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MAÍSA RAPOSO PEREIRA DE ARAÚJO

FDM 3D PRINTING OF DRUG-DELIVERY SYSTEMS

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Dissertação de Mestrado apresentada ao programa de Pós-Graduação em Ciências Farmacêuticas da Faculdade de Ciências da Saúde, Universidade de Brasília, como requisito parcial à obtenção do título de Mestre em Ciências Farmacêuticas.

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Aprovada em, _____ de _____ 2018.

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“Este trabalho é dedicado à comunidade científica e a todos a quem o conteúdo desta dissertação possa agregar conhecimento. ”

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“Por vezes sentimos que aquilo que fazemos não é senão uma gota de água no oceano, mas o oceano seria menor se lhe faltasse uma gota. ”

Madre Teresa de Calcutá

RESUMO

ARAÚJO RP, Maísa, FDM 3D printing of drug-delivery systems, Brasília, 2018, Dissertação (Mestrado em Ciências Farmacêuticas) – Faculdade de Ciências da Saúde, Universidade de Brasília, Brasília, 2018.

A impressão 3D por modelagem por deposição de fusão (FDM) atualmente tem sido explorada no campo da pesquisa para a elaboração de múltiplos medicamentos e é especialmente interessante para aplicações farmacêuticas, devido ao seu custo benefício e controle preciso e reprodutível das estruturas impressas. Este trabalho teve como objetivo apresentar uma atualização da impressão 3D FDM de dispositivos de liberação de fármacos, com base em dados publicados entre 2014 e 2018, combinada com outra tecnologia já adaptada para a indústria farmacêutica, a extrusão por fusão a quente (HME). A coparticipação entre indústrias farmacêuticas e farmácias de manipulação em uma cadeia de produção complementar também é proposta. A FDM é capaz de produzir formas farmacêuticas complexas com diferentes dosagens, formas e cinéticas de liberação, dando lugar a medicamentos personalizados. Nós sugerimos que a HME e a FDM são uma combinação ideal e que os filamentos extrusados a quente, carregados com o ingrediente farmacêutico ativo e diferentes polímeros de grau farmacêutico, devem ser fabricados industrialmente e comprados por farmácias de manipulação. Em seguida, uma impressora 3D farmacêutica adaptada com um software amigável ao prescritor deve ser desenvolvida e o medicamento projetado de acordo com a prescrição específica do paciente seria impresso e distribuído em farmácias locais. No final, essa nova tecnologia revelou-se altamente versátil e com uma capacidade inegável de produzir medicamentos personalizados. A parceria entre as indústrias farmacêuticas e farmácias de manipulação provou ser um caminho viável para o mercado, mas para este processo se tornar realidade, agências reguladoras e de patentes devem trabalhar lado a lado com as empresas.

Palavras-chave: Liberação modificada de fármacos, HME, Impressão 3D FDM, Indústria farmacêutica, Farmácia de manipulação

ABSTRACT

ARAÚJO RP, Maísa, FDM 3D printing of drug-delivery systems, Brasília, 2018, Dissertação (Mestrado em Ciências Farmacêuticas) – Faculdade de Ciências da Saúde, Universidade de Brasília, Brasília, 2018.

Fused deposition modeling (FDM) 3D printing has currently been explored in the research field for the elaboration of multiple drug products and seems especially interesting for pharmaceutical applications, due to its cost benefit, precise and reproducible control of the printed structures. This work aimed to present an up-to-date on FDM 3D printing of drug delivery devices, based on data published between 2014 and 2018, combined with another technology already adapted for the pharmaceutical industry, the hot melt extrusion (HME). A co-participation between pharmaceutical industries and compounding pharmacies in a complementary production chain is also proposed. FDM is capable of producing complex pharmaceutical forms with different dosage, shapes and release kinetics, giving place to customized medicines. We suggested that HME and FDM are an ideal match and that the hot-melt extruded filaments, loaded with the active pharmaceutical ingredient and different pharmaceutical grade polymers, should be fabricated industrially and purchased by compounding pharmacies. Then, an adapted pharmaceutical 3D printer with prescriptioner's friendly software need to be developed and the drug devices designed according to the patient's specific prescription would be printed and dispensed at local sites. In the end, this new technology revealed to be highly versatile and with an undeniable capability to produce personalized drug products. The partnership between pharmaceutical industries and compounding pharmacies demonstrated to be a viable pathway to market, but for this process to become a reality, regulatory and patent agencies should work side-by-side with companies.

Keywords: Modified drug release, HME, FDM 3D printing, Pharmaceutical industry, Compounding pharmacy

