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3D-Printed Modified-Release Tablets: A Review of the Recent Advances

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Abstract

The broad spectrum of applications of three-dimensional printing (3D printing, 3DP) has attracted the attention of researchers working in diverse fields. In pharmaceuticals, the main idea behind 3D printing products is to design and develop delivery systems that are suited to an individual's needs. In this way, the size, appearance, shape, and rate of delivery of a wide array of medicines could be easily adjusted. The aim of this chapter is to provide a compilation of the 3D printing techniques, used for the fabrication of oral drug delivery systems, and review the relevant scientific developments in particular those with modified-release characteristics.

Keywords: 3D printing, modified release, oral drug delivery, tablets

1. Introduction

3D printing is an object fabrication technique based on the sequential deposition of layers of materials. Using a computer-aided design (CAD) software, structures of various sizes and shapes can be produced. This method has found application in many sectors, from industrial engineering to personalized biomaterials and devices in medicine [1, 2]. Within the pharmaceutical field, 3D printing can produce small batches of medicinal products, with tailored dosages, shapes, sizes, and release characteristics [3]. These advantages of 3D printing facilitate the efforts towards personalized therapies. The need for the modification of a dose that will fit better a patient's individual needs arises from differences in the patient's age, weight, and severity of disease(s) [4]. Even though there are great advancements in drug administration methods, the orally administered drugs remain the most preferred choice by patients due to the fact that it is relatively safe, very convenient and cost-effective. The preference on oral solid pharmaceutical forms, especially tablets, has rendered the personalization of oral solid dosage forms a step forward in the healthcare system [4].

2. History

The increasing applications of 3D printing have made it a well-accepted concept at present times. Charles Hull is considered the pioneer of 3D printing, as he

developed, patented, and commercialized the first equipment for the 3D printing of objects in 1983. Hull's 3D printing technique was based on stereolithography. It consisted of a laser that moved across the surface of a liquid resin, curing it. This process was repeated layer by layer many times until the desired shape was formed. In 1988, Charles Deckard filed a patent for selective laser sintering. In this process, a laser beam is scanned over a powder bed to sinter or fuse the powder that is placed on a powder bed. The powder bed is then lowered, fresh powder is spread, and the process is repeated to produce a solid object. The un-bonded is then removed, and the structure can be further treated, for example, with heat, to enforce the bonding. In 1989, Scott Crump filed a patent on fused deposition modeling. Using this technique, the object is formed by depositing layers of solidifying materials (self-hardening waxes, thermoplastic resins, and molten metals) until the desired shape is formed [5, 6]. In 2015, the FDA approved Spritam®, the first 3D-printed prescription drug product to treat partial onset seizures, myoclonic seizures, and primary generalized tonic-clonic seizures. Since then, many innovations have been evolved using the 3DP technology.

3. Advantages and limitations

The oral dosage form production by the 3DP processes has many advantages specially for customizing drug delivery. The active ingredient can be included in the dosage form as per each patient requirements to achieve a personalized dose and release pattern. 3D printing aids also in achieving multidrug combinations with complex release profiles [7]. On-demand production and tailor-made products with specific geometries, designs, and shape forms can be achieved which otherwise would be difficult with the conventional tableting. Even though there has been intense research to circumvent the 3D printing flaws, this new technology has still some limitations. Few 3D printing techniques may produce relatively porous structures and uneven shapes of dosage forms [6]. When fused deposition modeling technique is utilized, the use of only thermostable drugs and the few available compatible excipients is a limiting step. Also, with stereolithography, the challenge lies on the potential drug degradation due to the exposure to UV light that induces polymerization reaction [5].

4. Various techniques used in 3D printing

Irrespective of the 3D printing technique employed, the process follows three basic steps: the creation of a computer-aided design file; followed by its transformation to a rapid prototyping stereolithography file (.stl), which describes the surface geometry of the 3D object; and finally, its conversion to a machine specific code (.gcode) which is recognized by the 3D printer machine and creates the final object [8] (Figure 1).

There are various ways to classify the 3D techniques, according to the additive process followed, the form of the raw materials used, the mechanism of layering, or even the kind of printing heads utilized [9]. Figure 2 illustrates the different 3D



Figure 1.
The basic steps of 3D printing process.

