https://doi.org/10.31925/farmacia.2024.6.3 **REVIEW**

THE ROLE OF 3D PRINTING IN THE DEVELOPMENT OF DOSAGE FORMS WITH TAILORED DRUG RELEASE

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Abstract

In recent years, there has been growing interest in the application of 3D printing technology in the production of drug delivery systems. The particular advantages of using 3D printing lie in the production of drug delivery systems with dose, appearance (size, shape, colour, etc.) and drug release pattern tailored to the characteristics of each patient. This enables more efficient therapy, improved patient compliance, reduced costs, and fewer side effects. Due to simple fabrication of very complex architectures, 3D printing offers far greater opportunities to achieve the desired drug release patterns compared to conventional methods of manufacturing dosage forms. Numerous studies describe the successful application of 3D printing in the development of drug delivery systems with different release patterns, from simple immediate and prolonged release to more complex multiphasic release systems and trigger-induced drug release systems. Tailored drug release from 3D-printed drugs can be achieved in two ways: by fabrication of dosage forms of appropriate design or fabrication of device that controls the release of drugs from inserted dosage form prepared by conventional techniques. This article provides a brief overview of different 3D printing approaches used in the development of dosage forms with tailored drug release.

Rezumat

În ultimii ani, a existat un interes tot mai mare pentru aplicarea tehnologiei de imprimare 3D în producția medicamentelor cu eliberare controlată. Avantajele utilizării imprimării 3D constau în realizarea de sisteme de eliberare a medicamentelor cu doză, aspect (dimensiune, formă, culoare, etc.) și profil de eliberare adaptate caracteristicilor fiecărui pacient. Acest lucru permite o terapie mai eficientă, o mai bună aderență a pacientului, costuri reduse și mai puține efecte secundare. Datorită posibilității de fabricare simplă a unor structuri foarte complexe, imprimarea 3D oferă oportunități mult mai mari de a obține profilele dorite de eliberare a medicamentelor comparativ cu metodele convenționale de producție a formelor farmaceutice. Numeroase studii descriu aplicarea cu succes a imprimării 3D în dezvoltarea sistemelor de eliberare a medicamentelor cu profile diferite de eliberare, de la eliberare imediată și prelungită până la sisteme mai complexe cu eliberare multifazică și eliberare indusă de factori declanșatori. Eliberarea personalizată a medicamentelor din formele obținute prin imprimare 3D poate fi realizată în două moduri: prin fabricarea formelor farmaceutice cu un design adecvat sau prin fabricarea unui dispozitiv care controlează eliberarea medicamentelor din forma de dozaj inserată, pregătită prin tehnici convenționale. Acest articol sintetizează diferitele abordări de imprimare 3D utilizate în dezvoltarea formelor farmaceutice cu eliberare personalizată.

Keywords: 3D printing, tailored drug release, controlled release, gastroretentive drug delivery systems, personalised medicine

Introduction

Three-dimensional (3D) printing is a method for fabrication of objects by deposition of material in layers, whereby a 3D object is created in a shape that is specified by computer-aided-design (CAD) software. This process is also known as additive manufacturing (AM), rapid prototyping (RP) or solid free-form technology (SFF) [1].

For most patients, conventional therapy is still based on the administration of predefined drug doses. However, the administration of the same drug doses can cause different reactions in different people. The consequences of using drug doses that do not meet the individual needs of patients can be the occurrence of side effects, the absence of a therapeutic effect or a suboptimal therapeutic effect. With the progress of science and methods of genome analysis, it has been shown that the metabolism of most drugs and thus also the therapeutic response is influenced by the genetic characteristics of the individual patient, which makes it necessary to adjust the dose to the individual patient characteristics. In addition, the therapeutic response may vary depending on the age, weight, organ function and specific characteristics of the disease being treated [2, 3]. To avoid the above problems and improve the quality and outcomes of healthcare, it is necessary to work on the development of dosage forms that are adapted to the needs of individual patients. Adjustment refers not only to the dose of the active substance, but also to the drug release pattern, as well as other characteristics of the dosage form such as shape, size,

colour, taste, odour, etc. Solid dosage forms, especially tablets, make up the largest share of the pharmaceutical market. Conventional manufacturing processes at industrial level are not able to adapt the dosage of drugs to the specific needs of patients and are therefore not suitable for the production of drugs adapted to the characteristics of the individual patient [4].