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ABREVIATIONS LIST

3D – Three Dimensional

API – Active Pharmaceutical Ingredient

DDD - Drug Delivery Device

FDM – Fused Deposition Modeling

GMP – Good Manfacturing Practices

HME – Hot Melt Extrusion

PLA - Polylactic Acid

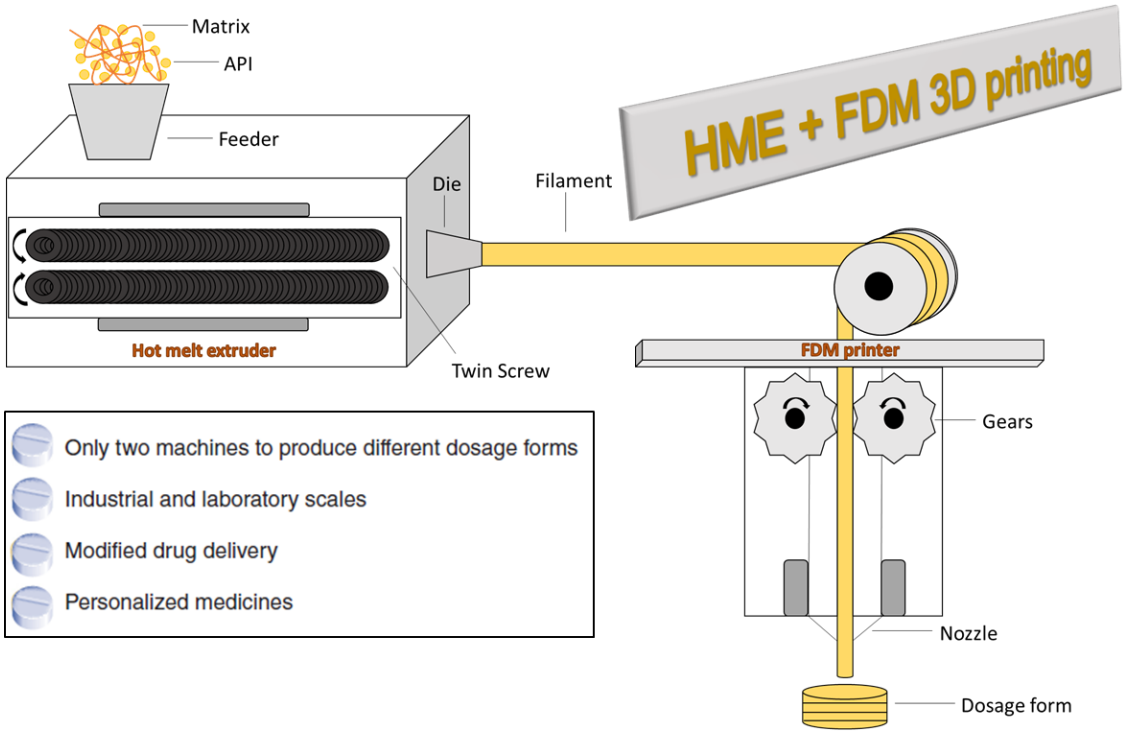
SUMMARY

1. CHAPTER 1

FDM 3D printing of modified drug-delivery systems using hot melt extrusion: a new approach for individualized therapy

Paper published in Therapeutic Delivery, 8 Nov. 2017, vol. 8, pages 957–966.
doi: 10.4155/tde-2017-0067.

1.1 GRAPHICAL ABSTRACT



1.2 ABSTRACT

The production process of 3D-printed drugs offers unique advantages such as the possibility of individualizing the drug therapy and easily associating different drugs and release technologies in the same pharmaceutical unit. Fused deposition modeling, a 3D printing technique, seems especially interesting for pharmaceutical applications, due to its low cost, precise and reproducible control of the printed structures, and versatility for industrial and laboratory scale. This technique combined with another

technology already adapted for the pharmaceutical industry, the hot melt extrusion, is able to incorporate various mechanisms of modified drug release. This special report aims to bring together data of the experimental progress achieved using the fused deposition modeling 3D printing combined with hot melt extrusion technique and its potential in drug delivery.

Keywords: 3D printing, FDM, fused deposition modeling, HME, hot melt extrusion

1.3 EXECUTIVE SUMMARY

3D printing of drugs:

- Individual characteristics such as age, weight, stage of disease, in addition to genetic and biological factors, demand doses and drug-release kinetics adapted to each condition.
- 3D printing can provide the association of different drugs, high control of the printing process, modification in the geometry and dosage of the pharmaceutical form, adapting it to each patient needs.
- Drug-delivery devices (immediate, prolonged, controlled and vectorized) or therapeutic nanosystems can be produced affordably and in large scale.

Fused deposition modeling 3D printing of drugs:

- Fused deposition modeling (FDM) is more suitable for drug production because of its simple handling, low cost and the use of polymeric matrices, although high temperature can degrade thermosensitive drugs.
- There are critical parameters in the printer that need to be observed, such as resolution, temperature, nozzle diameter, infill, layer height, speed and raft.
- There are polymers, fillers, plasticizers and active pharmaceutical ingredients already studied to produce filaments.

Hot melt extrusion filaments for FDM 3D printing of drugs:

- FDM printing combined with the hot melt extrusion (HME) technique can improve the solubility of poorly soluble drugs and assists in more uniform dispersion of the drug in the polymeric medium.
- To produce HME filaments, the active pharmaceutical ingredient and the excipients are inserted on the HME feeder for heating and mixing, preferably by twin-screw, and the homogenized product is collected as a filament.

1.4 INTRODUCTION

For decades, technological advances have been launched in the pharmaceutical field as a promise of revolutionizing the segment through a new therapeutic approach involving a modified drug delivery. Emblematic examples include the Ocusert® , an ophthalmic insert for glaucoma treatment from the 1970s and the osmotic pump capsule Oros® developed in the 1990s [1]. More recently, the so-called ‘intelligent drug-delivery devices’ capable of responding to patients’ physiological conditions, and nanosystems developed to modulate drug release into specific organs and tissues have already become a reality [2–4].

Such new technologies have often presented insurmountable difficulties of scale-up for industrial production, mainly due to high cost and/or formulation stability issues. This explains at least in part why, despite recognized therapeutic advantages, the vast majority of currently marketed drug products do not comprise any modified drug-delivery technology. As a general rule, most pharmaceutical formulations currently marketed are nothing but a simple vehicle for storage and administration of drugs.

Still, technologies continue to evolve and 3D printing of medicines have emerged as a new feasible tool for production of modified drug-release systems, raising high hopes that it may actually be the one capable of revolutionizing the segment. Among different 3D printing technologies, for example, stereolithography, selective laser sintering, powder bed and fusion

deposition modeling (FDM), FDM presents clear advantages for drug-delivery purposes. Also known as fused filament fabrication or fused filament modeling, FDM is considered of simple handling, low cost and presents the unique ability of producing dosage forms from polymeric matrices [5–7]. FDM 3D printing uses a plastic filament as an ‘ink,’ which is hot molded through the printer nozzle delivering consecutive layers over a platform, following desired geometry as established by a computational program [5]. There, however, resides the greatest challenge for pharmaceutical applications, such as ‘plastic ink’ must be biodegradable and impregnated with the drug. In this scenario, hot melt extrusion (HME) stands out among the most promising tools to produce the ideal infill materials.

HME is a technology to produce modified drug-release systems already employed in more than a dozen products marketed around the world. Besides easy processing scale-up, remarkable advantages include avoidance of organic solvents and possibility of continuous manufacturing. Also worth mentioning is HME versatility in production of modified drug-release systems (accelerated, delayed, controlled and vectorized) and the possibility of easily incorporating other technologies, for example, the insertion of nanocarriers into stable and scalable polymeric solids [8,9]. From recent publications, it is clear that HME potentials are broaden with the conjunction of 3D printing, which could provide higher process control capable of delivering large production of ‘individualized’ systems.

This review intends to analyze and discuss the challenges and future opportunities involved in coupling these two technologies.

1.5 3D PRINTING OF DRUG PRODUCTS

3D printing, also known as ‘additive manufacturing’ and ‘rapid prototyping’, is the deposition of printed materials in layers in the x, y and z-axes, following a computational control to generate a 3D structure. 3D printing is not exactly new and has already been used in a wide range of activities, as construction, automotive industry and in various areas of engineering for rapid creation of models and prototypes [10–12]. Application examples in biomedical field are recent, as production of medical implants, tissue

reconstitution [13,14], and the launch of the 3D orodispersible tablet Spritam® (levetiracetam), in the USA by Aprecia Pharmaceuticals [15].

