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REVIEW ARTICLE

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An overview of poly(vinyl alcohol) and poly(vinyl pyrrolidone) in pharmaceutical additive manufacturing

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Abstract

Recently, drug personalization has received noticeable attention. Problems arising from standard generalized drug treatments have aroused over the years, particularly among pediatric and geriatric patients. The growing awareness of the limitations of the "one-size-fits-all" approach has progressively led to a rethinking of the current medicine's development, laying the basis of personalized medicine. Three-dimensional printing is a promising tool for realizing personalized therapeutic solutions fitting specific patient needs. This technology offers the possibility to manufacture drug delivery devices with tailored doses, sizes, and release characteristics. Among additive manufacturing techniques, fused deposition modeling (FDM) is the most studied for oral drug delivery device production due to its high precision and cheapness. By playing with factors such as drug loading method, filament production, and printing parameters, the medication release profile of a drug delivery device produced by 3D printing can be tailored depending on the patient's requirements. This review focuses on the applications of FDM in drug fabrication using poly(vinyl alcohol) (PVA) and poly(vinyl pyrrolidone) (PVP) as drug-loaded matrices. The authors aim to provide an overview of the current trends in this research field, with special attention to the effect of the printing parameters, tablet shape, and drug distribution and concentration on drug customization and personalized drug release.

KEYWORDS

3D printing, FDM, personalized medicine, PVA, PVP

1 | INTRODUCTION

In the last years, drug personalization has drawn significant attention due to issues with standard generalized medication therapies, such as undesirable side effects and inadequate drug therapy, particularly among pediatric and geriatric patients.[1,2] It has been recorded that 3%–7% of all hospitalizations are the result of adverse drug reaction (ADR) and serious ADRs were found to be the fourth to sixth causes of death in hospitalized patients in the US.[3] On the other hand, several are cases of patients for whom drugs are ineffective. A recent study has

revealed that 75% of people diagnosed with cancer and 70% of Alzheimer's patients do not adhere to the drug regimen. These findings should not be shocking because the bulk of pharmaceutical drugs are mass produced in a few distinct strengths based on the dosage necessary to generate their therapeutic effect in the majority of patients, according to the so-called one-size-fits-all approach.[4,5] In this way, the administered dose could be below or above the optimum drug concentration for individual patients, resulting in toxicity, adverse effects, or minimal effectiveness.[4] In other words, each person requires a different dosage, since needs may alter depending on a wide range of patient- and drug-related factors, such as the patient's disease state, genetic profiles, metabolism, age, weight, gender, and the pharmacokinetics of the drug.[5]

The current solutions to these problems, i.e., tablet splitting or compounded medication, are largely ineffective. Crushing a solid tablet can result in dose variation and, particularly in the case of drugs with a narrow therapeutic index, this can lead to therapeutic failures or adverse effects.[1] Furthermore, compounded medications frequently suffer from dose accuracy issues and may lose their efficacy when patients disregard dosing recommendations.[4] The growing awareness of the limitations and problems of the one-size-fits-all approach has led to a rethinking of the current medicine's development, laying the basis of personalized medicine.[6] The shift to personalized medicine started approximately 20 years ago and has undergone an impressive acceleration over the past few years. The idea of such a patient-centric drug production approach is well described in the sentence "Providing the right treatment to the right patient, at the right dose at the right time".[6] The dose and the delivery of medicines to individuals occur safely and effectively only following a deep study of all the patient's characteristics (Figure 1).[7,8]

Three-dimensional (3D) printing, also termed additive manufacturing (AM) or rapid prototyping (RP), is one of the most innovative and potent methods in the pharmaceutical industry for the creation of individualized medications.[10] 3D printing is a technology that builds products in a layer-by-layer manner from a digital file and it has received great attention from academia and industry due to its ability to fabricate complex and custom structures with reduced material waste.[11,12] Since the first 3D-printed drug tablet Spritam® (levetiracetam) was approved by Food and Drug Administration (FDA) in 2015, research interest in 3D printing technology in the pharmaceutical field has significantly grown.[1,5] Several are the advantages that this manufacturing process could offer over conventional drug manufacturing methods, especially for customizing drug production. More specifically, 3D printing technologies present the following benefits[1,5]:

- They are less expensive for personalized drugs and small-scale drug production, such as orphan drugs, which are needed to treat rare diseases and are thus consumed by a limited number of patients;
- By precisely controlling the printing parameters, they are able to produce dosage forms with complex and regulated drug release profiles and allow drug dosage form, dosing and release profiles to be customized for each patient;
- They can potentially make complicated drug manufacturing processes simpler and standardized;
- Because of the potential of portable and decentralized manufacturing, they could be very useful in difficult-to-reach areas (disaster zones, middle-income countries, space etc.) to increase pharmaceutical access.[13]

Therefore, using 3D printing in medication manufacture to customize dose and fine-tune drug release could address the aforementioned issues with pharmacological therapies.[1]

Among the polymers currently exploited for the 3D printing of personalized medicines, the most common are poly(vinyl alcohol) (PVA) and poly(vinylpyrrolidone) (PVP). PVA and PVP are synthetic, water-soluble, biodegradable, and biocompatible polymers that, due to their versatile properties, have received great attention

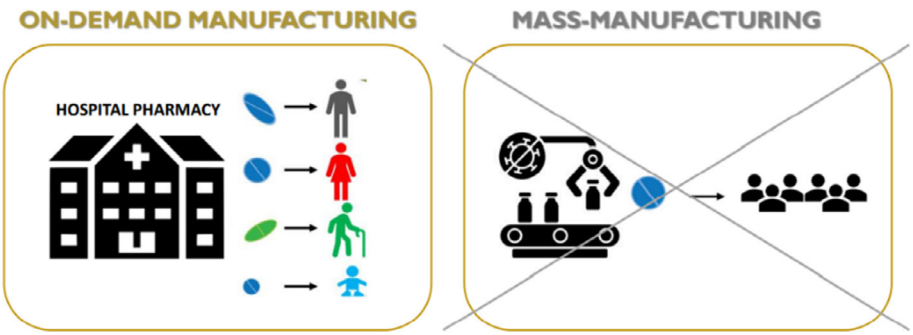


FIGURE 1 On-demand manufacturing and mass manufacturing (duplicated from Reference [9]).

for applications in the pharmaceutical and medical field.[14,15]

For many pharmaceutical drugs, the oral route of administration—particularly the delivery of solid oral dosage forms—remains the preferred route of administration due to its practicality, mobility, suitability for self-administration, and other factors.[16] Therefore, this review focuses on the applications of 3D printing in oral drug fabrication using PVA and PVP as drug-loaded matrices. The authors aim to provide an overview of the current trends in this research field with special attention to the effect of the printing parameters, tablet shape, and drug distribution and concentration on drug customization and personalized drug release.

2 | ADDITIVE MANUFACTURING

Additive manufacturing is a rapid prototyping technology that builds products from the bottom up by adding material one cross-sectional layer at a time. Recently, it has gained interest across several industrial fields,[17–20] among which the pharmaceutical one can be mentioned.[21] In this section, an overview of the 3D printing history will be presented, along with a description of the most widely used rapid prototyping technologies in the pharmaceutical field.

2.1 | History

The first 3D printers appeared in 1982, when Charles Hull developed stereolithography that is, a 3D printing technology that fabricates 3D objects by solidifying layers of a photopolymer using UV light. Hull gave birth to the first example of commercial rapid prototyping by founding the 3DSystems company, still at the top of the 3D printing world.[22,23] In 1985 he filed the patent, obtained it in 1986, and from that moment on he opened the door to those who followed him. In 1989, Scott Crump patented another additive manufacturing method called "fused deposition modeling", based on a different principle than that of Charles Hull's printers. In this case, molten material was deposited on a platform layer by layer, to produce the final object. Emanuel Sachs, an MIT scientist, invented 3D printing processes based on joining powder using binding materials in the 1990s. However, additive manufacturing becomes better known and accessible at the beginning of the 21st century. Taking inspiration from FDM patents, Adrian Bowyer fabricated the RepRap (replicating rapid prototyper), characterized by free software of the equipment, an open-source code, and 57% of the mechanical printer components manufactured through 3D printing. Thanks to these achievements, the first low-cost 3D printer appeared in 2004. During the last few years, several additive manufacturing techniques have evolved and, in the next chapter, they will be presented in detail.