Conventional immediate release drug delivery systems allow for rapid release and onset of action, but when used, it is difficult to maintain therapeutic concentrations of the drug over a prolonged period of time. Therefore, such preparations are usually administered several times a day, but even then significant fluctuations in drug concentrations outside the therapeutic range can occur. Frequent administration of drugs also has a negative impact on patient compliance and can therefore jeopardise the success of the therapy used. Prolonged-release systems are therefore becoming an increasingly attractive option in therapy. The use of these systems enables drug release during an extended period, which enables longer maintenance of the drug concentration and a reduction in the dosing frequency, with fewer side effects [5, 6]. In addition to extended-release systems, different types of diseases require different drug release patterns, which imposed need for development of pulsatile and gastroretentive dosage forms, or dosage forms with drug release controlled by an internal or external trigger signal [7, 8, 9].

The ability to fabricate objects with complex architecture defined by CAD software, containing multiple materials, with precise deposition of each material, makes 3D printing a promising technique for the development of dosage forms with tailored drug release. This gives 3D printing clear advantages over the conventional manufacturing processes, where drug release is usually modulated by changing the composition of the formulation. This review discusses current achievements in the application of 3D printing for the development of drug delivery systems with tailored drug release. A brief overview of the basic principles of 3D printing techniques with potential application in the fabrication of dosage forms is provided followed by a discussion of different examples of 3D printing applications in the development of drug delivery systems with tailored drug release.

Key Features of 3D Printing

3D printing is a technology that enables the production of objects with the desired design and is therefore widely used in various industries such as aviation, robotics, the food industry and the production of medical devices [10]. In recent years, 3D printing has been increasingly explored in the context of fabrication of drug delivery systems, as it offers the possibility of providing personalised therapy, increasing treatment adherence and reducing healthcare costs [3]. Another application could be the production of drugs with a short shelf life close to the point of administration [11].

The first 3D printing technique described is stereolithography (SLA), which was developed by Charles Hull in 1986, while other techniques were developed very soon after. Initially, this technique was primarily used in architecture and for the production of aesthetic and functional prototypes due to its speed and low cost, but it evolved into a technique suitable for the production of small series of products tailored to specific needs as well as for large-scale industrial production [12]. Although most 3D printing techniques date back to the 1980s and 1990s, significant progress in this field has only been seen since the beginning of the 21st century, after patent protection for most 3D printing techniques expired. The real expansion of the use of 3D printing for the production of pharmaceutical dosage forms occurred after the FDA approval of the first 3D printed drug, the orally disintegrating tablet Spritam® in 2015 [12, 13].

The main advantage of 3D printing is the ability to customise the design of the object, *i.e.* the production of series of personalised products, so that each product can be different without the price being high due to the simultaneous production of a large number of objects. This enables the production of pharmaceuticals with customised drug doses as well as dosage forms with multiple active ingredients that can also be released in completely different ways. Another advantage of using 3D printing is the ability to produce objects at the point of care, in hard-to-reach areas and in regions affected by war or natural disasters [4, 10]. This improves the availability of healthcare and ensures rapid access to medicines that can save patients' lives.

Although the principles of material deposition and solidification differ between the various 3D printing techniques, the basic phases of producing an object using 3D printing remain the same. Firstly, the object is designed using CAD (Computer Aided Design) software. The CAD file is then converted into an STL file format, which describes the outer surface of the 3D model and serves as a guide for layer-by-layer printing. As the STL file only describes the surface geometry of the designed object, novel file formats were developed, such as the Additive Manufacturing File Format (AMF) or the 3D Manufacturing Format (3MF), which contain additional data about the object structure, colour and texture as well as material properties. The STL format can easily be converted to AMF or 3MF format, and backwards conversion to STL is possible, but the advanced features available in AMF and 3MF are lost. While additive manufacturing relies primarily on the use of the STL format, the enhanced features of newer formats will likely lead to wider adoption as the 3D printing industry continues to evolve. In the next step, the STL file is sliced to translate it into 2D layers and G-code is created, which serves as instructions for printing in a numerically

controlled programming language. After these steps, the printing process is performed, which varies depending on the printing technique used, followed by post-processing of the printed object if necessary [3, 12, 13]. The limited number of materials available for 3D printing of pharmaceuticals and other medical products is one of the greatest challenges that need to be overcome before the widespread adoption of this technology. Therefore, there is a great need for the development of safe materials that can be used for printing medical products. Another limitation of 3D printing is the poor mechanical properties of the resulting objects as well as the presence of defects in the structure and on the surface, which is particularly pronounced in certain techniques [14]. As a result, additional post-processing of the printed objects is sometimes required. In addition, the speed of the printing process is lower compared to industrial processes. In recent years, however, considerable progress has been made in improving the techniques themselves, which has increased the speed and improved the properties of the end products.