One of the greatest appeals of 3D printed drug products is the possibility to individualize therapy according to patient's need, which has been lost since the industrial revolution of the 19th century. Specific characteristics of each individual such as age, weight, disease stage, in addition to genetic and biological factors, demand doses and drug-release kinetics adapted to each condition [16–18]. Not coincidentally, inadequacy of drug dosage responds for 75–85% of medicine side effects [13]. The only way of adapting industrial standard pharmaceutical dosage and presentation of tablets (the most common dosage form) is through its subdivision. However, this very common practice can lead to significant dose variations also compromising drug stability, representing a serious risk to the patient [19].

3D printing enables material combination, on a same printing process, to generate multilayer tablets including, not only different drugs but systems with different drug-release profiles [20,21]. Technological variables such as geometry and shape of the dosage form could be modified on demand, implying important advantages for patients with difficulty of swallowing or dysphagia [22,23].

Nonetheless, for the successful exploitation of this technology several known and still unknown challenges must be overcome. For instance, available 3D printers must be adapted to specific needs of drug products manufacturing, as include mechanisms for product contamination control [24]; new pharmaceutical excipients might be needed as well as studies to evaluate the impact of printing production variables on the quality parameters of the 3D-printed medicine.

1.6 FDM 3D PRINTING TECHNOLOGY

The completely automated process of 3D printing by FDM allows a surgical precision of each millimeter of the printed dosage form in terms of size, composition and shape, providing a superior reproducibility and suitability [23]. At least in theory, this technology presents less risk of generating quality deviations. Lastly, its versatility for both industrial and

laboratory scales highlights the FDM process from other 3D-printing methods. 3D FDM is one of the most commercialized home printers in the world and its industrial use is well established, for example, in the production of medical devices [25]. In this sense, it is possible to glimpse a large-scale manufacturing as well as the use of FDM printer in commercial drugstores for personalized printing of the formula.

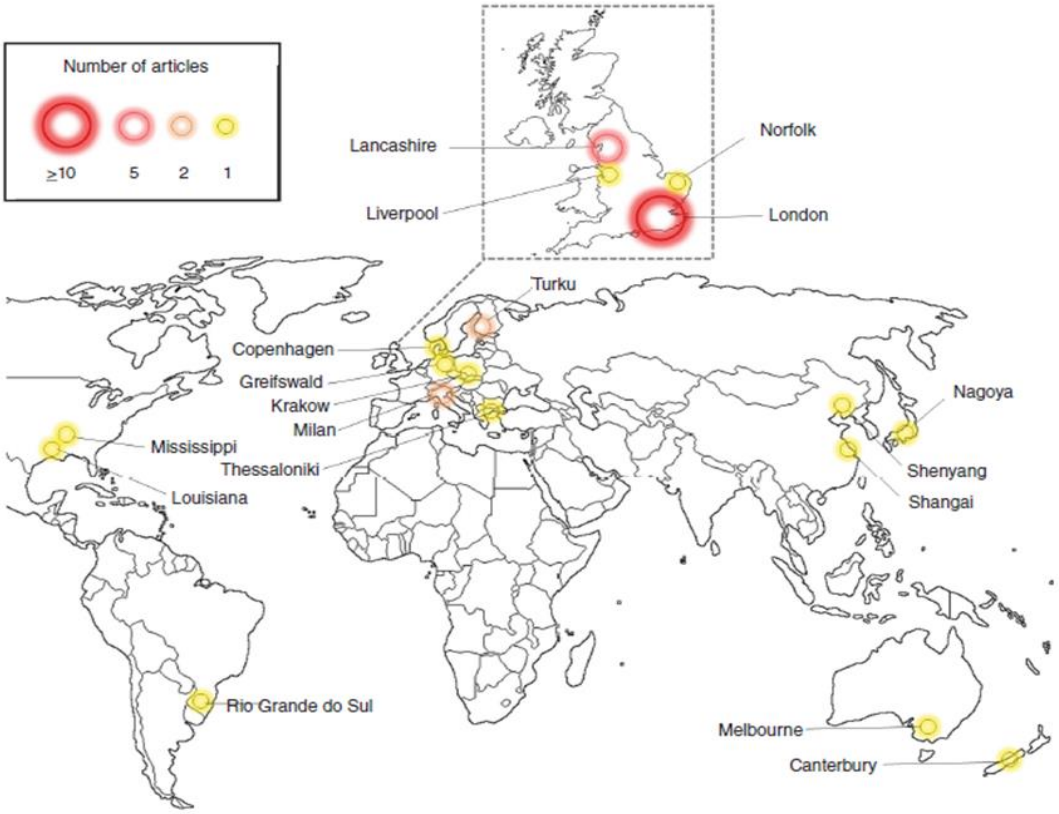


Figure 1. Geographic distribution of research papers published in fused deposition modeling 3D printing of drug-delivery systems.

Figure 1 shows the geographic distribution of research papers published on FDM 3D printing of drugs, according to PubMed® and SciFinder® databases. More than 30 papers were published on this subject focusing mainly on tablets development and on the effect of FDM-printing parameters. Novelty is evidenced by the fact that 90% of the papers have been published in the last 30 months. Most of the work has been conducted in the UK. Start-up companies have emerged on highlighted regions; hence, patents request involving the pharmaceutical use of 3D printing by FDM should arise in the coming months. Considering data dissemination in recent congresses, it is

possible to assume many of those blanks depicted in Figure 1 will be quickly swallowed in coming months.

From commercial 3D printers commonly used for research, 78% is a MakerBot® printer model replicator 2X (New York, USA) equipped with two independent nozzles. Experiments have also been performed using Multirap M420® (Riedhaunsen, Germany), Clouovo Delta-MK2® (ShenYang, China), FDM-200W® (Shizuoka, Japan), Prusa i3® (Prague, Czech Republic) and Wanhao Duplicator 4® (Zhejiang, China) [2,3,20,24,26]. Several parameters are required to be set up, for example, resolution, nozzle and plate temperatures, nozzle diameter, infill, layer height, speed traveling, speed extruding, extrusion rate, time per product and raft. Table 1 shows the usual machine conditions described in published papers, as determined following empirical tests [22,27,28].

Table 1. Fused deposition modeling 3D printer parameters used in printing dosage form.