2.2 | Procedure for 3D printing

The 3D printing workflow consists of three main steps: computer-aided design (CAD) file development, product printing, and post-processing.[24] At first, a CAD model is generated using 3D modeling software, such as Solidworks, Onshape, Rhino, and so forth. The model is then converted into an STL (stereolithography) file that uses triangles (polygons) to describe the surface of the object without any information on color, texture, or other CAD model attributes. Once the STL file is generated, it is loaded into a slicer software that converts the 3D model into specific instructions for the printer. In particular, the slicer divides the object into horizontal layers, each of which describes the necessary movements to deposit the material. Finally, the AM machine creates the 3D object by forming each layer via the selective placement of material. Post-processing methods, such as sanding, painting, and polishing, can be utilized to finalize the 3D object.[1,11] These generalized steps are shown in Figure 2.

FIGURE 2 Additive manufacturing processes (duplicated from Reference [11]).

2.3 | Types of 3D printing

Since it enables the creation of original, distinctive, and complicated dosage forms, 3D printing has the potential to change the pharmaceutical industry. The features of the drug and the excipients are just two of the variables that influence the choice of 3D printer for drug production. Selective laser sintering (SLS), fused deposition modeling (FDM), powder bed fusion and 3D inkjet printing are the main 3D printing methods utilized for the manufacture of drug delivery devices.[10,25–27]

2.3.1 | Fused deposition modeling

Fused deposition modeling (FDM) is a rapid prototyping technology using thermoplastic polymers such as polylactic acid (PLA) or polyvinylacetate (PVAc) in a semi-molten form. In this technique, a filament of thermoplastic polymer is moved by two rollers inside the liquefier (where the temperature is raised above the material melting point) and subsequently pushed through the nozzle die by the still-solid upstream polymer filament. The extruded semi-molten material is deposited onto a building platform and, when a layer is completed, the base platform descends and the following layer is placed. Figure 3 illustrates the FDM process.[28] Typically, hot melt extrusion (HME) is employed to fabricate the filament used in 3D printing. This technique is used in the pharmaceutical industry for both oral and patch-type medications.[21,29]

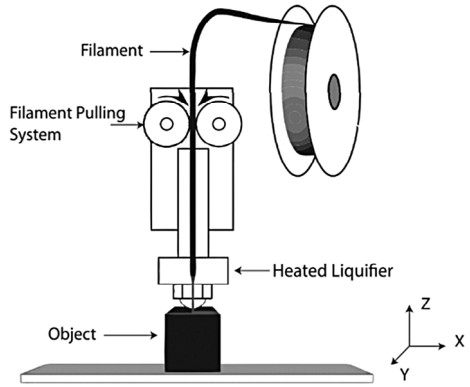


FIGURE 3 Fused deposition modeling technique (duplicated from Reference [28]).

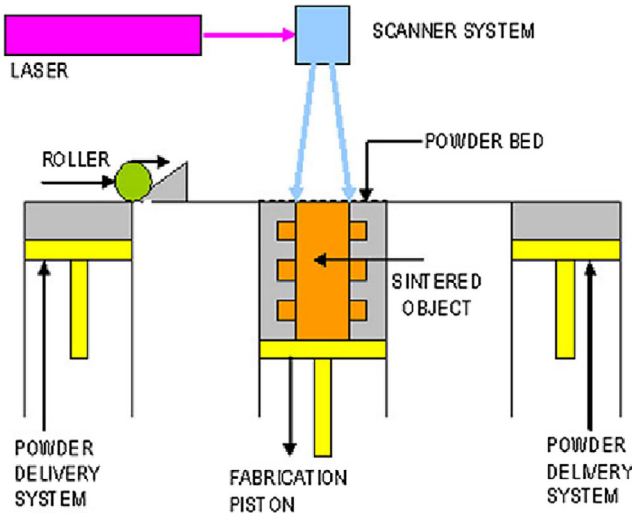


FIGURE 4 Scheme of selective laser sintering (duplicated from Reference [1,30]).

2.3.2 | Selective laser sintering

Selective laser sintering (SLS) is a powder-based additive manufacturing process developed by Carl Deckard at the University of Texas in 1989. Figure 4 shows a schematic illustration of this technique. At first, the powder made of thermoplastic polymer is spread by a roller over the surface of the working platform. Under the guidance of a scanner system, a laser beam is then used to scan the surface and selectively melts and sinters the powder it strikes. Once a layer of consolidated powder is generated, the piston moves down one-layer thickness to accommodate a further layer of powder and the procedure is repeated until the object is fabricated. The excess powder in each layer helps in supporting the part during printing. A temperature just below the melting point of the polymer is maintained in the sealed fabrication chamber. In this way, for sintering to occur, the temperature just needs to be slightly raised by the laser's heat.[30] SLS offers several advantages, such as the capability to create objects with high porosity and pore connectivity, the fact that solvents are not used in the entire process, and the possibility to recycle and reprocess the feedstock materials.[31] However, the need to use a powder with good flowability represents a limitation. For applications in the pharmaceutical field, SLS seems suitable for manufacturing immediate-release (IR) drug systems due to the highly porous nature of the structures produced.

2.3.3 | Powder bed fusion

The concept of Powder Bed printing is similar to SLS. The only difference is that, after the roller lays the powder on the working platform, this method uses a liquid binder to bind the powder bed polymer and produced,

layer by layer, the final 3D object. The typical height of the powder bed layer is 200 μm, while the size of the powder bed particles is between 50 and 100 μm.[1] PBF can be used in pharmaceutics to make dosage forms with distinctive structural and functional features that are normally difficult or impossible to produce using traditional methods or other printing technologies because no support materials are required.[31]

2.3.4 | Three-dimensional inkjet printing

Inkjet printing is an additive manufacturing method in which a specific quantity of ink is forced through a nozzle tip and, based on the object profile that has to be produced, delivered onto a polymer powder bed on the working platform. The ink binds the polymer powders and, after a layer is generated, the working platform is lowered, and a roller or powder jetting device applies a second coating of free powder. The process proceeds in this manner until the 3D object is fabricated. Depending on the ink ejection mode, inkjet printing can be classified as continuous inkjet printing (CIJ) or drop-on-demand printing (DOD).

Continuous jet printers

Pressure is used by CIJ printers to push liquid ink toward the nozzle tip (diameter ranging from 50 to 80 mm) for extrusion, creating a continuous ink flow. The extrusion of the ink is controlled by a charged deflector at the nozzle tip, which directs it either toward the working platform for printing or the waste chamber for recycling and reuse during the subsequent printing (Figure 5A).[32,33]

Drop-on-demand printers

DOD printers release a single drop of ink only when required and in response to a trigger thermal or piezoelectric signal.[34] In thermal DOD printing (Figure 5B), the liquid ink is heated, which causes a bubble to form inside the ink reservoir. The bubble then pushes an ink droplet out of the print head through a tiny hole. Thermal printers are restricted only to volatile liquids and, since the temperatures that are involved could reach 300°C, the risk of bioactive compound degradation is quite high, limiting the use of such printers for pharmaceutical applications.[25] On the other hand, piezoelectric printing uses a piezoelectric actuator to drive the DOD process.[32,33] Consequently, piezoelectric printers are more suited for the development of pharmaceuticals since they can operate at room temperature and with less volatile and more biocompatible liquids.[25]

For applications in the pharmaceutical field, active pharmaceutical ingredients (APIs)-loaded inks are used. By changing ink during the process, the benefit of using inkjet printing technology is that it can create tablets that are filled with various medications.[21]