3D Printing Techniques

3D printing techniques differ in terms of the type of material used for printing, the method of layer-by-layer material deposition and the properties of the final product. Techniques that have been used for the fabrication of pharmaceutical dosage forms include: binder jetting, fused deposition modelling (FDM), semi-solid extrusion (SSE), vat photopolymerisation, and selective laser sintering (SLS).

Binder jetting 3D printing. Binder jetting 3D printing is based on the controlled deposition of liquid droplets on a suitable substrate (Figure 1). An active ingredient can be dissolved or dispersed with other excipients in a liquid phase that is sprayed, or it can be part of a powder mixture onto which the binder solution is sprayed. Depending on the method of spraying the binder solution, continuous and drop-on-demand binder jetting 3D printing techniques can be distinguished [15, 16].

In continuous binder jetting, the binder solution is sprayed continuously under the pressure generated by a pump. The disadvantage of this technique is a higher consumption of binder solution, but on the other hand the risk of nozzle clogging is lower. In drop-on-demand binder jetting, spraying onto the substrate is precisely controlled and only takes place when required during the printing process. Droplet spraying in drop-on-demand binder jetting is based on nozzles with piezoelectric crystals or thermal elements. Drop-on-demand binder jetting offers a higher printing speed and resolution with significantly lower binder consumption [3, 16].

Drop-on-demand binder jetting can be performed in a drop-on-drop manner, where generated droplets are deposited on top of each other to form a solid object after solvent evaporation. On the other hand, in the drop-on-powder method of binder jetting 3D printing, droplets of a liquid phase are sprayed onto a layer of powder material. After spraying onto a layer of material, the next layer of powder is applied using a printer roller. This process is repeated, alternately spraying droplets of liquid and applying a new layer of powder, until the entire object is formed [17].

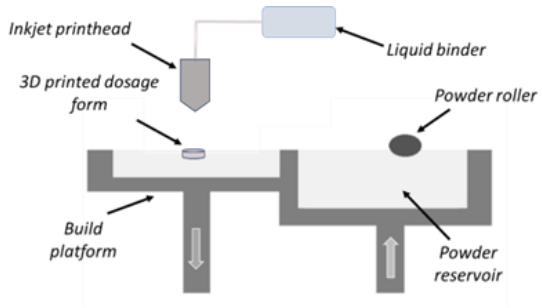

Figure 1.
Schematic presentation of binder jetting 3D printing

Binder jetting 3D printing is capable of producing highly porous dosage forms that rapidly disintegrate, which is the reason why this technique was used for production the first FDA-approved 3D printed drug - Spritam®, orally disintegrating tablets with a high drug dose [16].

Fused Deposition Modelling (FDM) 3D printing. Fused deposition modelling (FDM) 3D printing is based on the layer-by-layer deposition of molten material according to a predefined model. This printing technique uses thermoplastic filaments that are fed into a heated printer nozzle, where they are melted and extruded layer-by-layer onto a heated build platform (Figure 2).

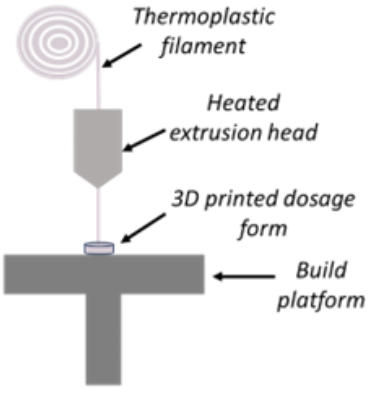

Figure 2.
Schematic presentation of fused deposition modelling (FDM) 3D printing

The printer nozzles can move in an X-Y direction, allowing the material to be deposited within the predefined shape of the model. After each layer is deposited, the build platform moves down by the

layer thickness to allow for the deposition of the next layer of material [10, 13].