Parameters	Conditions tested
Printer software	MakerWare
Document format	Stereolithography (.stl)
Minimum filament length	20 cm
Filament diameter	1.75 ± 0.05 mm
Configuration	Adjusted for PLA
Resolution	Low (340 µm), standard (270 µm), high (100 µm)
Nozzle temperature	95- 250°C
Plate temperature	20- 90°C
Nozzle diameter	0.20, 0.25, 0.30, 0.40 mm
Infill	0-100%
Layer height	100, 200, 300, 400, 600 µm
Speed traveling	50- 150 mm/s
Speed extruding	10- 90 mm/s
Time per product	2-5 min
Raft	With and without
Platform adherence	Scotch blue painter'stape

PLA: Polylactic acid.

Regarding 3D-printing parameters, nozzle temperature has significant importance. Filament must be heated above polymers glass transition temperature and considering the short residence time of the material in the nozzle and the small shear of the process, temperature must be higher than employed in HME. Depending on the material, temperature difference between HME and FDM could reach more than 100ºC [29]. Molten material is then deposited in juxtaposed layers that need to stick together. The rapid cooling can affect layers bond and preclude structure construction. In this way, printing base should be thermostated, being slightly heated to allow a gradual cooling and an appropriate consolidation of the 3D structure [30].

Other important parameter is the infill of the 3D structure. Faster release of the active pharmaceutical ingredient (API) occurs for higher infill, even though the authors could not establish a relation between porosity and drug release rates [6]. The infill of the 3D impression can assume very small values or produce compact structures with direct reflexes on the drug release [31]. The geometric shape of 3D dosage form has also shown to influence decisively the drug release due differences in the ratio surface area and volume, as described by Goyanes et al. for tablets produced in different shapes, for example, cube, pyramid, cylinder, sphere and torus [23].

The printer resolution refers to the quality of the printed material and can be quite relevant in 3D printing. A high resolution leads to a more detailed printed structure, which is obtained with small movements of the extruder, and reduced the thickness of each layer, in consequence increasing the time required for printing. In fact, printing time may be the main limiting factor for this technology, since producing a regular tablet using a tablet machine takes few seconds while 3D printing can last for minutes [10]. Preliminary studies with theophylline tablets, though, have showed that resolution did not affect significantly the weight or the drug dissolution rate of 3D tablets [30]. Although this is an encouraging result for large-scale production, other studies involving different materials and more detailed analyzes are still needed.

Some plastic polymers, such as polylactic acid (PLA), polyvinyl alcohol and acrylonitrile butadiene styrene, are ideally suited for the FDM-printing process and are very popular in the different sectors that use this technology. The pharmaceutical use of those materials, however, initially involved the

drug impregnation into the commercial filaments. The simplest option for this is the immersion of the filaments into concentrated drug solutions; however, this method allows only a limited drug loading, generally below 10% [5,27]. In addition, acrylonitrile butadiene styrene and PLA are insoluble in water, which produce inert matrices that present low therapeutic adherence since they remain intact throughout the entire transit of the GI tract and can provoke intestinal obstructions [32].

In such context, the previous processing of a formulation by HME may be a solution to overcome the limitations of polymers that are commonly used in 3D FDM printing, allowing the exploitation of 3D technology in the pharmaceutical field. In fact, HME can expand exponentially the materials that can be used in FDM 3D printing by obtaining filaments with higher drug loading [22].

1.7 HME AS AN IDEAL MATCH FOR FDM 3D PRINTING

HME is a technology raised in the plastic and food industries in the 1970s, which is recently being inserted in the pharmaceutical field to improve drugs' physicochemical properties and develop new drug-delivery systems [33,34]. Examples of drug products in the market containing this technology in their production are the tablets Onmel® (itraconazole), Covera-HS® (verapamil HCL) and Zithromax® (azithromycin); the intraocular implant Ozurdex® (dexamethasone); and the subcutaneous implants Zoladex® (goserelin acetate) and Implanon® (etonogestrel) [35].

The hot melt extruder is basically composed by a feeder in which the drugs and excipients are added, a barrel containing a single-screw or twin-screws where the mixing and heating of the products takes place and a die, through which the final product is ejected [35]. The high temperature and shear forces the drug to be melted and dispersed into the polymer [36]. Thus, HME can improve the bioavailability of drugs from different biopharmaceutical classes giving rise to controlled, sustained or immediately drug-release systems [35,37].

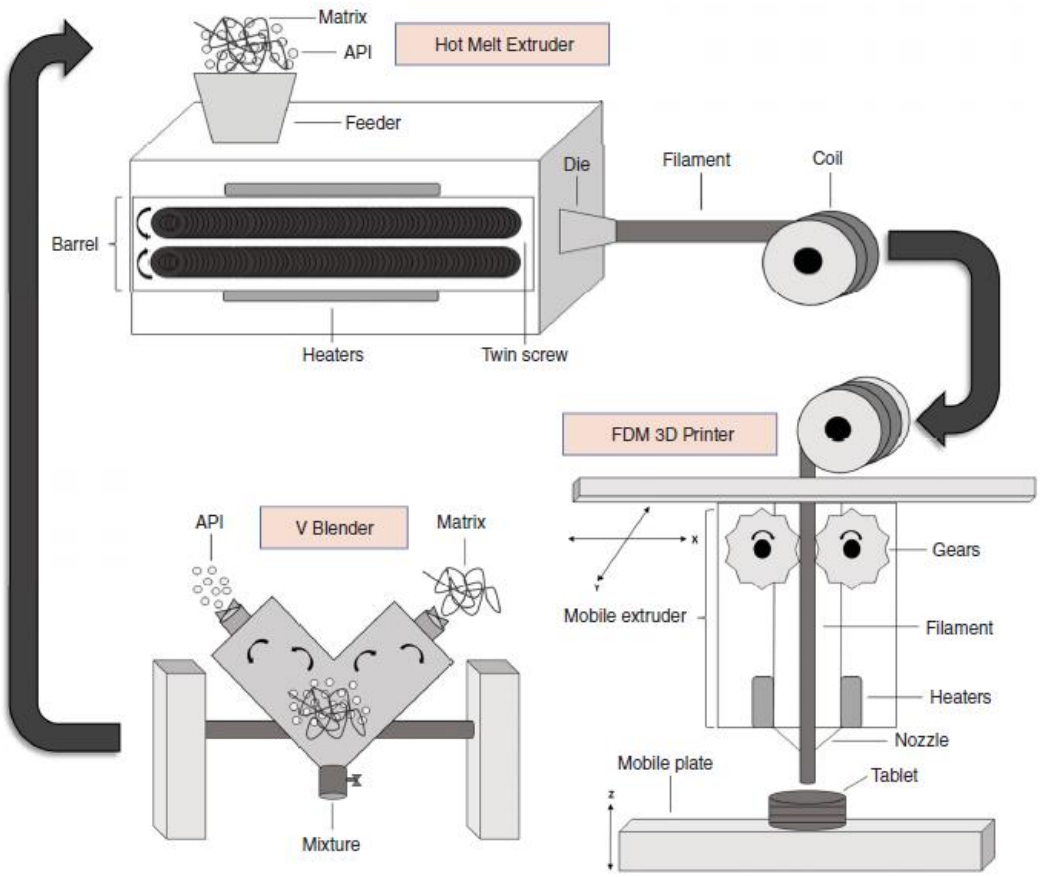


Figure 2. Schematic of the producing process of fused deposition modeling 3D printing of drug products using hot melt extrusion filaments.