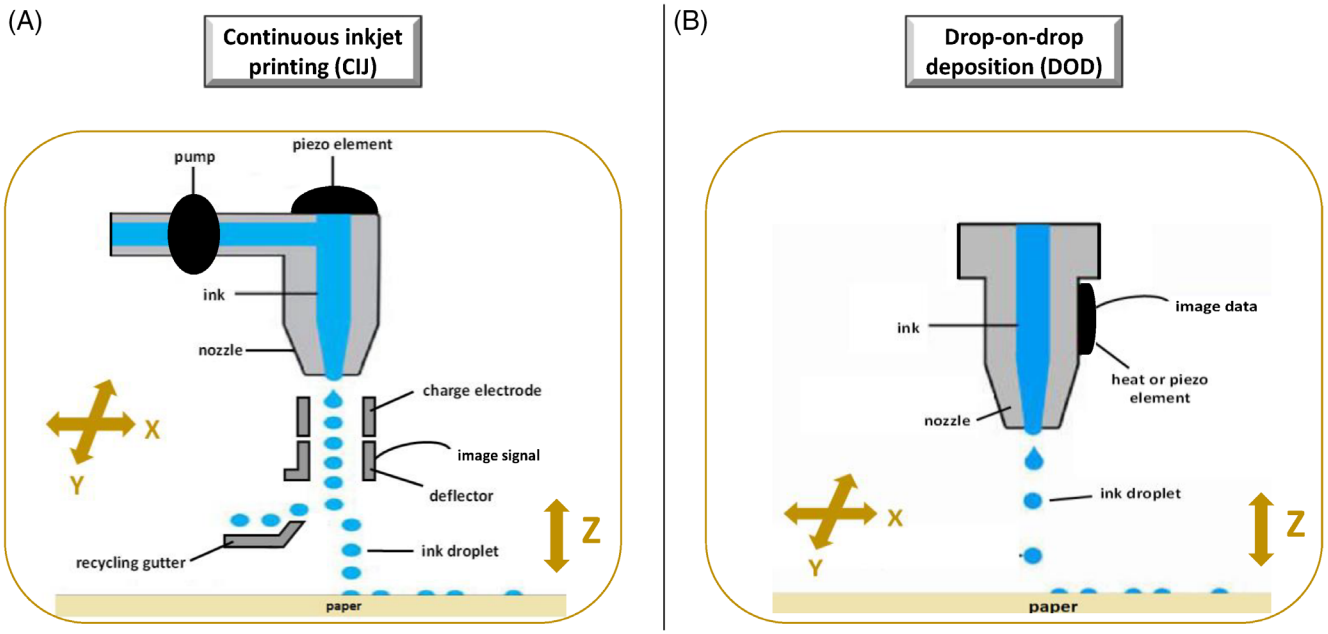


FIGURE 5 Scheme illustrating. (A) Continuous inkjet printing, and (B) drop-on-drop deposition techniques (duplicated from Reference [9]).

3 | THREE-DIMENSIONAL PRINTING IN PHARMACEUTICAL APPLICATIONS: A SPECIAL FOCUS ON FDM

3D printing seems to be very promising in the pharmaceutical sector since it could pave the way for personalized medication regimens. Every day, many people are assuming medicines that will not help them. Just as an example, statins, commonly used to lower cholesterol, are effective only for 1 in 50 people. All this is the result of the fact that current pharmaceutical processing methods produce drugs without meeting the individual needs of patients such as age, gender, severity, and stage of the disease. Indeed, conventional pills are mass-produced in a few distinct strengths depending on the dosage needed to have a therapeutic impact on the majority of individuals, causing adverse effects or not adherence to the treatment in many people.[35] This has prompted scientists to a rethinking of the current medicine's development, laying the basis of personalized medicine. The term "personalized medicine" refers to a recent approach that separates people into different groups, taking into account lifestyle, environment, sex, age, genetic profile, and other specific patient needs, and offers each group a targeted therapy, reducing adverse effects (Figure 6).[36]

Recent developments have demonstrated how powerful 3D printing can be as a tool for realizing individualized therapeutic solutions that are tailored to the demands of individual patients. With the use of this technology, a patient may be linked to all of its actual needs as well as specially formulated medications and therapies, thereby addressing the need to administer "the appropriate drug at the right dose at the right time".[9] One example is the design of drug delivery systems with a specific drug release for pediatric and geriatrics subpopulations. Apart from dose flexibility, the peadiatric population presents a number of problems with the pharmaceutical formulation such as taste masking, patient compliance, and fear or difficulty to swallow tablets—all of which could be overcome by the customizable nature of 3D printing. An increasing number of studies are concentrating on comprehending the preferences of young patients in order to provide guidelines for future advancements in pediatric-appropriate medicine employing 3D printing technologies.[37] Furthermore, 3D printing could allow the preparation of tailored polypills loaded with multiple doses, not forcing the patient to assume several tablets for the medical treatment of different diseases.[35] This strategy would also lower the price of packaging, distributing, and prescribing medicines.[38] Last but not least, AM may soon be a useful tool for developing telemedicine, the remote provision of medical services that makes use of communication technologies whenever doctors and patients are not in close proximity, even for example in cases of pandemic.[38] The application of additive manufacturing in the pharmaceutical field has become more significant since 2012 when the first 3D-printed drug product Spritam® was approved by the US

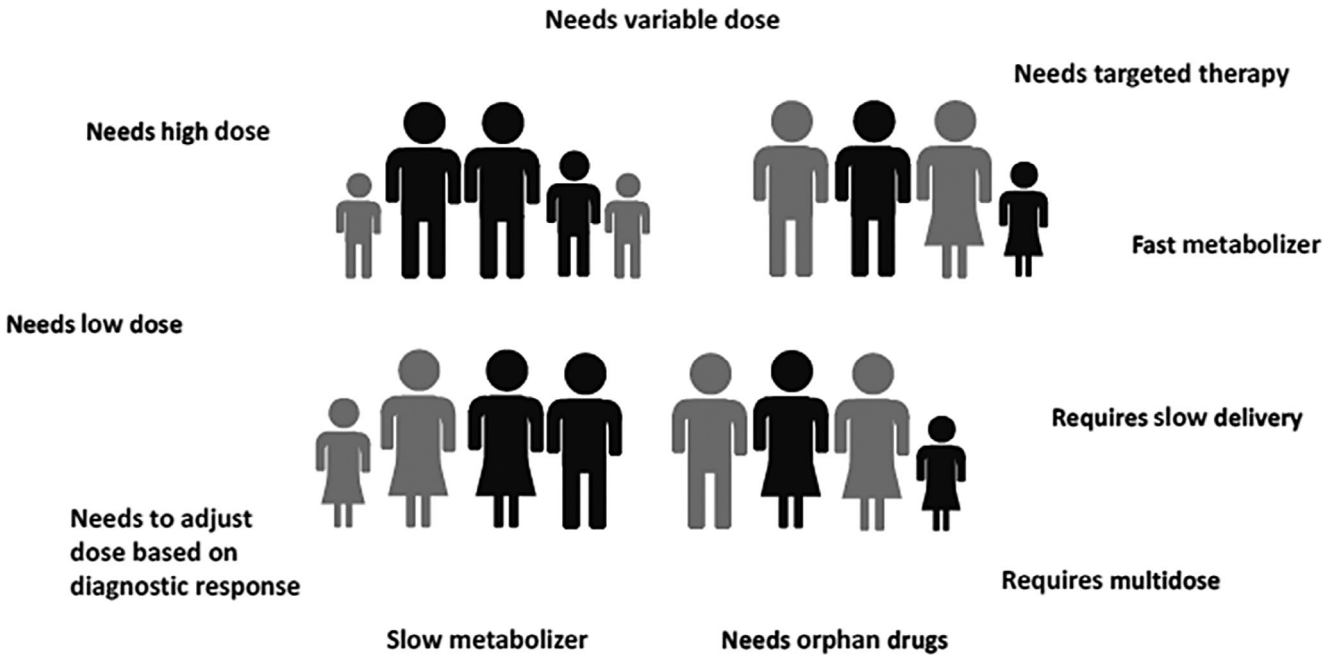


FIGURE 6 Advantages deriving from personalized therapy (duplicated from Reference [9]).

Food and Drug Administration (FDA). Spritam® is a levetiracetam-filled antiepileptic oro-dispersible tablet obtained by Aprecia Pharmaceuticals. Its FDA approval has led to a fast increase in the number of scientific researches on 3D printing technologies with interesting results for the development of tablets and caplets.[7,9,10,39–41]

3D printing based on FDM seems to be very promising for the development of customized drug delivery systems due to its high precision, feasibility, cheapness, versatility, and high resolution, which make it possible to obtain better dosing accuracy.[22] Before fabricating the drug delivery device with this AM technique, the target drug(s) should be loaded into the polymeric filament.[42] Two different approaches can be followed. In the first case, the active pharmaceutical ingredients (APIs) and the excipients are uniformly mixed with the thermoplastic polymer and then processed by HME into a filament form. In the second case, the neat polymeric filament is immersed in a drug-loaded solution (generally a non-solvent for the polymer, such as ethanol) where the diffusion of the drug into the filament takes place, followed by a drying process to ensure the drug entrapment in the polymer.[41] Both these two approaches present pros and cons. The preparation of drug-loaded filaments by HME ensures better drug-loading efficiency, but the exposure of the drug to high temperatures during filament fabrication and printing may cause the degradation of the drug. For the soaking method, the preparation of drug-loaded filaments reported so far has shown that just limited and not very reproducible drug concentrations can be obtained (<2% w/w), resulting applicable mainly for highly potent drugs that do not need significant quantities of dosages to achieve the desired results. However, this method is simple and does not require heating.