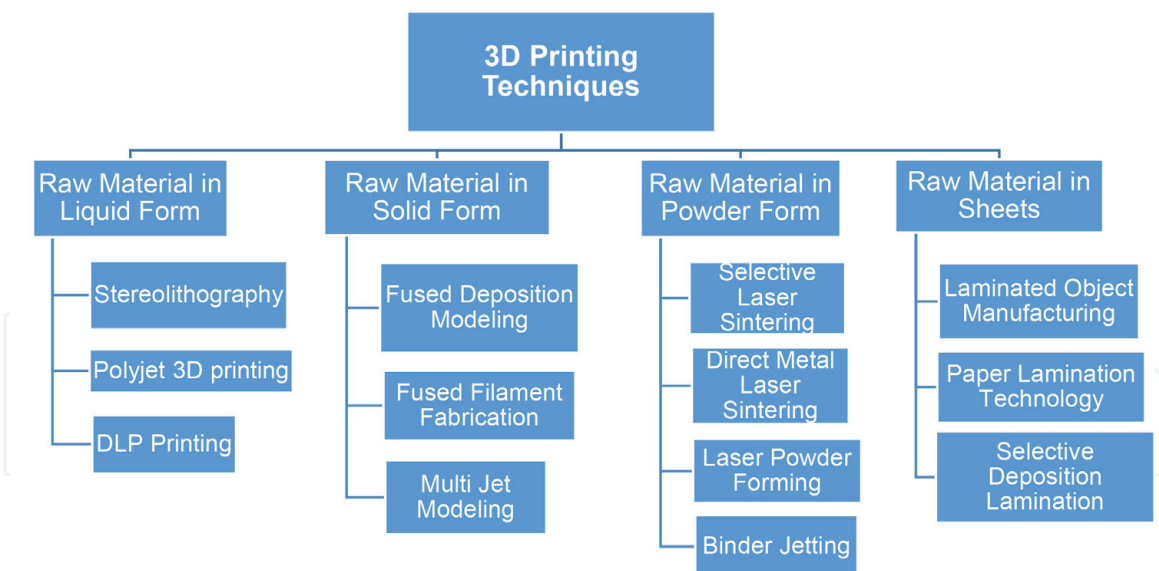


Figure 2.
3D printing technique categorization.

printing techniques categorized by the raw materials employed. Among them, stereolithography, selective laser sintering, binder jetting, and fused deposition modeling are the most used techniques in the literature for the production of pharmaceutical dosage forms [10].

Stereolithography employs raw materials in the liquid form, such as photosensitive/photopolymerizable liquid resins. A high-energy light source like ultraviolet irradiation solidifies the liquid resins, creating the 3D object [6]. Among the advantages of this technique are the high accuracy and good surface quality of the object. This method has been widely used for implant design and manufacture as well as for creating accurate 3D models acquired from various anatomical scans of a patient.

Selective laser sintering (SLS) technique utilizes raw materials in a powder form, and the laser used melts and bonds the layers of material powders together. SLS has been used for the manufacturing of artificial tissue.

On the other hand, binder jetting technique, also called drop-on-demand inkjet printing or 3D printing, is able to create 3D objects from powder materials by depositing liquid binder droplets onto a powder substrate and sticking the particles together [9, 10]. This technique along with the continuous inkjet printing belongs to the printing-based inkjet systems and has been utilized for the fabrication of implants and solid dosage forms, such as the first commercially printed tablet Spritam®.

Finally, the most widely spread technique is the fused deposition modeling (FDM), and it belongs to the nozzle-based printing techniques. FDM is characterized by the use of thermoplastic polymers that pass through a pre-heated printing head and is melted and extruded through a precise nozzle with a specific diameter. In contact with the cold printing surface, the polymers solidify and thus create the 3D object. A variation of this type of 3D printing technique is the semisolid extrusion system, in which semiconductors (gels, ointments) are printed through a syringe-shaped extruder [10]. In the recent years, these techniques have been extensively used for the research and development of various pharmaceutical forms such as hydrogels or coated solid dosage forms [11].

Figure 3 depicts the main additive manufacturing technologies which either experimentally or industrially have been used for the manufacturing of pharmaceutical dosage forms.