Due to the widespread availability and low cost of FDM printers, this technology has been extensively investigated for potential applications in the development of drug delivery systems. The availability of a wide range of thermoplastic polymers approved for pharmaceutical use and the ability to rapidly create highly complex architectures support its application in pharmaceutical field. However, a limitation of this technique is high temperature used in this process, which can lead to degradation of the active pharmaceutical ingredient (API). Since there are no commercially available filaments with APIs, they must be produced separately by hot melt extrusion prior to printing, making the process even more complex and exposing the material to high temperatures [10, 16].

Semi-solid extrusion (SSE) 3D printing. In semi-solid extrusion (SSE) 3D printing, the mixture of API and excipients is first converted into a gel or paste form by adding a liquid phase or by gentle heating. The key step in this printing technique is the extrusion of the semi-solid mass through a syringe and printer nozzle under the action of compressed air or mechanical pressure (Figure 3). The subsequent printing process is similar to FDM 3D printing and involves the layer-by-layer deposition of the semi-solid material from a nozzle that moves in the X-Y direction [18, 19].

The final stage in forming the desired object depends on how the semi-solid mixture was obtained. If the mixture was converted to a semi-solid state at high temperatures, the object solidifies by cooling to room temperature. In cases where solvents were used in the preparation of the mixture, subsequent drying of the object is required [19].

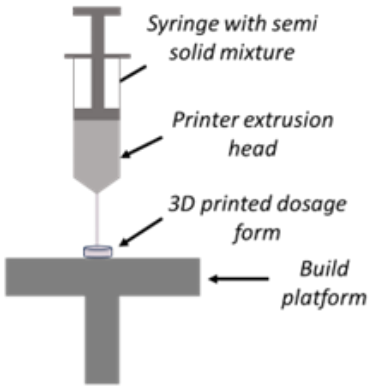

Figure 3.
Schematic presentation of semi-solid extrusion (SSE) 3D printing

The advantages of SSE printing are the absence of extreme conditions that could affect the stability of the substances used and the possibility of using a wide range of pharmaceutical excipients. However, the limiting factors of SSE 3D printing include lower print resolution and longer processing times, especially when subsequent drying of the printed objects is required.

Vat photopolymerisation. Vat photopolymerisation refers to a group of techniques in which objects are formed by solidifying liquid resin after irradiation with a specific wavelength. This 3D printing technique uses photopolymers that polymerise after irradiation and photoinitiators that chemically transform upon irradiation to initiate the polymerisation reaction. Based on the design of the printer, the two most common types of this technique are stereolithography (SLA) and digital light processing (DLP) [20].

In stereolithography (SLA), a laser beam scans the surface of the liquid resin according to the shape defined by the 3D model and solidifies a layer of resin on the printer platform (Figure 4). After solidification, the platform moves down by the layer thickness, the laser exposure is repeated, and the next layer solidifies [3, 20].

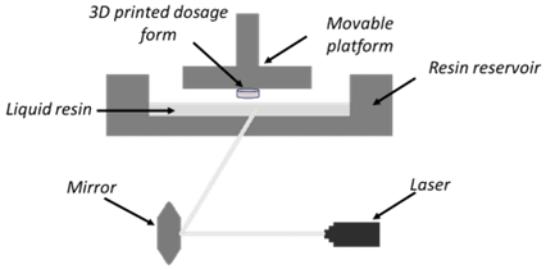

Figure 4.
Schematic presentation of stereolithography (SLA)

DLP printing, on the other hand, uses a digital projector or liquid crystal panel to project the entire layer of the desired object onto the resin surface, solidifying the entire layer at once (Figure 5). This speed up the printing process considerably compared to SLA 3D printing, where the solidification of the resin only occurs on a small area exposed to laser radiation at a time. The main advantage of photopolymerisation-based techniques is their high print resolution. However, a major limitation of these techniques is the lack of photopolymers approved for use in oral dosage forms [20, 21].