Several factors have a substantial effect on the drug release profile of an FDM-3D printed drug delivery device, among which the following can be mentioned:

- Filament production
- Drug loading method
- Initial material characteristics and additives' presence
- Printing parameters such as the layer height, size, and shape, infill density and pattern, porosity, nozzle temperature, and surface area of the formulation.

Recent studies have demonstrated that by playing properly with these parameters it is possible to tune the drug release profile depending on the needs.[9,43] This review provides an overview of the effect of these factors on 3D-printed oral drug delivery systems produced using PVA and PVP as drug-loaded matrixes. The most interesting results obtained in recent works will be presented in the next two chapters.

4 | INTRODUCTION TO POLY(VINYL ALCOHOL)

Polyvinyl alcohol (PVA) belongs to the family of synthetic vinyl polymers and was invented by W. O. Hermann and W. Heahnel in Germany in 1924.[44] It is a linear thermoplastic polymer, biodegradable and biocompatible, characterized by good solubility in water and good mechanical properties. Nowadays, due to its peculiar properties, PVA is used in a wide range of food, medicine, commercial and industrial applications. It is synthesized through the free radical polymerization of vinyl acetate, which yields poly(vinyl acetate) (PVAc), and the subsequent hydrolysis of acetate groups found along the chains of PVAc. Since the hydrolysis reaction cannot be completed, PVA can be produced with various degrees of hydrolysis (DH), resulting in a copolymer of PVA and PVAc. The DH can range from 80.0% to 98.5%, when PVA is partially hydrolyzed (Figure 7B), to a value higher than 98.5% when it is highly hydrolyzed (Figure 7A). From a structural perspective, it shows a chemical formula with a macromolecular chain of C–C atoms with pedant acetate and hydroxyl groups.[45–49]

Depending on the reaction conditions (acidic or alkaline) and the length of initial PVAc chains, the PVA macromolecules can present different tacticity and a wide range of M_w (generally between 9.0×10^3 to 4.0×10^5 g/mol). The DH, the reaction conditions, and the length of initial PVAc chains all contribute to the chemical and physical properties of this polymer, such as the melting point, solubility in water, crystallinity, adhesion, and mechanical strength.[45]

For example, the PVA melting point could range from 180°C, when it is partially hydrolyzed, to 220°C when it is fully hydrolyzed. The viscosity scale moves from 3.4–52 to 4.0–60.0 mPa s with increasing DH and, as regards the water solubility, the lower the DH (around 80/85%), the

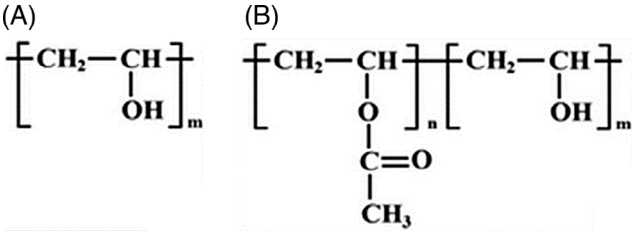


FIGURE 7 The chemical structure for (A) fully hydrolyzed poly(vinyl alcohol), and (B) partially hydrolyzed PVA.[45]

higher the solubility of PVA and the easier its crystallization. This can be seen in Figure 8 where the solubility of a PVA sample characterized by a number average molecular weight of 77 000 is shown as a function of the DH at dissolution temperatures of 20 and 40°C. It is clear the higher the DH, the lower the solubility. High dissolution temperatures and holding times are required for highly hydrolyzed PVA in order to break the intra- and interchain hydrogen bonds.[45,49]

PVA presents a glass transition of 85°C and a degradation temperature in the range of 350–450°C.[25] The main characteristics are synthesized in Table 1.

To reduce its water solubility, PVA can be physically or chemically crosslinked into a hydrogel. The physical, mechanical, chemical, and diffusional properties and amount of fluid uptake of the hydrogel can be easily tailored as a function of the degree of crosslinking.[51]

Over the years, a number of studies on the biocompatibility and oral toxicity of PVA have been conducted, concluding that it is a suitable polymer for biomedical applications.[44,54] For example, PVA has become attractive for repairing and regenerating tissues and organs, such as heart valves and cartilage tissue substitutes, for developing vascular stents, contact lenses, and artificial meniscus. However, only very recent studies have highlighted that it could be an optimum candidate for the preparation of drug delivery systems.[16,55]

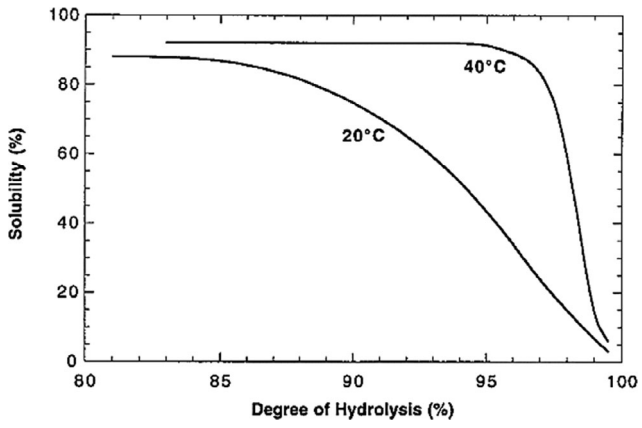


FIGURE 8 Solubility of poly(vinyl alcohol) (PVA), as a function of degrees of hydrolysis, at dissolution temperatures of 20 and 40°C.

5 | PVA-BASED 3D PRINTED DRUG DELIVERY SYSTEMS

Due to its biodegradability, biocompatibility, edibility, and non-toxicity, PVA could be a suitable candidate for several biomedical pharmaceutical applications and, in particular, for the development of sustained-release drug delivery systems by FDM. Sustained-release dosage forms are systems formulated to release the active ingredients gradually over a prolonged period. These formulations are useful to reduce the frequency of dosing, for example from four times a day to once a day.[56]

Goyanes et al. successfully prepared extended-release PVA-based tablets by FDM and investigated the effect of their internal structure (micropore volume), composition, and drug loading on dissolution behavior.[55] PVA filaments containing paracetamol and caffeine were prepared by HME and used to manufacture caplets for oral administration by FDM 3D printing. Some of the 3D-printed caplets are shown in Figure 9A. Due to their thermal stability and different solubility, paracetamol and caffeine were chosen as model drugs. In particular, coffee is a mild stimulant that helps relieve weariness while paracetamol (acetaminophen) is good at reducing mild to moderate discomfort and fever. In the PVA filaments, the chosen theoretical drug concentrations were 5 and 10 wt % but the effective drug loadings were slightly lower (4.3 and 8.2 wt% for paracetamol and 4.7 and 8.2 wt% for caffeine).

The drug release tests performed in bio-relevant media showed different drug release profiles for different types of caplets. In particular, as observable in Figure 9B, a faster drug release was found in formulations containing the drug characterized by greater solubility (caffeine) and concentration, while the delivery rate resulted to be unaffected by the caplets' porosity. Drug loading percentage and drug-specific factors primarily influenced the drug dissolution profiles.[57] Therefore, these aspects were revealed to be fundamental to tailoring the drug release.

The combination of drug therapy is common for treating diseases such as cancer, diabetes, and infections, and, in many cases, drugs are combined in the same dosage to improve compliance. Nowadays, drug combinations are usually manufactured as immediately-release formulations of fixed doses; however, for optimal absorption or to achieve the intended therapeutic impact, the

TABLE 1 Properties of poly(vinyl alcohol) (PVA).

	T_m (°C)	T_m* (°C)	T_g (°C)	η (mPa s)	η* (mPa s)	References
PVA	180	220	85	3.4–52.0	4.0–60.0	[25,50–53]

Note: T_m, melting temperature of partially hydrolyzed PVA; T^*_m, melting temperature for fully hydrolyzed PVA; η, viscosity for partially hydrolyzed PVA; η*, viscosity of partially hydrolyzed PVA.