The extruded filament or film produced by HME is cut in the requested size, or coupled with others devices to produce granules, pellets, transdermal implants, films, patches, modified release tablets and others [35]. Original filaments obtained by HME are themselves ideal substrates for FDM 3D printers, which can preserve, after the printing process, their modified drug-release properties. The production process from the association of these technologies consists of few steps illustrated in Figure 2.

The apparent simplicity of coupling the two technologies, however, masks a practical difficulty, which are the requirements that filaments must meet for FDM 3D printing. Concerning their dimensions, filaments need to obey narrow-range set of commercial 3D printers. Studies have demonstrated that the filament needs to be at least 20-cm longer in order to go through the printer's feed gears [38]. Additionally, round shape and regular diameter are needed according to printer nozzle. For the most commonly used nozzle (0.20-mm diameter), filament must have a diameter of 1.75 ± 0.05 mm

[29,30]. Other ideal mechanical and thermoplastic requirements are not completely clear yet. For example, filaments must be resistant and flexible at the same time, so they do not break into the printer [29,39]. Nonetheless, viscoelastic properties can obviously be modified by other components addition [29]. The class of materials most recommended to change polymers properties is plasticizers, which are low-molecular-weight compounds that increase free space between the polymer chains and improve its processing conditions [22,40]. More specifically, plasticizers can flexibilize the polymer and reduce the polymer glass transition temperature, which should enable the use of thermolabile drugs [11]. The popular HME pharmaceutical polymers, Soluplus® and Eudragit E®, have not shown appropriate filament for FDM 3D printing. In such case, the use of polymer blends or its association with fillers (Table 2) could overcome these issues, interfering directly in filament rheological properties [22,41]. Oily lubricants with high melting points, like castor oil and oleic acid, were used around the filaments during the 3D printing, to avoid sticking of the filament inside the printer and clogging of the nozzle. According to some published studies, use of these components does not influence the drug stability or its dissolution rate [27,28,42].

Polymers usually exploited in FDM 3D printing as well as several polymers used in HME not yet evaluated are listed in Table 2. Other pharmaceutical adjuvants and drugs tested so far using FDM 3D printing are also included. Noticeably, the number of drugs tested using this technology is still quite low. Nonetheless, stability maintenance after thermal processing by both HME and 3D printing was achieved in all the drugs tested, in other words, theophylline, captopril and prednisolone, even following manipulation at temperatures above 100ºC [22].

The range of polymers evaluated to produce release systems by HME/FDM 3D printing includes well-known materials such as PLA, polyglycolic acid, polyvinylpyrrolidone, Eudragits® , cellulose derivatives, ethylene vinyl acetate and hypromellose acetate succinate [22,29,30,39,43]. Still, several others as chitosan, xanthan gum, polyacrylic acid, polyglycolic acid, already used in HME systems could be exploited (Table 2) [35].

Table 2. Components utilized to produce drug-delivery systems by fused deposition modeling 3D printing using hot melt extrusion filaments and pharmaceutical materials with potential for this use.

Component	Raw material
Pharmaceutical HME polymers already used in 3D FDM	Polylactic acid (PLA), poly-ε-caprolactone (PCL), polyurethane (PU), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), Eudragit, polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft (SLP), polyvinyl alcohol–polyethylene glycol graft (KIR), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), ethyl cellulose (EC), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), poly-L-lactide (PLLA), ethylene vinyl acetate (EVA)
Pharmaceutical HME polymers not yet used in 3D FDM	Polyacrylic acid (PAA), polyglycolic acid (PGA), polylactide-co-glycolide, ε-caprolactone, L,D-lactide, glycolide, polyortho esters (POE I, II, III, IV), polyanhydride, starch, chitosan and xanthan gum
Fillers and plasticizers	Triethyl citrate (TEC), tricalcium phosphate (TCP), tribasic phosphate (TBP), triacetin, talc, spray-dried lactose (SD), directly compressible lactose (DC), microcrystalline cellulose (MMC), polyethylene glycol (PEG), polysorbate, polyethylene oxide (PEO), methylparaben, mannitol
Lubricants	Castor oil, oleic acid, glycerol
Active pharmaceutical ingredients	Theophylline, 5-ASA, 4-ASA, captopril, prednisolone, budesonide, paracetamol, caffeine, salicylic acid, dipyridamole, felodipine, acetaminophen, furosemide, fluorescein sodium salt, quinine, indomethacin, nitrofurantoin monohydrate, nitrofurantoin anhydrate, hydroxyapatite, glipizide, curcumin, disulfiram, zinc, copper, silver, gentamicin, methotrexate, deflazacort

FDM: Fused deposition modeling; HME: Hot melt extrusion.

1.8 DRUG-DELIVERY SYSTEMS USING FDM 3D PRINTING & THE POTENTIAL OF 3D NANOCARRIERS

Researchers have preferably focused on the production of oral tablets with modified drug delivery with HME/FDM 3D-printing association, since the most diverse release profiles can be yield, for example, immediate release [22,28,30], delayed release [42], pulsatile release [38], enteric release [44] and controlled release [14,30,31]. The possibility of combining different drug-release profiles has already been probed in the development of double-drug tablets containing acetaminophen and caffeine, in which the drug release was fast for the coating tablet layer and retarded for the matrix content [21]. Also, topical drug delivery has been successfully explored through 3D printing of a nose mask containing an antiacne drug and antimicrobial wound dressings personalized according to the anatomy of the patient using a 3D scanning [45,46]. The potential of 3D technology application on pharmaceutical field, however, might be yet to be revealed. Wider applications might appear with the 3D printing of nanosystems. In fact, the first experimental approach coupling nanotechnology and 3D FDM has just been published. 3D tablets elaborated with Eudragit and poly-ε-caprolactone were impregnated with deflozacort nanocapsules, converting nanocapsule suspensions into a solid dosage forms [47].