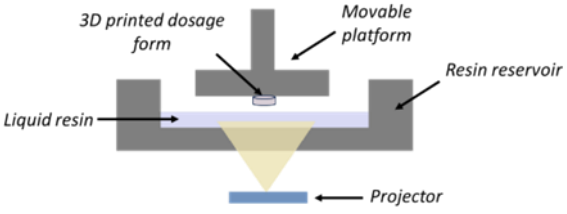

Figure 5.
Schematic presentation of digital light processing (DLP) 3D printing

Selective Laser Sintering (SLS). In selective laser sintering (SLS), a previously designed object is formed directly from the powder. The object is formed by

the bonding of powder particles due to the localised heating caused by the laser irradiation. The laser beam is precisely controlled, and irradiation of powder particles occurs only within the defined object boundaries. Once a layer of powder particles is solidified, the device chamber moves to allow deposition of the next layer, followed by another round of laser irradiation (Figure 6) [22, 23].

When lasers operating in the visible spectrum are used for printing, it is often necessary to add substances to the powder mixtures to enable absorption of the light from the laser source for successful printing. Pharmaceutically approved colours such as Candurin® Gold Sheen and Candurin® NXT Ruby Red are often used for this purpose. The use of powdered starting materials makes SLS and binder jetting 3D printing the most desirable techniques for the production of solid dosage forms, so a wider application of these techniques can be expected in the future [22, 23].

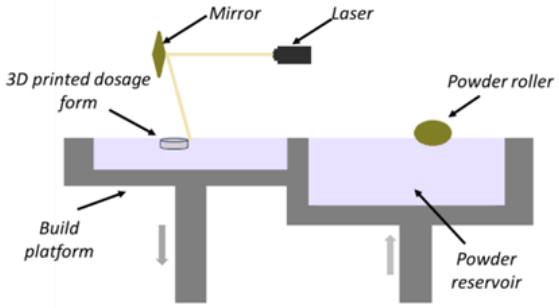

Figure 6.
Schematic presentation of selective laser sintering (SLS)

Table I summarises the advantages and disadvantages of the 3D printing techniques described.

Table I

The advantages and disadvantages of the 3D printing techniques used for fabrication of dosage forms

3D printing technique	Advantages	Disadvantages
Binder jetting	Suitable for pharmaceutical powder mixtures Fast disintegration of printed dosage forms Absence of extreme processing conditions	Low mechanical resistance of printed dosage form Drying step is usually required after printing Organic solvents are commonly used in printing
Fused deposition modelling	Low cost and solvent-free process High mechanical resistance of printed dosage forms Post-processing is usually not necessary	Preparation of drug loaded filaments before printing is necessary Adequate mechanical characteristics of filaments are required for printing Formulation is exposed to high temperature Low porosity of dosage form may prolong drug release
Semi-solid extrusion	Printing at room temperature Suitable for wide range of pharmaceutical materials	Solvents are used in the printing process Drying step is usually required after printing Low printing resolution Printing process is dependent from the mixture rheological behaviour
Vat photopolymerization	High printing resolution Printing at room temperature	Starting materials must have photocurable characteristics Lack of photocurable resins approved for pharmaceutical use Slow and incomplete drug release from printed dosage forms is common problem
Selective Laser Sintering	High printing resolution Suitable for wide range of pharmaceutical materials Solvent-free one step process High porosity of printed dosage forms causes very fast drug release	Powder mixture must absorb laser irradiation Rise in temperature due to laser irradiation may cause degradation of formulation components

Application of 3D Printing for the Fabrication of Dosage Forms with Tailored Drug Release

Similar to conventional manufacturing processes, the use of 3D printing enables the production of pharmaceutical dosage forms with different drug release profiles. However, in conventional manufacturing techniques, modification of drug release is typically achieved by changing the composition, in particular by using different excipients, and to a lesser extent by changing the dimensions of the dosage form, while the design of the dosage forms remains simple in most cases. The possibilities for producing dosage forms with complex geometries are very limited with conventional methods. In contrast, 3D printing offers much greater flexibility to achieve modified drug release. Apart from varying the composition of the formulation, 3D printing offers virtually unlimited possibilities to design and print different architectures that result in dosage forms with the desired drug release characteristics. In addition, 3D printing can be used to produce so-called

multi-compartmental dosage forms, which consist of multiple compartments, each of which allows independent control of drug release from its contents. The following section describes various examples of 3D printing applications in the design of pharmaceutical dosage forms with tailored drug release properties. The focus is on dosage forms where the controlled drug release is achieved through the complex structures created by 3D printing.