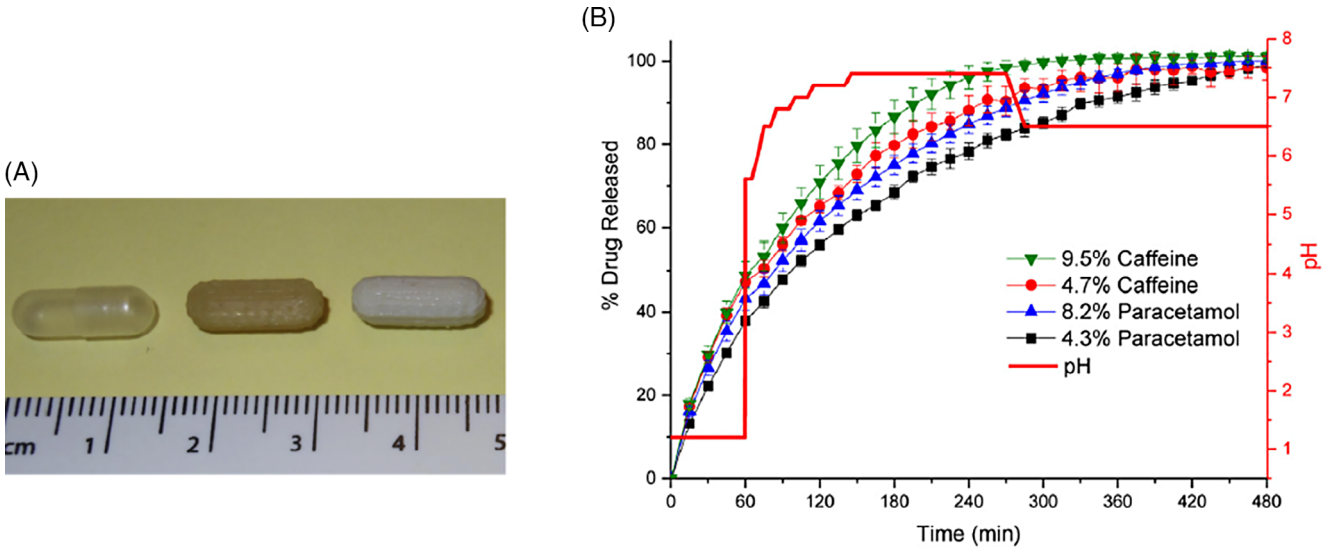
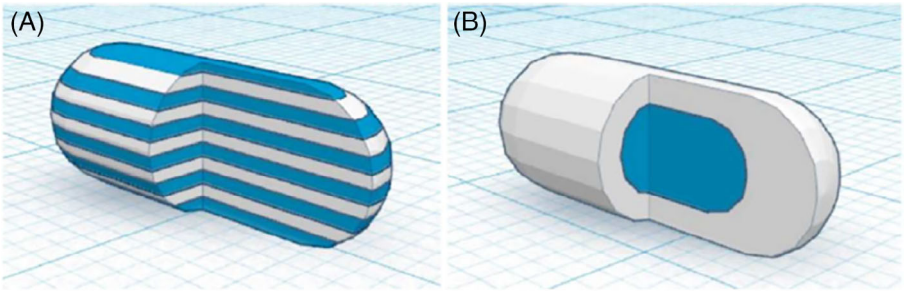


FIGURE 9 (A) 3D printed poly(vinyl alcohol) tablets loaded with caffeine and paracetamol (duplicated from Reference [52]); (B) Drug dissolution profiles from 3DP caplets of paracetamol or caffeine. The red line shows the pH values of the medium (duplicated from Reference [57]).

FIGURE 10 A sectioned multilayer device (A) and a sectioned DuoCaplet (caplet in caplet) (B) are depicted in 3D for the printed solid dosage forms (duplicated from Reference [58]).



simultaneous release of the medications is not always ideal. FDM 3D printing seems to be very promising to easily fabricate multiple-active tablets characterized by a tuned drug release profile. By using a multi-nozzle 3D printer, in another work, Goyanes et al. investigated the feasibility of incorporating both caffeine and paracetamol in the same printed PVA tablets for oral administration.[57] These drugs are often found combined in commercial medicines since caffeine has been observed to enhance the painkilling effect of paracetamol, which raises interest in their incorporation into one single tablet. At first, caffeine and paracetamol-loaded filaments of PVA were prepared by HME. The effective drug loadings were the same as in the previous work. Subsequently, the produced filaments were used to fabricate the oral drug delivery devices. In particular, the authors considered two design configurations of the 3D printed tablets: a multi-layer device, where the two drugs were contained in alternated layers (Figure 10A), and a two-compartment device having a smaller caplet encased by a bigger caplet (DuoCaplet), again, with the various actives contained in each compartment (Figure 10B).

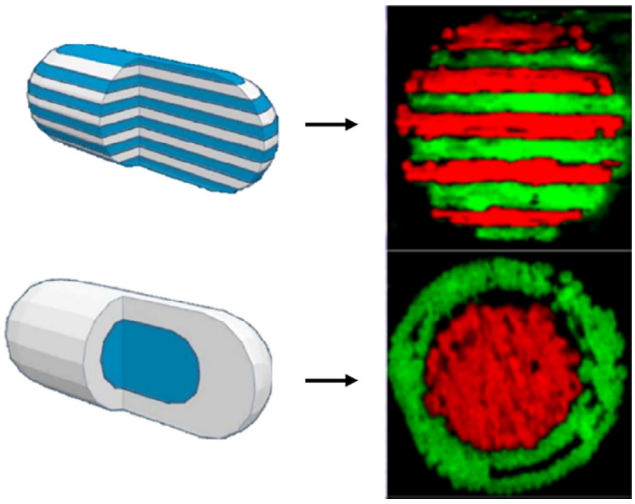


FIGURE 11 Pictures of the cross-section of the created caplets obtained by two-dimensional Raman mapping.[58]

Raman mapping (Figure 11) highlighted the paracetamol- and caffeine-loaded areas and evidenced a clear separation between the different drug layers.

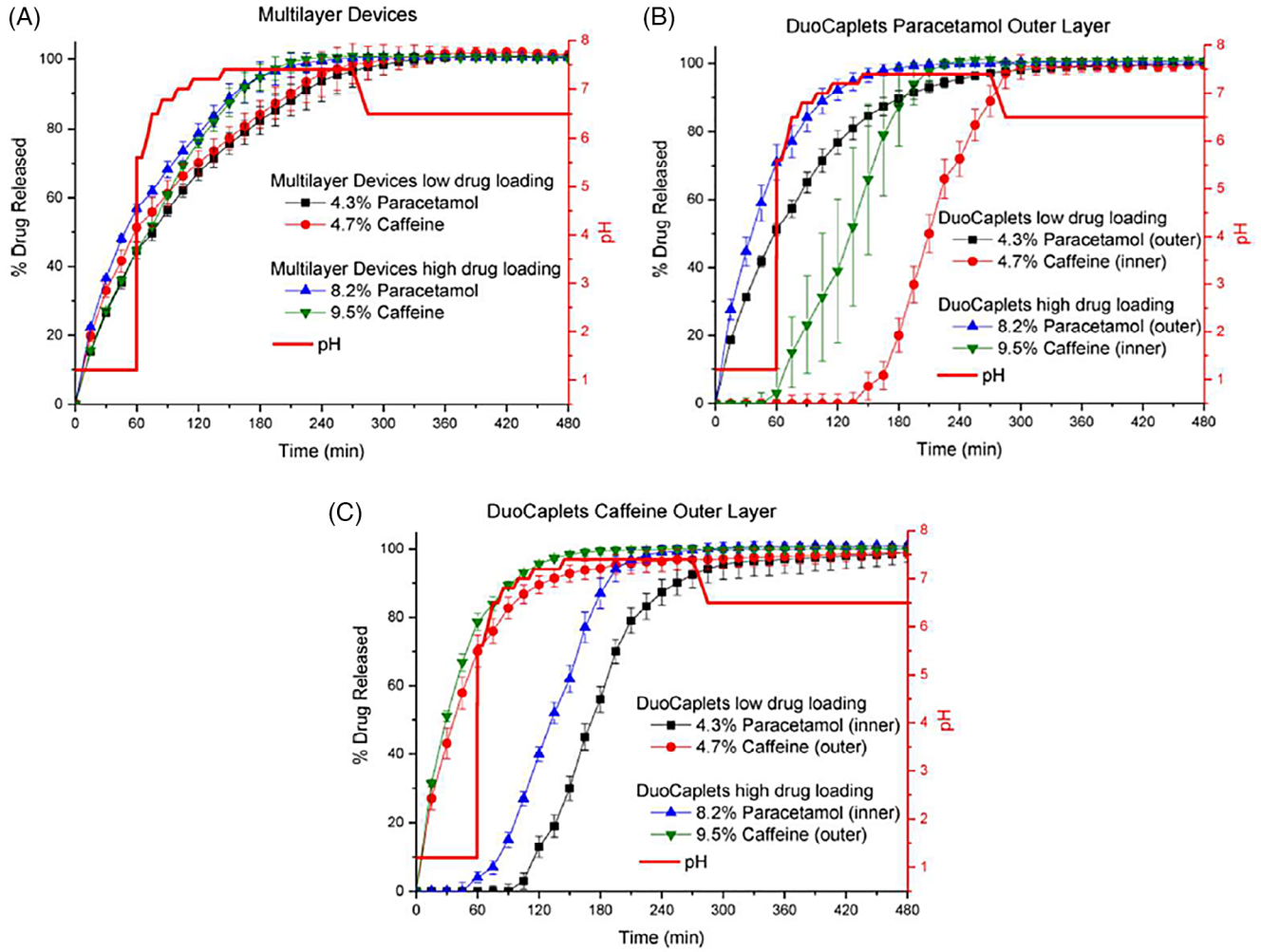


FIGURE 12 Drug dissolution profiles of caffeine and paracetamol from 3D-printed caplets. (A) Multilayer devices; (B) DuoCaplets having paracetamol in the outer layer; (C) DuoCaplets having caffeine in the outer layer (duplicated from Reference [58]).