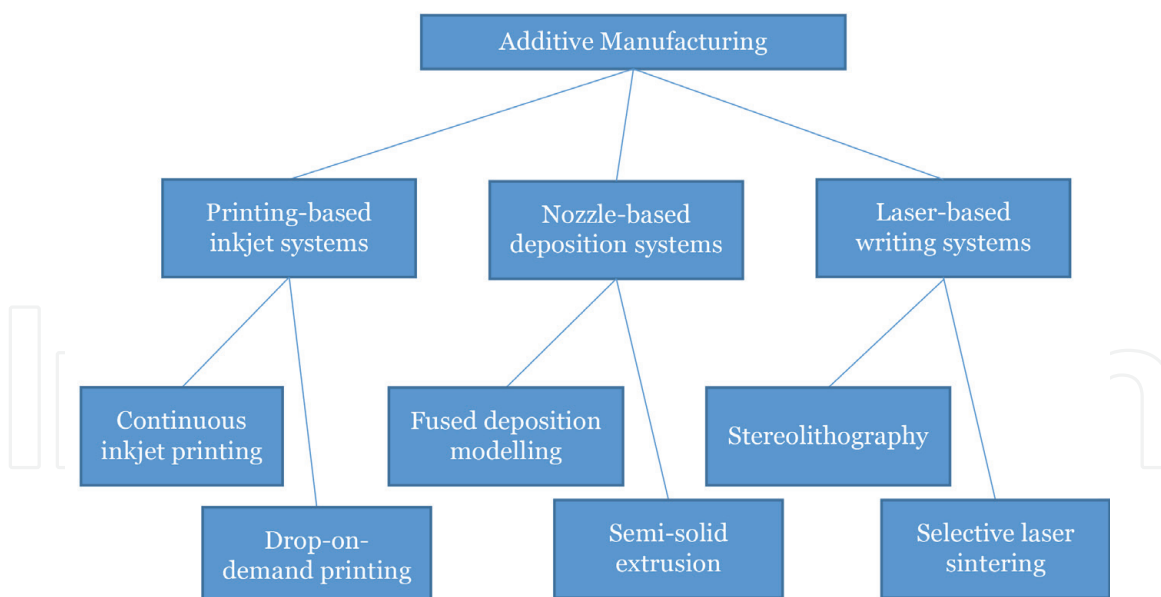


Figure 3.

Basic 3D printing techniques deployed for the manufacturing of pharmaceutical dosage forms.

5. Recent accomplishments in modified-release 3D-printed tablets

Orodispersible, sublingual, fast-dissolving drug delivery formulations that rapidly disintegrate in the oral cavity or immediate-release tablets by 3D printing have been produced [12–15].

Multipurpose therapeutic systems offering tailored combinations of drugs, drug doses, and the desired release kinetic properties have attracted increasing attention, due to the advantages that these personalized pharmaceutical products could offer. In this respect, many scientists have designed modified-release oral dosage medicines, using 3D printing. The drug release from modified-release formulations is changed on purpose from that of an immediate-release formulation to achieve a preferred therapeutic goal. The applications of 3DP on modified *per oral* drug delivery are summarized in **Table 1**.

Genina et al. [16] have shown that coupling fused deposition modeling 3D printing with the hot-melt extrusion offers a new method for manufacturing tailored-dosage medicines, with modified-release properties. In detail an oral dual-compartmental dosage unit (dcDU) has been designed, and the *in vitro* and *in vivo* release profiles of an antitubercular drug combination of rifampicin and isoniazid have been evaluated. These two active ingredients are considered as first-line therapy for tuberculosis but interact negatively with each other upon simultaneous release in acidic environment. This was circumvented by the compartmentalization of rifampicin and isoniazid into sealable compartments of 3D-printed dual-compartmental dosage units. This novel delivery system was characterized with focus on microscopic verification of the designed attributes, the modulation of drug release from dcDUs, and the pharmacokinetic profile of dcDUs in rats. In another study [17] an oral solid dosage form was developed by employing the fused deposition modeling, using a custom-built filament consisted of polyvinyl alcohol, mannitol, and hydrochlorothiazide, as a model drug, co-formulated via hot-melt extrusion. The dissolution studies performed demonstrated zero-order release kinetics. In another study [18], hot-melt extrusion and fused deposition modeling were used to produce different shaped tablets (cube, pyramid, cylinder, sphere, and torus) containing acetaminophen. It was found that drug's release was not