In general, nanosystems' production generates toxic organic solvent residues and does not allow a continuous fabrication process. Those methods also produce particles that can be uneven and instable, leading to aggregation. HME in some circumstances can also circumvent those problems [48,50]. Nanocrystal solid dispersions of efavirenz were obtained with high-pressure homogenization associated with HME, resulting in a highly stable formulation after a real-time-used storage conditions [48]. Solid–lipid nanoparticles of fenofibrate were produced using HME in a continuous and large-scale process, revealing important improvement in drug pharmacokinetic parameters [51]. HME has also been employed to convert a liquid-stabilized nanosuspension into a solid formulation in a one-step process by removing aqueous solvent following devolatilization, which successfully resulted in solidified polymer at the outlet-forming filaments containing

nanocrystals [4]. Despite the limited number of studies, HME technology has demonstrated great feasibility as a vehicle for nano-based drug-delivery systems. Nevertheless, many advances need to be made, especially in order to achieve a better insertion of the nanosystems elaboration directly into the HME process.

1.9 CONCLUSION

The results obtained so far in the development of drug products using HME associated with FDM 3D reinforce the envisioned potential of this technology of being capable of bringing modified drug-delivery systems to people's daily lives. Nevertheless, the adaptation of FDM 3D printing for pharmaceutical manufacturing needs to be better understood, especially regarding printer adjustments and expansion of available pharmaceutical materials.

1.10 FUTURE PERSPECTIVE

When a retrospective of the main innovations in the pharmaceutics field is taken in account, it is possible to affirm that no other technology attracted so much attention and created so many expectations as the 3D printing of drug products. However, the greatest challenge for FDM 3D-printing technique application is to obtain a suitable filament with appropriate drug loading. HME appears in this scenario as a perfect match for FDM 3D technology, being capable of producing filaments with high drug-load capacity that can modulate delivery of drugs. Hence, in the next few years, it is possible to foresee, not only these, but novel materials being tested for pharmaceutical purposes. Stability concern may remains for all heat-based or products that need thermal treatments. Nevertheless, with technology evolution novel machinery design with actual coupling of thermal extruders and 3D printers may overcome difficulties in meeting filament requirements and probably allow for a proper quality control, as nowadays critical aspects to meet product quality remain unclear. In a few years, after meeting primary

industrial production and regulation challenges, personalized medicines may become a reality.

1.11 FINANCIAL DISCLOSURE

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1.12 REFERENCES

1. Hoffman AS. The origins and evolution of ‘controlled’ drug-delivery systems. *J. Control. Rel.* 132(3), 153–163 (2008).

2. Kempin W, Franz C, Koster LC et al. Assessment of different polymers and drug loads for fused deposition modeling of drug loaded implants. *Eur. J. Pharm. Biopharm.* 115, 84–93, (2017).

3. Zhang J, Feng X, Patil H, Tiwari RV, Repka MA. Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets. *Int. J. Pharm.* 519(1–2), 186–197 (2017).

4. Khinast J, Baumgartner R, Roblegg E. Nano-extrusion: a one-step process for manufacturing of solid nanoparticle formulations directly from the liquid phase. *AAPS. PharmSciTech*. 14(2), 601–604 (2013).

5. Goyanes A, Buanz AB, Basit AW, Gaisford S. Fused-filament 3D printing (3DP) for fabrication of tablets. *Int. J. Pharm.* 476(1–2), 88–92 (2014).

6. Goyanes A, Kobayashi M, Mart´ınez-Pacheco R, Gaisford S, Basit AW. Fused-filament 3D printing of drug products: microstructure analysis and drug release characteristics of PVA-based caplets. *Int. J. Pharm.* 514(1), 290–295 (2016).

7. Wang J, Goyanes A, Gaisford S, Basit AW. Stereolithographic (SLA) 3D printing of oral modified-release dosage forms. *Int. J. Pharm.* 503(1–2), 207–212 (2016).

8. Patil H, Tiwari RV, Repka MA. Hot-melt extrusion: from theory to application in pharmaceutical formulation. *AAPS PharmSciTech.* 17(1), 20–42 (2016).

9. Tiwari RV, Patil H, Repka MA. Contribution of hot-melt extrusion technology to advance drug delivery in the 21st century. *Expert. Opin. Drug. Deliv.* 13(3), 451–464 (2016).

10. Norman J, Madurawe RD, Moore CM, Khan MA, Khairuzzaman A. A new chapter in pharmaceutical manufacturing: 3D-printed drug products. *Adv. Drug. Deliv. Rev.* 108, 39–50 (2017).

11. Prasad LK, Smyth H. 3D Printing technologies for drug delivery: a review. Drug. *Dev. Ind. Pharm.* 42(7), 1019–1031 (2016).

12. Yu DG, Zhu LM, Branford-White CJ, Yang XL. Three-dimensional printing in pharmaceutics: promises and problems. *J. Pharm. Sci.* 97(9), 3666–3690 (2008).

13. Alhnan MA, Okwuosa TC, Sadia M, Wan KW, Ahmed W, Arafat B. Emergence of 3D printed dosage forms: opportunities and challenges. *Pharm. Res.* 33(8), 1817–1832 (2016).

14. Masood SH. Application of fused deposition modelling in controlled drug delivery devices. *Assembly Automation* 27(3), 215–221 (2007).

15. Aprecia Pharmaceuticals. FDA approves the first 3D printed drug product. (2015). www.aprecia.com/pdf/ApreciaSPRITAMLaunchPressReleaseFINAL.PDF

16. Planchette C, Pichler H, Wimmer-Teubenbacher M. Printing medicines as orodispersible dosage forms: effect of substrate on the printed micro-structure. *Int. J. Pharm.* 509(1–2), 518–527 (2016).

17. Raijada D, Genina N, Fors D et al. A step toward development of printable dosage forms for poorly soluble drugs. *J. Pharm. Sci.* 102(10), 3694–3704 (2013).

18. Kolakovic R, Viitala T, Ihalainen P, Genina N, Peltonen J, Sandler N. Printing technologies in fabrication of drug-delivery systems. *Expert. Opin. Drug. Deliv.* 10(12), 1711–1723 (2013).

19. Teixeira MT, Sá-Barreto LCL, Gratieri T, Gelfuso GM, Silva ICR, Cunha-Filho MSS. Key technical aspects influencing the accuracy of tablet subdivision. *AAPS. PharmSciTech.* 18(4), 1393–1401 (2017).

20. Li Q, Wen H, Jia D et al. Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing. *Int. J. Pharm.* 525(1), 5–11 (2017).

21. Goyanes A, Wang J, Buanz A et al. 3D printing of medicines: engineering novel oral devices with unique design and drug release characteristics. *Mol. Pharm.* 12(11), 4077–4084 (2015).