The 3D-printed tablet architecture was shown to affect the drug release profiles in bio-relevant bicarbonate media. Regarding the multilayer device (Figure 12A), the release of both paracetamol and caffeine occurred at the same time and resulted to be independent of the drug solubility. The increase in the drug loading increased the drug release rate of both drugs. The reduced PVA content in the matrix, which regulates drug release, was attributed by the authors as the explanation for this experimental data. Since different drugs can be isolated in different tablet parts, a multilayer system like this one might be useful for delivering chemicals that are incompatible with one another or for releasing various medications with the same release profile. As regards the DuoCaplet design (Figure 12B,C), the drug loaded in the external layer was released first, and only when the external layer was dissolved the release of the drug in the internal layer occurred. Moreover, the properties of the external layer, such as the thickness, determined the lag time for the release of the drug contained in the core. These results highlighted that the production of various structures using 3D printing modifies the drug dissolving profiles of drug combinations and may be used in the future to create novel dosage forms for individualized dosing.[58]

The same research group also studied the effect of geometry on the drug release of 3D-printed tablets.[59] PVA filaments containing 4 wt% of paracetamol were prepared by HME and then used to fabricate 3D-printed tablets having different shapes by FDM. The cube, pyramid, cylinder, sphere, and torus were the 3D geometries chosen. Three tablet series were printed having the same surface area, surface area/volume ratio, and weight, respectively (Figure 13).

Tablets of all geometries were easily fabricated, demonstrating once again the potential of 3D printing in pharmaceutics. The dissolution tests evidenced that the geometry of the oral drug delivery devices

FIGURE 13 Images of the 3D-printed tablets at constant (A) surface area, (B) surface area/volume ratio, and (C) mass (scale bar in cm) (duplicated from Reference [59]).

influenced the API release profiles. Drug release rates were in the following sequence (fastest first) when the surface area was held constant (Figure 14A): pyramid, torus, cube, sphere, and cylinder. On the other hand, the rate order was sphere and cube, torus, cylinder, and pyramid when tablets were produced at a constant surface area/volume ratio (Figure 14B). Lastly, drug release characteristics from devices of constant weight (Figure 14C) were remarkably similar. The drug release probably occurred due to an erosion-mediated process and the erosion may explain why tablets of a similar mass showed no significant differences in the dissolution profiles. These results highlighted that the tablet geometry is one of the factors to play with to modulate the drug release profile.

Floating drug delivery systems (FDSs) are devices that float in gastric juice to ensure that drugs, embedded inside them, do not leave the stomach shortly. Singpanna et al. successfully prepared an FDS by FDM, using PVA as a filament, and investigated its drug release performance. Their research aimed at evaluating the effect of crosslinking time of PVA on the release of domperidone from the device[60] (Figure 15A). Domperidone is a drug used in case of nausea, vomiting, and gastrointestinal disorders. It dissolves well in an acidic environment, and therefore prolonging its residence time in the stomach could help in increasing its bioavailability.

The research group observed that the crosslinked FDSs sustained the drug release considerably better than the non-crosslinked FDSs. As can be noticed in Figure 15B, 100% of domperidone was delivered within 1 h from the non-crosslinked FDS. On the contrary, the FDSs crosslinked at 120°C exhibited a slower drug release. In particular, the optimal crosslinking condition was obtained at a temperature of 120°C for 6 h.[60]

Obeid et al. investigated the possibility of tailoring drug release through the use of excipients and the impact of infill patterns on the drug release of 3D-printed tablets.[61] PVA filaments containing excipients and amlodipine as a model drug were prepared by HME and then used to fabricate 3D-printed tablets by FDM. Four different formulations were prepared, each printed in four different infill patterns: cubic, concentric, zigzag and trihexagon. The excipient addition to the formulation and the type of excipient used resulted to influenced the dissolution profiles of the tablets. In addition, also the infill pattern and wall thickness were revealed to affect the drug release. This study demonstrates that both the composition of the formulation and the design of the tablet contributes to determining the drug dissolution profiles.[61]

Windolf et al. discovered that the drug release profile remained the same if the surface area/volume ratio of the 3D-printed tablets was kept constant.[62] The 3D-printed tablets were produced using PVA and a combination of vinylpyrrolidone-vinyl acetate copolymer (PVA-VA) and ethylene-vinyl acetate (EVA) as a polymer matrix, while pramipexole, levodopa and praziquantel were the model drugs selected. HME was used to produce the drug-loaded filaments and FDM was adopted to manufacture the 3D-printed tablets. This result is quite intriguing since it may be possible to alter the drug dosage without having an impact on the blood plasma level profile following consumption of the pill based on specific markers.

As it was mentioned in Section 3, the soaking method is another approach to incorporate the APIs into the polymer, generally favored when heat-sensible drugs are employed. However, only low drug concentrations can be achieved by this method. Recently, Mahmood et al. discovered that the drug loading efficiency of pre-fabricated PVA filaments can be strongly enhanced (even up to