Release behavior*	Dosage form	API(s)	Excipient(s)	Technique	Ref.
Modified	Dual-compartment tablet	Rifampicin and isoniazid	Polyethylene oxide, polylactic acid (PLA), polyvinyl alcohol (PVA)	FDM/HME	[16]
	Three-compartment tablet	Hydrochlorothiazide	Partially hydrolyzed PVA (Mowiol®4-88), mannitol	FDM/HME	[17]
	Tablets of various shapes	Paracetamol	Polyvinyl alcohol	FDM/HME	[18]
	Caplets	Budesonide	Polyvinyl alcohol, Eudragit® L 100, triethyl citrate, talc, isopropanol-water solution	FDM/HME and fluid bed coating	[19]
	Tablets	5-Aminosalicylic acid and 4-aminosalicylic acid	Polyvinyl alcohol	FDM	[20]
	Caplets	Paracetamol or caffeine	Polyvinyl alcohol	FDM	[21]
	Tablets	4-Aminosalicylic acid and paracetamol	Polyethylene glycol diacrylate, diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide, and (PEG 300)	Stereolithography	[22]
	Tablets	Acetaminophen	Methocel™ E50, polyvinylpyrrolidone (Povidone K30), ethyl cellulose, Eudragit® RS 100, stearic acid, sodium lauryl sulfate, fluorescein, colloidal silicon dioxide	Inkjet printing	[23]
Extended	Tablets	Acetaminophen	Benecel™ HPMC E5 and Aqualon™ EC N14 with either Klucel™ HPC EF and LF, Soluplus®, or Eudragit® L 100	FDM/HME	[24]
	Tablets	Theophylline	Eudragit RL 100, RS 100, and E and hydroxypropyl cellulose (SSL grade), triethyl citrate	FDM/HME	[25]
	Tablets	Prednisolone	Polyvinyl alcohol	FDM	[26]
	Tablets	Fluorescein	Polyvinyl alcohol	FDM	[27]
Controlled	Tablets	Fenofibrate	White beeswax	Inkjet printing	[28]
Sustained	Polypill	Captopril, nifedipine, and glipizide	Hydroxypropyl methylcellulose (HPMC 2208), polyethylene glycol (PEG 6000),	Extrusion	[29]

Release behavior*	Dosage form	API(s)	Excipient(s)	Technique	Ref.
			tromethamine, lactose, sodium chloride, D-mannitol, croscarmellose sodium, microcrystalline cellulose, sodium starch glycolate, hydroxypropyl methylcellulose (Methocel™), cellulose acetate		
Delayed	DuoCaplet	Paracetamol and caffeine	Polyvinyl alcohol	FDM/HME	[30]
	Tablets	Paracetamol	Hypromellose acetate succinate (HPMC LG, MG, HG), methylparaben NF grade, magnesium stearate	FDM/HME	[31]
	Shell-core tablets	Theophylline, budesonide, and diclofenac sodium	Core: Polyvinylpyrrolidone, triethyl citrate, talc or tribasic phosphate sodium, and API Shell: Eudragit® L 100–55, triethyl citrate, and talc	Dual FDM/HME	[32]
Pulsatile	Two-compartment capsular device	Acetaminophen	Poly(lactic acid), polyvinyl alcohol, hydroxypropyl methylcellulose (HPMC), HPMC acetate succinate, polyvinyl alcohol-polyethylene glycol graft copolymer, glycerol, polyethylene glycol (PEG 400, PEG8000), blue and yellow dye-containing formulations (Kollicoat®IR Brilliant Blue and Kollicoat®IRyellow)	FDM/HME injection molding	[33]
Immediate /sustained	Bilayer tablet	Guaifenesin	Hydroxypropyl methylcellulose (HPMC 2910 & 2208), poly(acrylic acid), microcrystalline cellulose, sodium starch glycolate	Extrusion	[34]
	Polypill	Aspirin, hydrochlorothiazide, ramipril, pravastatin sodium, atenolol	Cellulose acetate, D-mannitol, polyethylene glycol (PEG 6000) sodium starch glycolate, Polyvinylpyrrolidone	Extrusion	[35]

Release behavior*	Dosage form	API(s)	Excipient(s)	Technique	Ref.
			(Povidon K30), hydroxypropyl methylcellulose (Methocel™ K100MCR), lactose		
Immediate/extended	Tablets	Chlorpheniramine maleate	Microcrystalline cellulose powder, Eudragit® E 100, RLPO	Inkjet	[36]
Enteric dual pulsatory	Tablets	Diclofenac	Avicel PH301, lactose, Eudragit® L 100,	Inkjet	[36]
Dual pulsatory	Tablets	Diclofenac	Eudragit® E 100 and L 100	Inkjet	[36]

*The release behavior reported as defined by the author.

Table 1.