The ability to print a variety of shapes offers an enormous potential for 3D printing in the creation of pharmaceutical dosage forms with different drug release profiles. Robles Martinez *et al.* have demonstrated the successful printing of different geometric shapes (cube, disc, pyramid, sphere and torus) using the SLA technique, achieving different drug release rates from each shape. It was shown that drug release rate is determined by the surface area to volume (SA/V) ratio of the dosage form. Using multiple regression analysis, the following relationship was established between amount of drug released after 10 hours (%), SA/V ratio and tablet weight, which showed that drug release increases with increasing SA/V ratio:

$$\text{Drug release 10 h} = -1.573 + 60.9 \times \text{SA/V} - 0.014 \times \text{weight}, \quad (1).$$

The establishment of a mathematical relationship between the SA/V ratio and the amount of drug released allows the development of dosage forms with the desired drug release characteristics [24].

Fabrication of dosage forms with complex design and increased SA/V ratio by 3D printing can be used as an approach to accelerate drug release. An interesting example of such a concept is the "radiator-like" dosage form design described by Isreb *et al*. Dosage forms with this complex shape were printed by FDM technique using filaments containing theophylline, polyethylene glycol 6000 (PEG 6000) and polyethylene oxides of different molecular weights. Drug release rate from the printed objects was highly dependent on the distance between the parallel plates of the radiator-like design. Immediate release of theophylline was only achieved when the distance between parallel plates was higher than 1 mm. Sufficiently high spacing is required to prevent decrease in SA/V ratio due to adhesion between plates caused by swelling of polyethylene oxides [25].

Pyteraf *et al*. have shown that by varying the infill percentage of FDM-printed tablets, different dissolution profiles from tablets printed with the same filament can be achieved. Tablets printed with 35% and 50% infill released 3.3 and 2.3 times less ketoprofen after 2 hours, respectively, compared to tablets printed with 20% infill. A release profile equivalent to that of commercially available extended-release ketoprofen tablets was achieved by printing multilayer tablets with layers having 35% and 65% infill. However, reducing the infill percentage to achieve immediate drug release can increase tablet dimensions, potentially causing swallowing difficulties. To avoid this, immediate release was achieved by printing tablets with a ketoprofen-containing filament that also contained polyvinyl alcohol (PVA) and crospovidone, along with a placebo filament containing Kollicoat IR polymer. The addition of the placebo filament with a highly soluble polymer resulted in a faster ketoprofen release compared to tablets obtained by direct compression [26].

In addition to the infill percentage of the dosage form, the printing pattern also affects the drug release rate. Obeid *et al*. demonstrated a faster diazepam release from tablets printed with a zig-zag pattern compared to a linear pattern. The same study showed an unusual effect of infill percentage on drug release rate, which varied depending on the printing pattern. For tablets printed with a zig-zag pattern, the drug release rate increased as the infill percentage decreased, while the opposite effect was observed for tablets printed with a linear pattern [27].

Extended drug release is often achieved from dosage forms printed using photopolymerisation-based techniques. However, a common problem with such dosage forms is slow and incomplete drug release. Krkobabić *et al*. have shown that the release rate of paracetamol from DLP-printed tablets with polyethylene glycol diacrylate (PEGDA) polymer can be increased by the addition of hydrophilic excipients such as PEG 400, sodium chloride and mannitol. Mechanisms that explain the positive effect of hydrophilic excipients on drug release from the polymeric matrix include the formation of channels within the polymeric matrix, erosion of the matrix, or tablet capping due to an increase in osmotic pressure [28].

Increasing the contact area between the drug delivery system and the dissolution medium can enhance the drug release rate and overcome the problem of incomplete drug release from the polymeric matrix. This approach was successfully applied by Kadry *et al*. who described immediate drug release from a polyethylene glycol dimethacrylate (PEGDMA) polymeric matrix using tablets with six perforations [29]. A similar approach was used in the design of perforated caplets produced by FDM 3D printing, also formulated to increase the drug release rate. For caplets without perforations, printed with filaments containing Eudragit® E polymer as the base component and hydrochlorothiazide as the active ingredient, immediate drug release could not be achieved even with the addition of disintegrants. Immediate release of hydrochlorothiazide was only achieved by introducing channels with a width of ≥ 0.8 mm into the caplet structure, due to an increase in the SA/V ratio of the dosage form. A more effective approach, which resulted in faster caplet disintegration and release of the drug, was the introduction of a larger number of shorter channels [30].