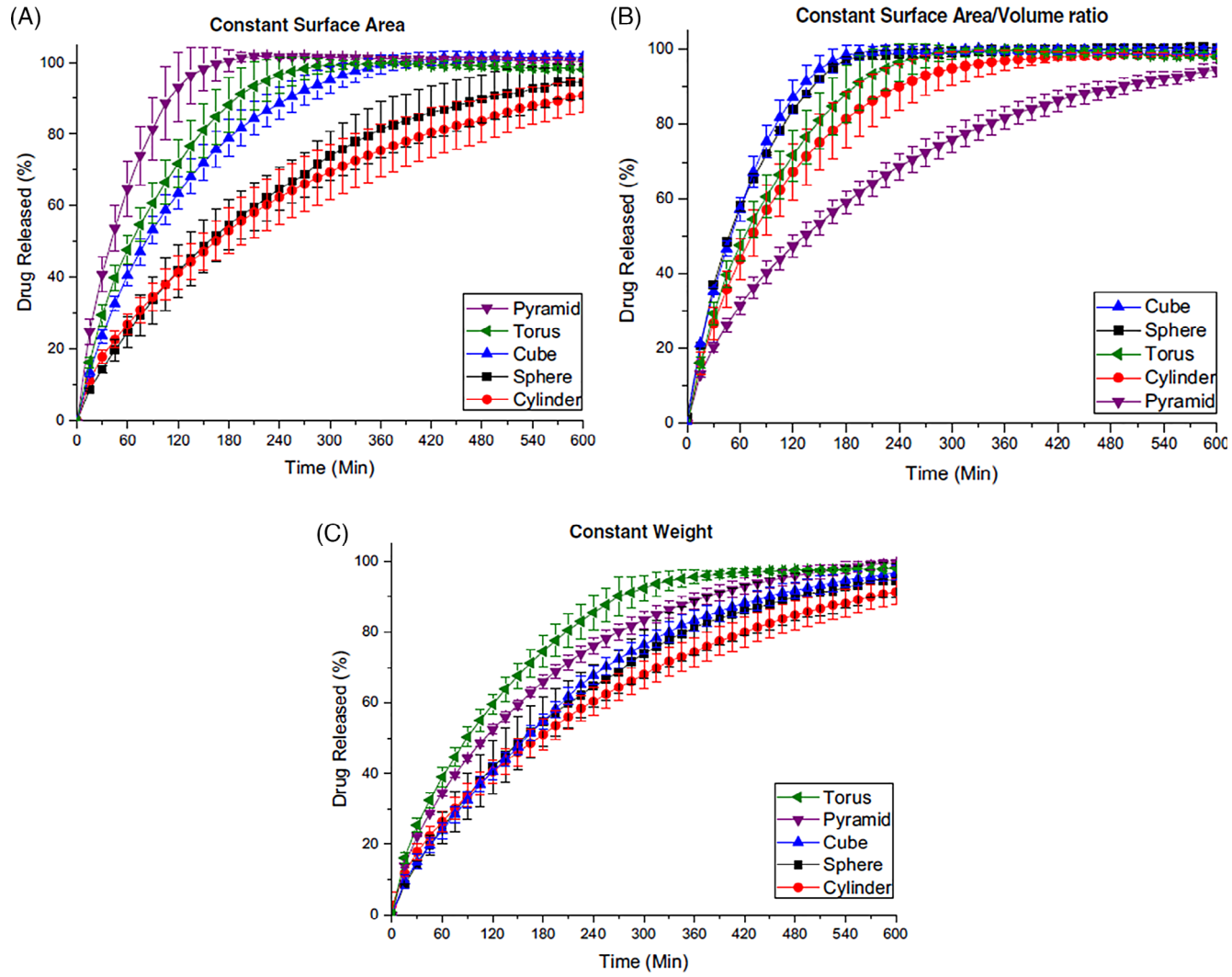


FIGURE 14 Drug dissolution profiles from 3D printed tablets of paracetamol having (A) constant surface area, (B) constant surface area/volume ratio, and (C) constant weight (duplicated from Reference [59]).

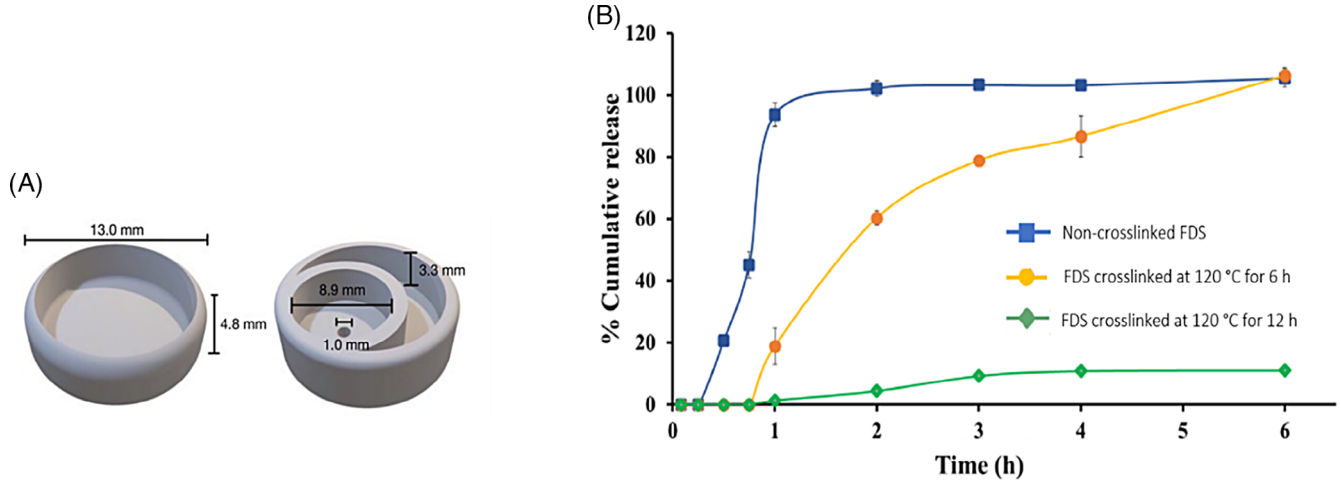


FIGURE 15 (A) The cap and the body of the floating drug delivery system (FDS) produced (duplicated from Reference [60]); (B) In vitro drug release of domperidone from the non-crosslinked FDS, FDS crosslinked for 6 h at 120°C and FDS crosslinked for 12 h at 120°C (duplicated from Reference [60]).

20 times) by introducing solubilizers and/or plasticizers, such as sodium lauryl sulfate and glycerine, in the drug solution.[63] This result is of great interest since could strongly improve and revolutionize the loading of heat-sensible APIs in PVA filaments, without compromising their printability. Ibrahim et al. produced 3D-printed metformin HCl-loaded PVA tablets by FDM and used a modified solvent approach to improve the drug loading.[64] PVA filaments were poured both in absolute ethanol and in a solvent mixture of ethanol–water (9:1) where API was previously dissolved. They discovered that the solvent mixture of ethanol-water accelerated and increased the metformin concentration in the PVA filament. Furthermore, they observed that the area/mass ratio of the tablets influenced the drug release.[64]

The effect of soaking method conditions on drug loading efficiency was investigated by Tagami et al. using curcumin as a model drug. They discovered that the drug loading and drug dissolution profile were significantly influenced by the type of organic solvent, temperature, and drug concentration. In their work, PVA filaments were incubated in a variety of organic solvents (IPA, MeOH, ACE, and EtOH) that contained a fixed amount of dispersed curcumin and, over time, the accumulation of curcumin in the filaments was registered. They observed that the curcumin amount in PVA depended on incubation time for all solvents and it changed with the solvent type in the following order (greater first): MeOH > EtOH > ACE > IPA. Furthermore, they found that by heating the drug solution, the curcumin amount was much higher than that without heating, and, by boosting the amount of drugs in the solvents, the curcumin concentration in PVA filaments increased as well. As regards the drug dissolution profile, a delayed dissolution was registered in PVA tablets containing higher amounts of curcumin.

The effect of different process parameters on the dissolution rate of fluorescein-loaded PVA tablets was studied by Sharma and his research group.[65] Fluorescein was loaded in PVA filaments through the impregnation route and the modified filaments were then used to fabricate tablets. It was found that the infill percentage followed by print speed and layer thickness were the most critical parameters affecting the dissolution rate. In particular, an increase in tablet dissolution rate was registered with increasing infill percentage and layer thickness.

6 | INTRODUCTION TO POLY(VINYL PYRROLIDONE)

Poly(vinyl pyrrolidone) (PVP) is a vinyl polymer characterized by very interesting properties, such as biodegradability, low cytotoxicity, high chemical and thermal resistance, good environmental stability, and affinity to both hydrophilic and hydrophobic substances.[45,55,66–68] As shown in Figure 16, it is synthesized by free radical polymerization from the monomer *N*-vinylpyrrolidone in the presence of azobisisobutyronitrile (AIBN). The amphiphilic nature of PVP is due to its chemical structure: while the lactam group in pyrrolidone offers hydrophilicity, the non-polar methylene moiety guarantees lipophilicity.

Dry PVP comes as a light flaky hygroscopic powder capable of absorbing up to 40 wt% of water. In solution it exhibits optimum wetting properties and easily forms films, making it ideal as a coating.[14] PVP was first produced in 1938 and initially used as a plasma substitute for trauma victims during world war II.[14,15] Nowadays, this polymer is used in a variety of applications and has received US Food and Drug Administration approval as a safe polymer for experiments because of its biocompatibility, ease of processing, and non-antigenicity.[45] When administered orally, recent studies have demonstrated that PVP having a low molecular weight, approximately $1.7{\cdot}10^3$ g/mol, is completely excreted through the kidneys and, therefore, could be an interesting candidate for oral drug delivery device fabrication.[45]

7 | PVP-BASED 3D PRINTED DRUG DELIVERY SYSTEMS

Approximately 70% of oral dosage formulations are designed to release the drug immediately or quickly after administration. This is needed when a fast onset of action is required for therapeutic reasons. For example, a painkiller-loaded tablet should disintegrate fast in the gastrointestinal tract to allow a rapid uptake into the body.[56] PVA was discovered to be unsuitable for the production of dosage forms for immediate release. Conversely, recent works in the literature have evidenced that PVP might be an ideal candidate to produce 3D-printed tablets by FDM with an immediate release profile.[69]

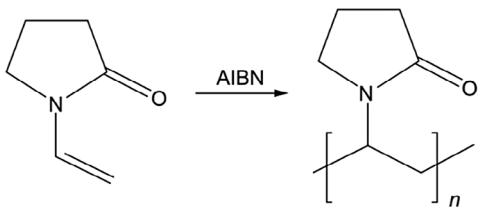


FIGURE 16 Synthesis of poly(vinyl pyrrolidone).[15]