An overview of the 3DP technique applications in modified per oral drug delivery (FDM, fused deposition modeling; HME, hot-melt extrusion).

dependent on the tablet surface area, but on the surface-area-to-volume ratio, indicating the effect of the shape on the release profile. The results showed that the tablets of similar mass showed little difference in dissolution profiles that could be explained by the erosion-mediated process that controlled the drug release. Tablets of various shapes may alter the drug dissolution profiles and can aid in the design of new dosage forms with specific pharmacokinetic characteristic targeted to different sites in the gastrointestinal track. Fused deposition 3D printing technology alongside with hot-melt extrusion and fluid bed coating was used to fabricate modified-release budesonide dosage forms. The drug was loaded into polyvinyl alcohol filaments which were then engineered into capsule-shaped tablets and coated with a layer of enteric polymer. The dissolution studies showed that the drug release from the caplet formulation started at the small intestine and continued in a sustained manner throughout the large intestine and colon [19]. The same group of researchers has also produced tablets containing as model drugs the two aminosalicic acid isomers, 5-aminosalicylic acid and 4-aminosalicylic acid, using fused deposition modeling. The results indicated that the release profiles obtained could be easily modified by the proper selection of the printing parameters [20]. Furthermore, fused deposition modeling was used to produce acetaminophen or caffeine caplets from polyvinyl alcohol filaments. The dissolution tests performed in biorelevant bicarbonate media revealed distinctive modified-release profiles, which were dependent on drug solubility and drug loading. The results indicated that the drug release can be faster from formulations incorporating the drug with higher solubility and higher loading [21]. Additionally, Wang et al. [22] managed to formulate modified-release tablets of paracetamol and 4-aminosalicylic acid using polyethylene glycol diacrylate as monomer and diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide as a photoinitiator in stereolithographic 3D printing. Also, in another study [23], researchers employed the powder bed/jetting method to construct a methacrylic or ethylcellulose matrix tablet to achieve a modified release of acetaminophen. Erosion and in vitro dissolution studies in ethylcellulose-containing tablets indicated that the drug was released via a two-dimensional surface erosion mechanism and 98% of the drug could be released linearly in 12 h. Tablets with other release-retardation materials, such as sodium lauryl sulfate, stearic acid, and

Eudragit RS-100, showed similar release-retardation effects by different release mechanisms.

Zhang et al. fabricated solid-dispersion filaments with acetaminophen dissolved or dispersed in a polymer matrix by hot-melt extrusion technology, which was suitable for fused deposition modeling-based 3D printing. The 3D printed tablets showed more extended drug release rates than the directly compressed tablets [24]. In another study [25], using the same methods, scientists presented a flexible dose tablet system, suitable for both immediate and extended-release tablets. As excipients three methacrylic polymers (Eudragit RL, RS, and E) as well as a cellulose-based material (hydroxypropyl cellulose, HPC SSL) were used, while theophylline was used as a model drug substance. Moreover, in another report [26], the feasibility of using a fused deposition modeling-based 3D printer to fabricate extended-release tablets, using prednisolone loaded poly(vinyl alcohol) filaments, and to control its release was investigated. The results indicated that the *in vitro* drug release was extended up to 24 h, showing that the fused deposition modeling is a promising method to control the dose of extended-release tablets. Moreover in another work, polyvinyl alcohol filaments have been loaded with fluorescein as a model drug, by swelling of the polymer in ethanolic drug solution, and 10-mm-diameter tablets of polyvinyl alcohol/fluorescein using fused deposition modeling 3DP were printed. The dissolution tests that were conducted in modified Hank's buffer indicated controlled-release profiles [27].

Kyobula et al. [28] have prepared drug-loaded solid dosage forms with complex geometries such as honeycomb based, using hot-melt 3D inkjet printing. The model drug used was fenofibrate, and the relevant studies indicated controlled release. This study verified an alternative production approach for solid dosage forms with different geometry, which could achieve various release profiles for personalized drug products.

Khaled et al. [29] have employed 3D extrusion-based printing as a technique for the production of multi-active tablets with well-defined and separate controlled-release profiles for three different drugs, namely, captopril, nifedipine, and glipizide. This "polypill" incorporated an osmotic pump for captopril and sustained release compartments for nifedipine and glipizide. The dissolution testing showed that the captopril portion exhibited the expected zero-order drug release from an osmotic pump, while the others showed either first-order release or Korsmeyer-Peppas release kinetics dependent on the active/excipient ratio used.

