
987 Auricchio F., Cerea M., Foppoli A., Maroni A., Zema L., Gazzaniga A., 2019b, Expandable drug
988 delivery system for gastric retention based on shape memory polymers: Development via 4D
989 printing and extrusion, Int. J. Pharm., 571: 118700.

990 Melocchi A., Uboldi M., Parietti F., , Cerea M., Foppoli A., Palugan L., Gazzaniga, A., Maroni A.,
991 Zema L., 2019c, Capsular delivery platform based on molded and 3D-printed Lego-inspired
992 modular units for the development of personalized dietary supplements, submitted for publication.

993 Mir T. A., Nakamura M., 2017, Three-Dimensional Bioprinting: toward the era of manufacturing
994 human organs as spare parts for healthcare and medicine, Tissue Eng. Part B Rev., 23: 245-256.

995 Mirza M. A., Iqbal Z., 2018, 3D Printing in pharmaceuticals: regulatory perspective, Curr. Pharm.
996 Des., 24: 5081-5083.

997 Musazzi U. M., Selmin F., Ortenzi M. A., Mohammed G. K., Franzé S., Minghetti P., Cilurzo F.,
998 2018, Personalized orodispersible films by hot melt ram extrusion 3D printing, Int J Pharm., 551:
999 52-59.

1000 Nober C., Manini G., Carlier E., Raquez J. M., Benali S., Dubois P., Amighi K., Goole J., 2019,
1001 Feasibility study into the potential use of fused-deposition modeling to manufacture 3D-printed
1002 enteric capsules in compounding pharmacies, Int J Pharm., 569: 118581.

1003 Norman J., Madurawe R. D., Moore C. M. V., Khan M. A., Khairuzzaman A., 2017, A new chapter
1004 in pharmaceutical manufacturing: 3D-printed drug products, Adv. Drug Deliv. Rev., 108: 39-50.

1005 Novák M., Boleslavská T., Grof Z, Waněk A., Zadražil A., Beránek J., Kovačík P., Štěpánek F.,
1006 2018, Virtual prototyping and parametric design of 3d-printed tablets based on the solution of
1007 inverse problem, AAPS PharmSciTech., 19: 3414-3424.

1008 Okwuosa T. C., Soares C., Gollwitzer V., Habashy R., Timmins P., Alhnan M.A., 2018, On
1009 demand manufacturing of patient-specific liquid capsules via co-ordinated 3D printing and liquid
1010 dispensing, Eur. J. Pharm. Sci., 118: 134-143.

1011 Palekar S., Nukala P.K., Mishra S. M., Kipping T., Patel K., 2019, Application of 3D printing
1012 technology and quality by design approach for development of age-appropriate pediatric
1013 formulation of baclofen, Int. J. Pharm., 556: 106-116.

1014 Pereira B. C., Isreb A., Forbes R. T., Dores F., Habashy R., Petit J. B., Alhnan M. A., Oga E. F.,
1015 2019, 'Temporary Plasticiser': a novel solution to fabricate 3D printed patient-centred
1016 cardiovascular 'Polypill' architectures, Eur. J. Pharm. Biopharm., 135: 94-103.

1017 Pham D. T., Gault R. S., 1998, A comparison of rapid prototyping technologies, Int. J. Mach. Tools
1018 Manuf., 38: 1257-1287.

1019 Prasad L. K., Smyth H., 2016, 3D printing technologies for drug delivery: a review, Drug. Dev. Ind.
1020 Pharm., 42: 1019-1031.

1021 Preis M., Breitkreu J., Sandler N., 2015, Perspective: concepts of printing technologies for oral film
1022 formulations, Int. J. Pharm., 494: 578-584.

1023 Preis M., Öblom H., 2017. 3D-printed drugs for children-are we ready yet?, AAPSPharmSciTech.,
1024 18: 303-308.

1025 Rahman Z., Ali S.F.B., Ozkan T., Charoo N. A., Reddy I. K., Khan M. A., 2018, Additive
1026 manufacturing with 3D printing: progress from bench to bedside, AAPS J., 20: 101.