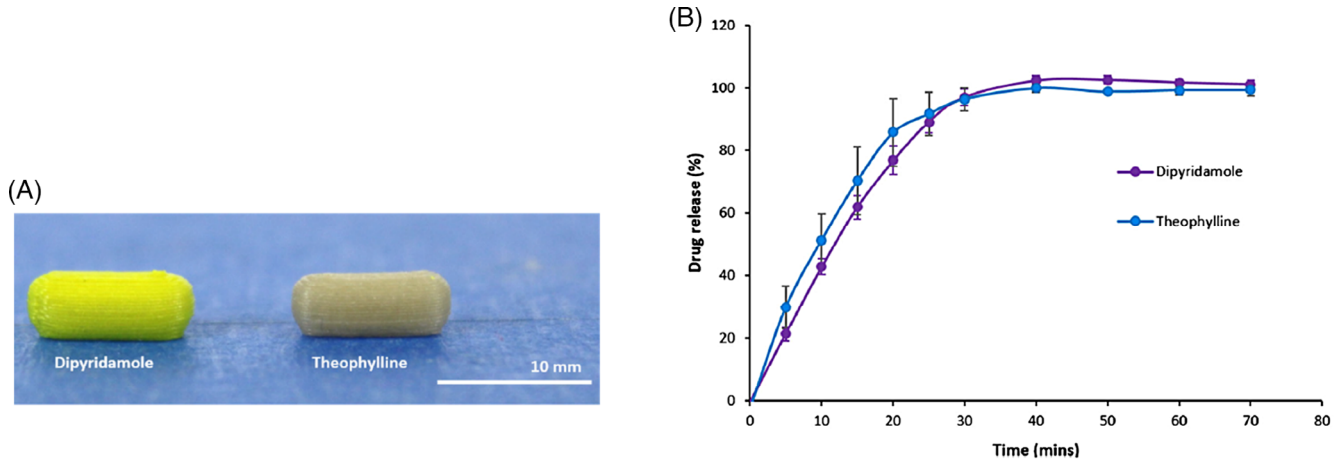


FIGURE 17 (A) Poly(vinyl pyrrolidone) (PVP) 3D-printed drug-loaded tablets (duplicated from Reference [69]); (B) In vitro dissolution of profiles from PVP-based 3D printed tablets (duplicated from Reference [69]).

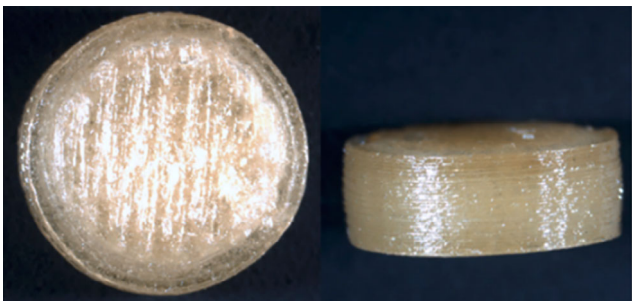


FIGURE 18 Reflected light microscope pictures in top and side view of printed poly(vinyl pyrrolidone) tablets containing the active pharmaceutical ingredient (duplicated from Reference [70]).

Okwuosa and his research group first employed PVP in FDM 3D printing in 2016 and investigated the drug release profile of PVP tablets printed at temperatures as low as 110°C.[69] Theophylline, used in the therapy of respiratory diseases (melting point 270°C), and dipyridamole, an antiplatelet agent (melting point 165°C), were used as model drugs. PVP filaments loaded with the APIs were prepared by HME and then used to fabricate caplet shape tablets by FDM (Figure 17A).

It was discovered that 3D-printed tablets disintegrate faster than 15 min. In addition, the in vitro dissolution tests evidenced that within the first 30 min, more than 85% of theophylline and dipyridamole were released, highlighting the suitability of PVP to fabricate immediate-release formulations. In Figure 17B the drug dissolution profiles from PVP tablets are reported. The optimum results obtained by this research group and the low printing temperature revealed that a wider range of pharmacological compounds, frequently utilized in immediate-release dosage forms, may be adaptable to FDM.[69]

The possibility to achieve an accelerated drug release from 3D-printed PVP tablets by playing with processing parameters was explored by Kempin et al.[70] Pantoprazole sodium, a thermo-sensitive medicine used to treat stomach and esophagus problems, was selected as a model drug. PVP filaments containing 10 wt% (w/w) of API were prepared by HME and adopted to print by FDM cylindrical shape tablets, as shown in Figure 18. The tablet size was chosen to contain 20 mg of the drug and the effect of three infill densities (100%, 90%, and 50%) on drug release was considered.

The authors registered an accelerated drug dissolution with decreasing infill densities, thus increasing the tablet porosity. They observed a similar drug release profile for tablets having 100% and 90% infill density, while a significative faster drug dissolution for the 50% infill tablets. In particular, the total medication release time decreased from 10 to 3 min, reaching the fastest drug release time from FDM-printed tablets described in the literature.

8 | CONCLUSIONS AND FUTURE PERSPECTIVES

3D printing could change the ways of conventional drug manufacturing, allowing the production of high-quality tailored dosage forms for each patient according to their individual needs. In fact, with drug dosing and drug release profile personalization, this technology offers the possibility to overcome widespread problems in the pharmaceutical field, such as medication non-adherence, ineffective treatment, and patient compliance.

Among the AM techniques, FDM has received noticeable attention due to its high precision, cheapness,

resolution, and feasibility. By playing properly with factors such as drug loading method, filament production, and printing parameters (layer height, shape, size, etc.), one can tune the drug release profile of an FDM-3D printed drug delivery device depending on the needs.

Recent studies have brought to light the potential of PVA and PVP as API-loaded matrices for manufacturing oral drug delivery devices by FDM. Due to their attractive properties (e.g. biocompatibility, non-toxicity, biodegradability, good mechanical stability, edibility, etc.), PVA and PVP have been widely studied for biomedical applications. However, only very recent works have highlighted that they could be optimum candidates for the preparation of drug delivery systems. The literature meta-analysis reported in this review highlighted that: PVA is suitable for the development of systems for sustained-release medication delivery, while PVP of immediate-release devices; the low printing temperatures of PVP (approx. 100–110°C) allow the incorporation of heat-sensible drugs into the filaments; the solubility and concentration of the APIs affect the drug release profile; by varying the tablet geometry, it is possible to modulate the API release; infill density, print speed, and layer thickness are the most critical parameters affecting the dissolution rate; when the soaking procedure is used to load the APIs into the polymers, the solvent type, the drug concentration, and temperature greatly affect the drug loading and drug dissolution profile.

Despite the benefits that 3D printing could have for the pharmaceutical industry and the achievements reached in understanding the most influencing parameters to tailor and tune the drug release, there are still limitations and challenges to face.[13] Prior to customized 3D printed products being readily accessible to patients, there is obviously much work to be done.[38] Currently, 3D printing is not appropriate for larger-scale pharmaceutical manufacturing, and issues concerning regulatory requirements by FDA have to be considered.[1] Indeed, guaranteeing that 3D-printed medicines are as effective and safe as those created using traditional methods still presents a serious challenge.[25,38] Generating real-world evidence to support precision dosing and the use of customized dosage regimens in clinical practice are other two obstacles that come up during the new medication development process.[38] Furthermore, as it was possible to understand, the entire process of producing an FDM-3D printed drug delivery device typically involves iterative adjustments to the formulation composition or/and numerous printing parameters (extrusion temperature, layer height, percentage infill etc.). Due to the multifunctional nature of FDM 3D printing, conventional systemic methods of evaluating each input variable on printing success and drug release characteristics of the 3D printed drug delivery devices are often time-consuming.[71] Machine learning (ML), a branch of artificial intelligence that enables pattern recognition from large and complex datasets, would seem to be a potential tool to optimize and accelerate pharmaceutical 3D printing. The data generated by ongoing research in pharmaceutical 3D printing could be used by ML to predict the performance of medication delivery devices. In 2022, using ML models, Ong et al. developed an updated web application to provide predictions on filament characteristics, printability, FDM processing temperatures, and drug release profiles.[71] However, for the optimal predictive performance of ML models, a balanced dataset is necessary, but data available from published works often only include positive successful outcomes.

Despite these challenges, the results obtained so far are very promising and demonstrate that the revolution in medication manufacturing methods is just getting started.

AUTHOR CONTRIBUTIONS

Marica Bianchi: Conceptualization, Writing-original draft; **Giulia Fredi and Alessandro Pegoretti:** Writing-review and editing.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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