22. Sadia M, Sósnicka A, Arafat B et al. Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets. *Int. J. Pharm.* 513(1–2), 659–668 (2016).

23. Goyanes A, Robles Martinez P, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. *Int. J. Pharm.* 494(2), 657–663 (2015).

24. Davies MJ, Costley E, Ren J, Gibbons P, Kondor A, Naderi M. On drug base incompatibilities during extrudate manufacture and fused deposition 3D printing. *J. 3D Print. Med.* 1(1), 31–47 (2017).

25. Cicala G, Latteri A, Del Curto B, Lo Russo A, Recca G, Far`e S. Engineering thermoplastics for additive manufacturing: a critical perspective with experimental evidence to support functional applications. *J. Appl. Biomater. Funct. Mater.* 15(1), 0 (2017).

26. Tagami T, Fukushige K, Ogawa E, Hayashi N, Ozeki T. 3D printing factors important for the fabrication of polyvinylalcohol filament-based tablets. *Biol. Pharm. Bull.* 40(3), 357–364 (2017).

27. Skowyra J, Pietrzak K, Alhnan MA. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. *Eur. J. Pharm. Sci.* 68, 11–17 (2015).

28. Okwuosa TC, Stefaniak D, Arafat B, Isreb A, Wan KW, Alhnan MA. A lower temperature FDM 3D printing for the manufacture of patient-specific immediate release tablets. *Pharm. Res.* 33(11), 2704–2712 (2016).

29. Melocchi A, Parietti F, Maroni A, Foppoli A, Gazzaniga A, Zema L. Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling. *Int. J. Pharm.* 509(1–2), 255–263 (2016).

30. Pietrzak K, Isreb A, Alhnan MA. A flexible-dose dispenser for immediate and extended release 3D printed tablets. *Eur. J. Pharm. Biopharm.* 96, 380–387 (2015).

31. Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. *Eur. J. Pharm. Biopharm.* 89, 157–162 (2015).

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

33. Maniruzzaman M, Rana MM, Boateng JS, Mitchell JC, Douroumis D. Dissolution enhancement of poorly water-soluble APIs processed by hot-melt extrusion using hydrophilic copolymers. *Drug. Dev. Ind. Pharm.* 39(2), 218–227 (2013).

34. Maniruzzaman M, Boateng JS, Bonnefille M, Aranyos A, Mitchell JC, Douroumis D. Taste masking of paracetamol by hot-melt extrusion: an in vitro and in vivo evaluation. *Eur. J. Pharm. Biopharm.* 80(2), 433–442 (2012).

35. Stankovi´c M, Frijlink HW, Hinrichs WL. Polymeric formulations for drug release prepared by hot melt extrusion: application and characterization. *Drug. Discov. Today.* 20(7), 812–823 (2015).

36. Zhang Y, Luo R, Chen Y, Ke X, Hu D, Han M. Application of carrier and plasticizer to improve the dissolution and bioavailability of poorly water-soluble baicalein by hot melt extrusion. *AAPS. PharmSciTech.* 15(3), 560–568 (2014).

37. Moulton SE, Wallace GG. 3-dimensional (3D) fabricated polymer based drug-delivery systems. *J. Control. Rel.* 193, 27–34 (2014).

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

39. Genina N, Holl¨ander J, Jukarainen H, M¨akil¨a E, Salonen J, Sandler N. Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices. *Eur. J. Pharm. Sci.* 90, 53–63 (2016).

40. Madan S, Madan S. Hot melt extrusion and its pharmaceutical applications. *Asian. J. Pharm. Sci.* 7(2), 123–133 (2012).

41. Alhijjaj M, Belton P, Qi S. An investigation into the use of polymer blends to improve the printability of and regulate drug release from pharmaceutical solid dispersions prepared via fused deposition modeling (FDM) 3D printing. *Eur. J. Pharm. Biopharm.* 108, 111–125 (2016).

42. Okwuosa TC, Pereira BC, Arafat B, Cieszynska M, Isreb A, Alhnan MA. Fabricating a shell-core delayed release tablet using dual FDM 3D printing for patient-centred Therapy. *Pharm. Res.* 34(2), 427–437 (2017).

43. Goyanes A, Fina F, Martorana A, Sedough D, Gaisford S, Basit AW. Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing. *Int. J. Pharm.* 527(1–2), 21–30 (2017).

44. Goyanes A, Chang H, Sedough D et al. Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing. *Int. J. Pharm.* 496(2), 414–420 (2015).

45. Goyanes A, Det-Amornrat U, Wang J, Basit AW, Gaisford S. 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug-delivery systems. *J. Control. Rel.* 234, 41–48 (2016).

46. Hassan ZM, Goyanes A, Clark V, Basit AW, Hilton ST, Gaisford S. Patient-specific 3D scanned and 3D printed antimicrobial polycaprolactone wound dressings. *Int. J. Pharm.* 0378–5173(17), 30387–30393 (2017).

47. Beck RCR, Chaves PS, Goyanez A et al. 3D printed tablets loaded with polymeric nanocapsules: an innovative approach to produce customized drug-delivery systems. *Int. J. Pharm.* 0378–5173(17), 30498–30502 (2017).

48. Ye X, Patil H, Feng X et al. Conjugation of hot-melt extrusion with high-pressure homogenization: a novel method of continuously preparing nanocrystal solid dispersions. *AAPS. PharmSciTech.* 17(1), 78–88 (2016).

49. Waard H, Frijlink HW, Hinrichs WL. Bottom-up preparation techniques for nanocrystals of lipophilic drugs. *Pharm. Res.* 28(5), 1220–1223 (2011).