1027 Rehnberg M, Ponte S., 2016, 3D Printing and global value chains: how a new technology may
1028 restructure global production, GPN Working Paper Series,
1029 http://gpn.nus.edu.sg/file/Stefano%20Ponte_GPN2016_010.pdf.

1030 Sandler N., Preis M., 2016, Printed drug-delivery systems for improved patient treatment, Trends
1031 Pharmacol. Sci., 37: 1070-1080.

1032 Sarabu S., Bandari S., Kallakunta V. R., Tiwari R., Patil H., Repka M. A., 2019, An update on the
1033 contribution of hot-melt extrusion technology to novel drug delivery in the twenty-first century: part
1034 II, Expert Opin. Drug Deliv., 16: 567-582.

1035 Scoutaris N., Ross S. A., Douroumis D., 2018, 3D printed "starmix" drug loaded dosage forms for
1036 paediatric applications, Pharm. Res. 35: 34.

1037 Shin S., Kim T. H., Jeong S. W., Chung S. E., Lee D. Y., Kim D.-H., Shin B. S., 2019,
1038 Development of a gastroretentive delivery system for acyclovir by 3D printing technology and its in
1039 vivo pharmacokinetic evaluation in Beagle dogs, PLoS ONE, 14: e0216875.

1040 Smith D. M., Kapoor Y., Klinzing G. R., Procopio A. T., 2018a, Pharmaceutical 3D printing:
1041 design and qualification of a single step print and fill capsule, Int. J. Pharm., 544: 21-30.

Smith D., Kapoor Y., Hermans A., Nofsinger R., Kesisoglou F., Gustafson T. P., Procopio A., 2018b, 3D printed capsules for quantitative regional absorption studies in the GI tract, Int. J. Pharm., 550: 418-428.

Söderlind E., Abrahamsson B., Erlandsson F., Wanke C., Iordanov V., Von Corswant C., 2015, Validation of the IntelliCap® system as a tool to evaluate extended release profiles in human GI tract using metoprolol as model drug, J. Control. Release, 217: 300-307.

Tagami T., Hayashi N., Sakai N., Ozeki T., 2019, 3D printing of unique water-soluble polymer-based suppository shell for controlled drug release, Int. J. Pharm., 568: 118494.

Tan D.K., Maniruzzaman M., Nokhodchi A., 2018, Advanced pharmaceutical applications of hot-melt extrusion coupled with fused deposition modelling (FDM) 3D printing for personalised drug delivery., Pharmaceutics, 10: 203.

Tran T., 2017, On the bottleneck of adopting 3D printing in manufacturing, Virtual and Physical Prototyping, 12: 333-334.

Trenfield S. J., Awad A., Goyanes A., Gaisford S., Basit A.W., 2018a, 3D printing pharmaceuticals: drug development to frontline care, Trends Pharmacol. Sci., 39: 440-451.

Trenfield S. J., Madla C. M., Basit A. W., Gaisford S., 2018b, The shape of things to come: emerging applications of 3D printing in healthcare. In 3D printing of pharmaceuticals, 1st Ed.; Basit A. W., Gaisford S., Eds.; Springer: London (UK) Volume 31.

Trenfield S.J., Goyanes, A., Telford R., Wilsdon D., Rowland M., Gaisford S., Basit A.W., 2018c, 3D printed drug products: Non-destructive dose verification using a rapid point-and-shoot approach, Int. J. Pharm., 549: 283-292.

Trenfield S. J., Awad A., Madla C. M., Hatton G. B., Firth J., Goyanes A., Gaisford S., Basit A. W., 2019, Shaping the future: recent advances of 3D printing in drug delivery and healthcare, Expert. Opin. Drug Deliv., 16: 1081-1094.

1066 Wang P., Kricka L.J., 2018, Current and emerging trends in point-of-care technology and strategies
1067 for clinical validation and implementation, Clin. Chem., 64: 1439-1452.