A very interesting system for the controlled drug release triggered by an external stimulus was described by

Wei *et al*. This system is based on a scaffold fabricated by coaxial 3D printing, in which the shell consists of a mixture of polydopamine and alginate and the core contains a temperature-sensitive hydrogel of doxorubicin and gelatine. The designed system is intended for the localised therapy of residual breast cancer and the prevention of recurrence after surgery. The release of the drug is controlled by irradiation from an external NIR source. Due to the photothermal effect of polydopamine, the temperature in the fibres increases, leading to a gel-sol transition in the core and causing the release of doxorubicin from the fibre core [31].

A significant portion of research on the application of 3D printing techniques for developing modified drug release systems is dedicated to the development of gastroretentive floating systems. Two main concepts are distinguished in these studies: first, where the pharmaceutical form itself is designed to float, and second, where 3D printing is used to create a floating device without the active ingredient, into which a dosage form produced by conventional techniques is placed.

A relatively simple gastroretentive system that enables pulsatile release of artesunate has been described by Yan *et al*. The system consists of multilayer tablets produced by SSE 3D printing. The surface layer of the tablet is designed to provide an immediate release of the drug upon contact with the dissolution medium and consists of the drug, polyvinylpyrrolidone K30 (PVP K30) and croscarmellose sodium, which are polymers that enhance the drug dissolution rate. Beneath this layer is a drug-free shell made of octadecanol, hydroxypropylmethylcellulose K15M, PVP K30 and poloxamer F68, which delays the drug release from the tablet core. The composition of the tablet core is identical to that of the surface layer. The multilayer tablets described were shown to achieve a multiphase drug release, with a rapid drug release from the surface layer followed by a period of very slow drug release until the central shell dissolves, whereupon a more rapid drug release from the core occurs. These tablets exhibited flotation *in vitro* for 8 - 12 hours and gastric retention in *in vivo* tests for up to 20 hours [32].

The application of 3D printing allows achieving dosage form flotation by varying shape and infill percentage, as demonstrated in the study by Qian *et al*. in which a floating system with verapamil hydrochloride was produced using FDM 3D printing. The floating systems described were printed from filaments containing the drug, HPMC HME 100lv and Soluplus® polymers, with cylindrical, capsule and hemispherical shapes printed with infill percentages of 0% and 15% (Figure 1). All printed dosage forms showed flotation for at least 4 hours and extended verapamil hydrochloride release for at least 12 hours. Although longer flotation time was expected for hemispherical and capsular shapes compared to cylindrical shapes, the opposite results were observed. The shorter flotation time of hemispherical and capsular shapes is explained by their less rigid structure, which leads to faster penetration of the dissolution medium and disruption of the dosage form, preventing further flotation [33].

3D printing holds great potential for the creation of complex architectures that enable controlled drug release from tablets or capsules inserted into the printed device. These systems, which control drug release, are usually printed using commercially available polymeric filaments. Such filaments have better mechanical properties than those made with the active ingredients, which facilitates the printing process and results in objects with better characteristics. Another advantage of this concept is that the active ingredient does not have to be exposed to extreme conditions, such as high temperatures.

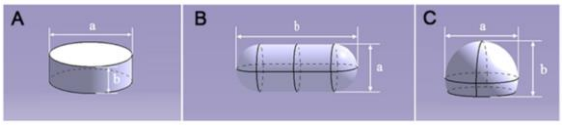

Figure 7.
Design of floating systems with cylindrical (A), capsular (B) and hemispherical (C) shapes for delivery of verapamil hydrochloride [33]

Based on this concept, a relatively simple system was developed for extended amoxicillin delivery in the stomach in the treatment of *Helicobacter pylori* infections. The floating system was fabricated by FDM printing of PVA filaments, followed by thermal treatment to increase the degree of cross-linking of the PVA chains, thereby reducing water solubility and improving floating properties. The resulting floating system successfully enabled prolonged floating and extended release of amoxicillin from commercially available capsules placed inside it [34].

A similar concept was described by Shin *et al*. in the development of a floating system for the delivery of acyclovir to improve the bioavailability of this drug, which is predominantly absorbed in the upper gastrointestinal tract (Figure 8). This floating system consists of a capsule fabricated by FDM printing with commercially available PLA filament, into which an acyclovir tablet produced by conventional methods is inserted. The capsule is designed to contain two air pockets that allow it to float, a central compartment for the tablet and openings through which the drug is released. This system achieved a floating time of more than 24 hours *in vitro*, which corresponds to a residence time in the stomach of more than 12 hours [35].