Goyanes et al. [30] used the fused deposition modeling 3D printing to fabricate novel oral drug delivery systems with paracetamol and caffeine filaments of poly(vinyl alcohol), with the intent of applying this process to the production of personalized products, tailored at the point of dispensing or use. The design included a multilayer device, with each layer containing drug, whose identity was different to the drug in the adjacent layers, and a two-compartment device, comprising of a caplet in caplet (DuoCaplet), with each compartment containing a different drug. The drug release tests in biorelevant bicarbonate media showed unique drug release profiles depending on the macrostructure of the devices. In the multilayer device incorporating two drugs, the drug release rate was similar for both drugs but faster when the drug loading was higher. In DuoCaplets the drug incorporated in the external layer was released first, and there was a lag time until the release of the drug contained in the core, depending on the characteristics of the external layer. Moreover, the same group [31] used the fused deposition modeling and the hot-melt extrusion to generate paracetamol-loaded tablets from filaments produced from three different grades of hypromellose acetate succinate. The dissolution tests showed that the drug release from the tablets depended on the polymer composition, the drug loading, and the internal structure of the formulations. Especially, all

HPMCAS-based tablets showed initial delayed release in the gastric medium and in the intestinal conditions, and the drug release was faster from the tablets prepared using polymers with a lower pH threshold. These results confirm that the fused deposition modeling 3DP makes possible the production of delayed-release printlets, without the need of enteric coating. Okwuosa et al. [32] managed to fabricate shell-core delayed-release tablets of theophylline, budesonide, and diclofenac sodium with dual fused deposition modeling 3D printing and hot-melt extrusion. For the core structure, filaments consisting of the polymer (PVP), plasticizer (triethyl citrate), filler (talc) or tribasic phosphate sodium, and the active ingredient were created with hot-melt extrusion. While for the shell, Eudragit L100–55, triethyl citrate, and talc were used. The created filaments were then used for the printing of caplets containing the active ingredient in the core, while the shell serves as an enteric coating. This study demonstrated the potential of fabricating patient-specific pH-responsive tablets in one step. In another article, Maroni et al. [33] have reported on the manufacture of a two-compartment capsular device conveying incompatible drugs or differing drug formulations using the fused deposition modeling and injection molding. Through the assembly of compartments that had different wall thickness and/or composition, the drug release could be characterized as pulsatile.

Khaled et al. [34] used the extrusion-based 3DP for the preparation of guaifenesin bilayer tablets with an immediate-release and a sustained-release layer. Drug release kinetics indicated Fickian diffusion drug release through the hydrated HPMC gel layer. The same group of researchers [35] used the same technique for the production of a novel complex geometry “five-in-one” polypill. The drugs, aspirin, hydrochlorothiazide, ramipril, and pravastatin atenolol, were physically separated in the polypill to avoid incompatibility issues and allow maximum flexibility. Release studies revealed immediate and sustained drug release mechanisms.

A research group formulated immediate–/extended-release tablets, which were composed of two drug-containing sections of different pH-based release mechanisms. The pulsed release of the model drug, chlorpheniramine maleate, took place after a lag time of 10 min followed by extended release of the compound over a period of 7 h. Furthermore, enteric dual pulsed-release tablets were constructed and the dissolution profiles showed that two pulses of diclofenac sodium, released, one immediately at $t = 1$ h and the second pulse began after a lag time of 4 h. The same group of researchers [36] also fabricated dual pulsed-release tablets, where one section eroded immediately in the acidic environment stage releasing diclofenac during the first 30 min, while the second section eroded 5 h later, at higher pH values.

6. Conclusions

The present chapter offers a review of the 3D-printed modified-release oral solid pharmaceutical formulations that have been created up to date. It aims at demonstrating the potential role of this technology in the tailored manufacture of pharmaceutical products. Even though 3DP has been introduced since the 1980s, there is still a lot of exploration in this field, especially for the creation of materials suitable for pharmaceutical and medical applications. One of the ongoing researches in the area is the 3DP of new, versatile materials that have the ability to change their properties under the influence of external factors or over time. The structural modification over time or otherwise called the fourth dimension, created a new term called “4D printing” [37]. In oral dosage forms, this technology allows the modification of drug delivery, since the timely release profile can be triggered by stimuli, such as pH, temperature, enzymes action, and time [38].

Conflict of interest

The authors declare no conflict of interest.

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