1068 Weisman J. A., Ballard D. H., Jammalamadaka U., Tappa K., Sumerel J., D'Agostino H. B., Mills
1069 D. K., Woodard P. K., 2019, 3D printed antibiotic and chemotherapeutic eluting catheters for
1070 potential use in interventional radiology: *in vitro* proof of concept study, Acad Radiol., 26: 270-274.

1071 Wen C. L., 2017, Telemedicine, eHealth and remote care systems, in Global health informatics:
1072 how information technology can change our lives in a globalized world, Academic Pres, London
1073 (UK), pgg: 168-194.

1074 Wilde L., Bock M., Glockl G., Garbacz G., Weitschies W., 2014, Development of a pressure-
1075 sensitive glyceryl tristearate capsule filled with a drug-containing hydrogel, Int. J. Pharm., 461:
1076 296-300.

1077 Zema L., Maroni A., Foppoli A., Palugan L., Sangalli M. E., Gazzaniga A.,2007, Different HPMC
1078 viscosity grades as coating agents for an oral time and/or site-controlled delivery system: an
1079 investigation into the mechanisms governing drug release, J. Pharm. Sci., 96: 1527-1536.

1080 Zema L., Loreti G., Melocchi A., Maroni A., Gazzaniga A., 2012, Injection Molding and its
1081 application to drug delivery, J. Control. Release, 159: 324-331.

1082 Zema L., Loreti G., Macchi E., Foppoli A., Maroni A., Gazzaniga A., 2013a, Injection molded
1083 capsular device for oral pulsatile release: development of a novel mold, J. Pharm. Sci., 102: 489-
1084 499.

1085 Zema L., Loreti G., Melocchi A., Maroni A., Palugan L., Gazzaniga A., 2013b, Gastroresistant
1086 capsular device prepared by injection molding, Int. J. Pharm., 440: 264-272.

1087 Zema L., Cerea M., Gazzaniga A, 2013c, Injection molding nd its drug delivery applications. In
1088 Encyclopedia of Pharmaceutical Science and Technology, 4th Edition, Vol. I. James Swarbrick,
1089 Editor. CRC Press, Taylor & Francis Group: New York. pp. 1991-2002.

1090 Zema L., Melocchi A., Maroni A., Gazzaniga A., 2017, Three-Dimensional Printing of Medicinal
1091 Products and the challenge of personalized therapy, J. Pharm. Sci., 106: 1697-1705.

1092 Zhang J., Yang W., Vo A. Q., Feng X., Ye X., Kim D. W., Repka M. A., 2017, Hydroxypropyl
1093 methylcellulose-based controlled release dosage by melt extrusion and 3D printing: structure and
1094 drug release correlation, Carbohydr. Polym., 177: 49-57.

1095 Zhang J., Vo A. Q., Feng X., Bandari S., Repka M. A., 2018, Additive manufacturing: a novel tool
1096 for complex and personalized drug delivery systems, AAPS PharmSciTech., 19: 3388-3402.

1097 Zhao J., Xu X., Wang M., Wang L., 2018, A new model of a 3D-printed shell with convex drug
1098 release profile, Dissolut. Technol., 25: 24-28.

Figure captions

Figure 1: Outline of hollow systems assembled after production reviewed in the article.

Figure 2: Hollow systems fabricated and filled in a single manufacturing process reviewed in the article.