A more complex system was designed for the development of a floating system for the delivery of riboflavin. The system described consists of a two-part shell printed with PLA filaments, into which a riboflavin tablet produced by direct compression is inserted. Different shell structures were tested, with or without perforated structures in the body and/or

lid of the shell and with variations in the placement of the perforated structure (central or eccentric). The optimal system with perforations in both the body and the lid enabled flotation for up to 72 hours [36].

Figure 8.
Schematic representation and photograph of printed gastroretentive system with inserted acyclovir tablets [35]

One of the particular advantages of 3D printing is the ability to create drug delivery systems with multiple active ingredients, where the release for each active ingredient is controlled independently. Such systems are commonly denoted as polypills. The flexibility in dose adjustment in printed polypills according to the characteristics of each patient and the ability to achieve complex drug release patterns are the main advantages over conventional fixed dose combinations. One of the pioneering works in this field was conducted by Khaled *et al*. with the aim of developing multi-compartment delivery system containing three active ingredients by SSE 3D printing. The described system combines osmotically controlled drug release through a controlled porosity shell and diffusion-controlled drug release through a swollen gel matrix. Captopril was released from the osmotic compartment according to zero-order kinetics, whereas the release of glipizide and nifedipine from separate compartments was sustained and followed either first-order or Korsmeyer-Peppas kinetics, which depend on the drug-to-excipient ratio in the formulation [37]. The same authors described a more complex system with three separate sustained release compartments printed with hydrophobic cellulose acetate polymer containing pravastatin, atenolol or ramipril, above which is immediate release compartment containing aspirin and hydrochlorothiazide. Semi-solid mixtures of hypromellose and either pravastatin, atenolol or ramipril are filled into the cellulose acetate compartments, followed by printing of the immediate release compartment containing aspirin and hydrochlorothiazide, sodium starch glycolate and PVP. All five active ingredients were released according to the predefined pattern [38]. The development of a combined bilayer polypill by DLP-3D printing was described by Adamov *et al*. The fabrication of dosage forms with multiple drugs in separate compartments by DLP or SLA 3D printing is somewhat more complex, since the content of the resin tank is replaced between printing segments with each active substance. The results of this study show significant differences between the drug release profiles of single-layer tablets with each active ingredient and double-layer tablets with both active ingredients. The observed decrease in drug release rate is attributed to the lower SA/V ratio in the bilayer tablets, so further optimisation of the geometry and/or composition of the formulation is required [39].

Artificial intelligence tools can be useful in the development of controlled release systems using 3D printing. Madžarević *et al*. successfully applied artificial neural networks to predict the release of ibuprofen from extended-release tablets fabricated by DLP printing [40]. Hu *et al*. went a step further by developing a model capable of designing optimal architectures for 3D-printed pharmaceutical forms that should provide desired drug release. In the first step, a model for simulating drug release from the dosage form was created. A genetic algorithm was then used to optimise the capsule geometry in order to achieve the desired drug release profile. The capsules with the optimised geometry were successfully printed, resulting in a close match between the experimental drug release profile and the target profile [41].

Conclusions

Over the past decade, there have been major advances in the application of 3D printing for the development of drug delivery systems. The greater availability of low-cost 3D printers is certainly one of the main reasons for the expansion of research in this area. The ability to produce very complex architectures makes it possible to achieve tailored drug release profiles, which is often very difficult with conventional production methods. With this approach, it is possible to develop models that establish a relationship between drug release rate and the properties of the dosage forms. This enables the design of drug delivery systems with the desired characteristics and their rapid production by 3D printing. Although numerous studies have shown the suitability of 3D printing for fabrication of various types of drug delivery systems, there are several issues that need to be resolved before the full adoption of 3D printing in healthcare. These include the creation of

a regulatory framework and the development of 3D printers specifically designed for the pharmaceutical applications. The regulatory framework for 3D printing should be more flexible compared to conventional pharmaceutical manufacturing and more in line with pharmaceutical compounding. The development of several 3D printers for pharmaceutical applications, equipped with various tools for process and product control, is a major step towards the introduction of this technology in the healthcare sector.

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Conflict of interest

The authors declare no conflict of interest.

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