Figure 1

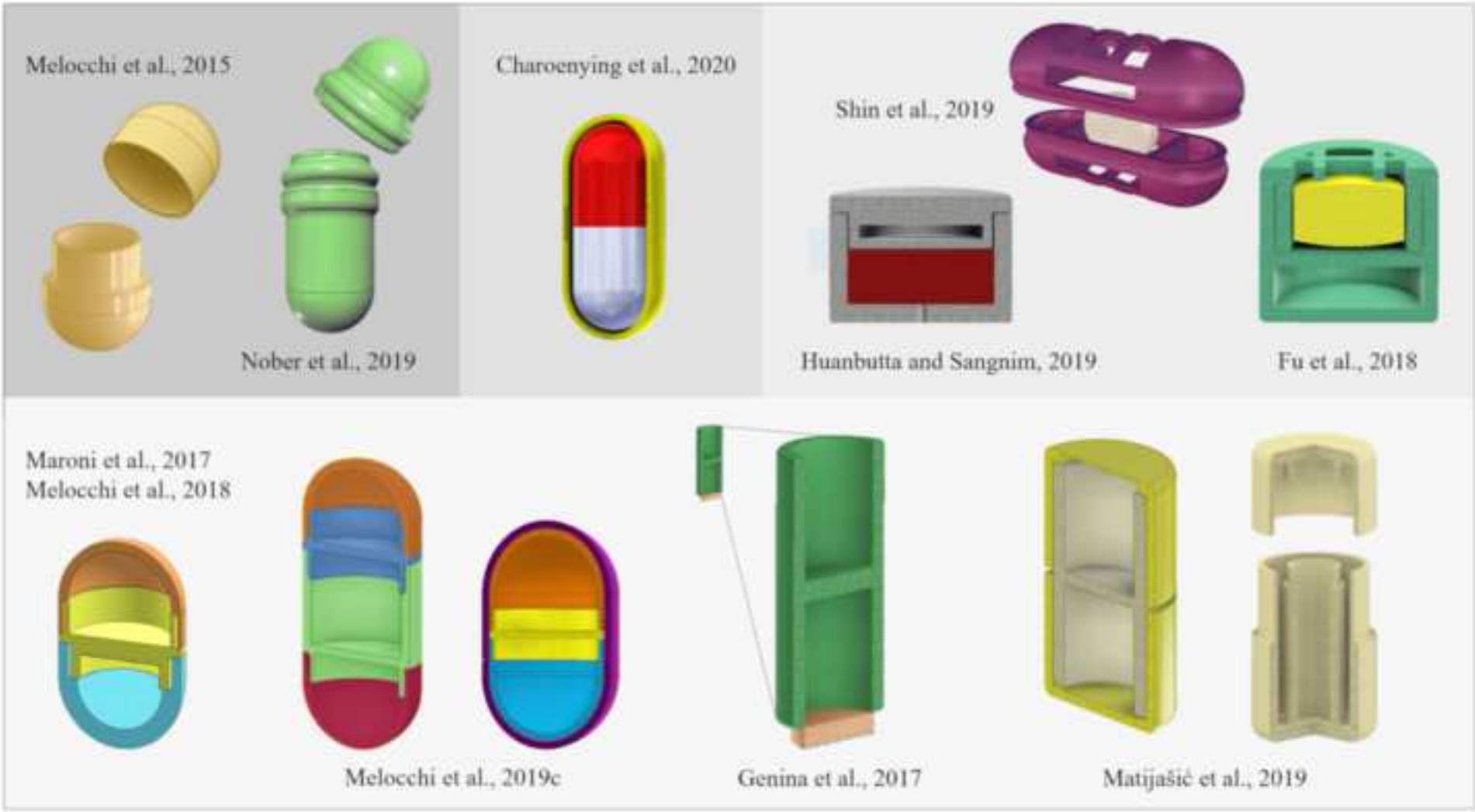
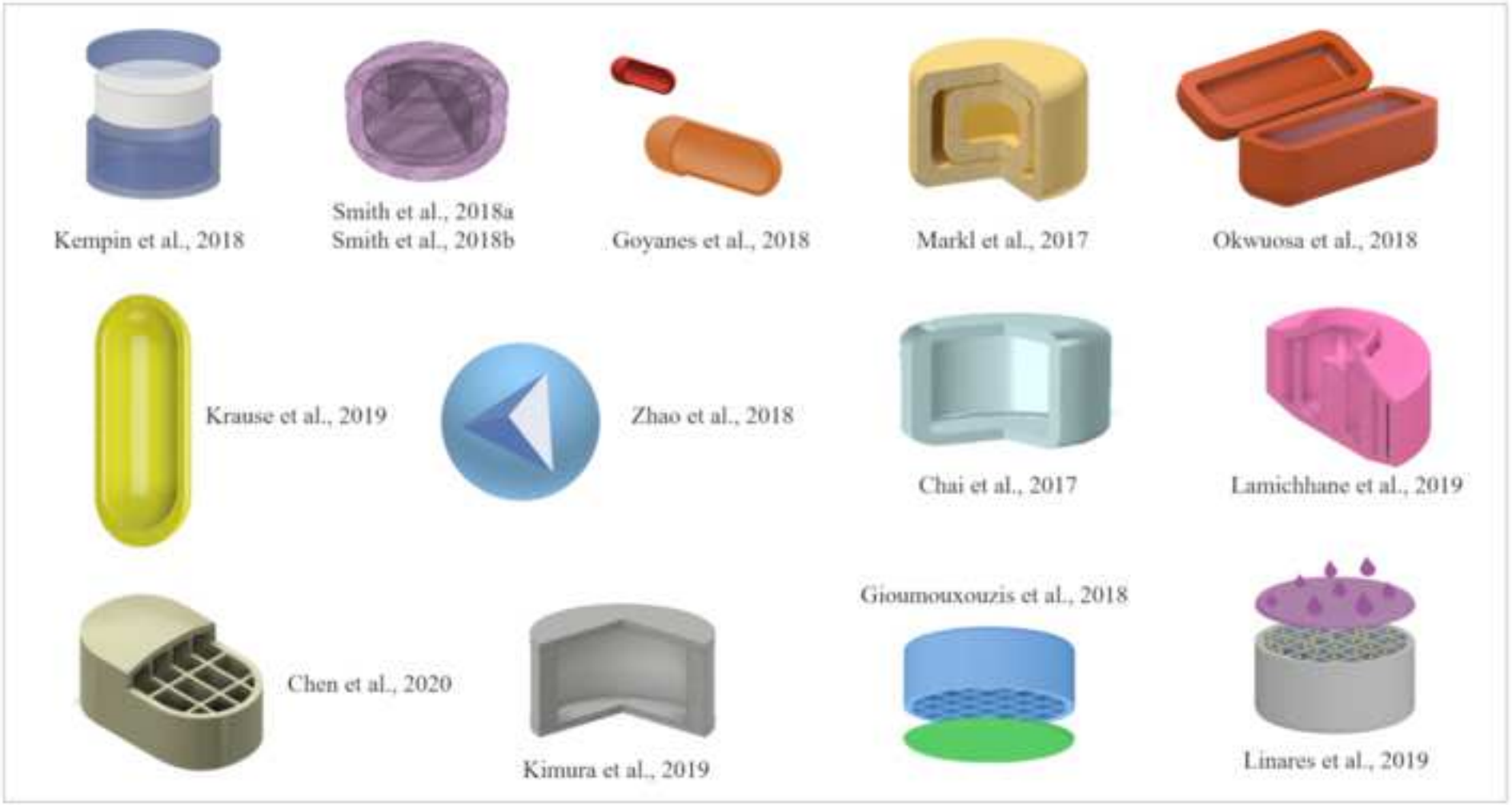

Melocchi et al., 2015
Nober et al., 2019
Charoenying et al., 2020
Shin et al., 2019
Huanbutta and Sangnim, 2019
Fu et al., 2018
Maroni et al., 2017
Melocchi et al., 2018
Melocchi et al., 2019c
Genina et al., 2017
Matijašić et al., 2019

Figure 2


Kempin et al., 2018
Smith et al., 2018a
Smith et al., 2018b
Goyanes et al., 2018
Markl et al., 2017
Okwuosa et al., 2018
Krause et al., 2019
Zhao et al., 2018
Chai et al., 2017
Lamichhane et al., 2019
Chen et al., 2020
Kimura et al., 2019
Gioumouxouzis et al., 2018
Linares et al., 2019

***Conflict of Interest**

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

***Credit Author Statement**