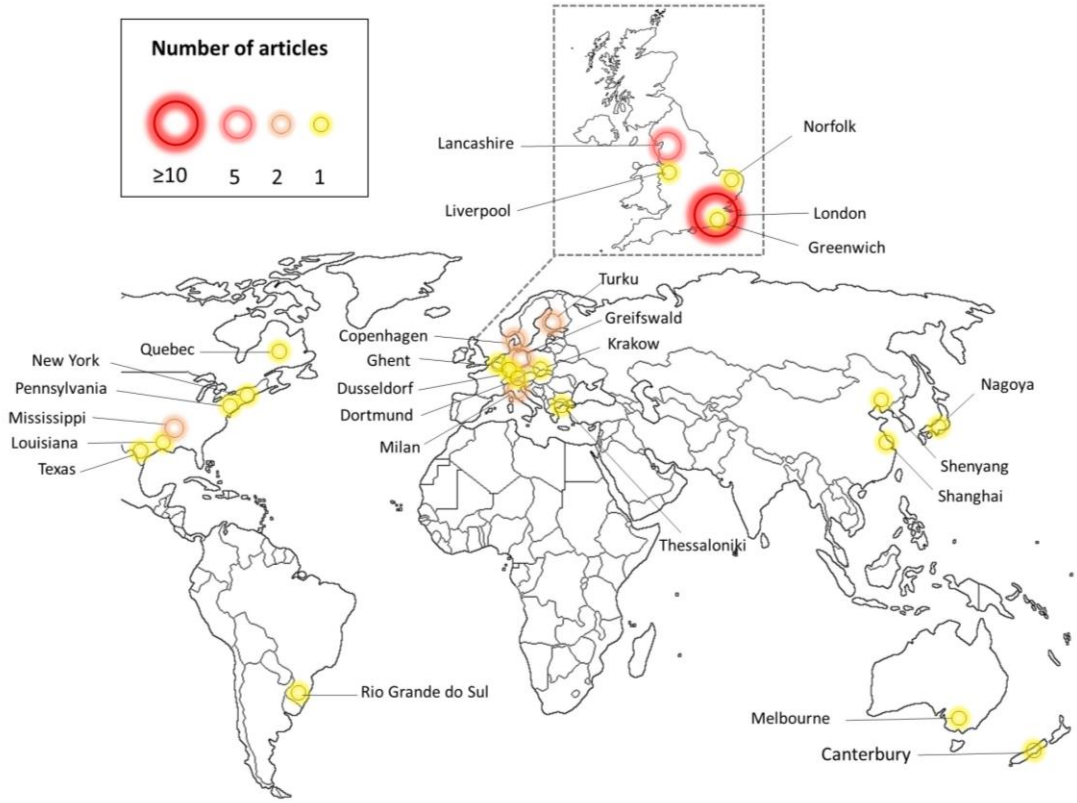
50. Repka MA, Majumdar S, Kumar Battu S, Srirangam R, Upadhye SB. Applications of hot-melt extrusion for drug delivery. *Expert. Opin. Drug. Deliv.* 5(12), 1357–1376 (2008).

51. Patil H, Feng X, Ye X, Majumdar S, Repka MA. Continuous production of fenofibrate solid lipid nanoparticles by hot-melt extrusion technology: a systematic study based on a quality by design approach. *AAPS. J.* 17(1), 194–205 (2015).

1.13 APENDIX

Figures and Tables from chapter 1 were updated with knew information and relevant complementary data was added on December 2018.

1.13.1 FIGURES AND TABLES UPDATE



Updated Fugure 1 - Geographic distribution of research papers published in fused deposition modeling 3D printing of drug-delivery systems.

Updated Table 1 - Fused deposition modeling 3D printer parameters used in printing dosage form.

Parameters	Conditions tested
Printer software	MakerWare
Document format	Stereolithography (.stl)
Minimum filament length	20 cm
Filament diameter	1.75 ± 0.05 mm
Configuration	Adjusted for PLA
Resolution	Low (340 µm), standard (270 µm), high (100 µm)

Nozzle temperature	54- 250°C
Plate temperature	20- 90°C
Nozzle diameter	0.20, 0.25, 0.30, 0.40, 0.50 mm
Infill	0-100%
Layer height	100, 200, 300, 400, 600 µm
Speed traveling	25- 150 mm/s
Speed extruding	3- 90 mm/s
Time per product	2-5 min
Raft	With and without
Platform adherence	Scotch blue painter'stape

PLA: Polylactic acid.

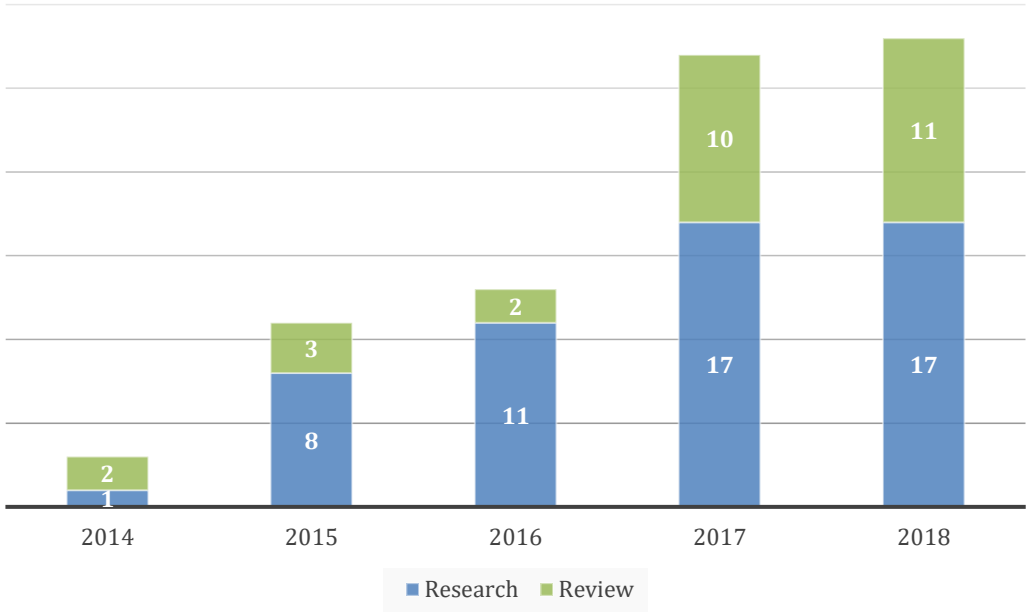
Updated Table 2 - Components utilized to produce drug-delivery systems by fused deposition modeling 3D printing using hot melt extrusion filaments and pharmaceutical materials with potential for this use.

Component	Raw material
Pharmaceutical HME polymers already used in 3D FDM	Polylactic acid (PLA), poly-ε-caprolactone (PCL), polyurethane (PU), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), Eudragit, polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft (SLP), polyvinyl alcohol–polyethylene glycol graft (KIR), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), ethyl cellulose (EC), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), poly-L-lactide (PLLA), ethylene vinyl acetate (EVA), vinylpyrrolidone-vinyl acetate copolymer, carboxy methyl cellulose (CMC), acrylonitrile butadiene styrene (ABS), polyethylene glycol (PEG)
Pharmaceutical HME polymers not yet used in 3D FDM	Polyacrylic acid (PAA), polyglycolic acid (PGA), polylactide-co-glycolide, ε-caprolactone, L,D-lactide, glycolide, polyortho esters (POE I, II, III, IV), polyanhydride, starch, chitosan and xanthan gum

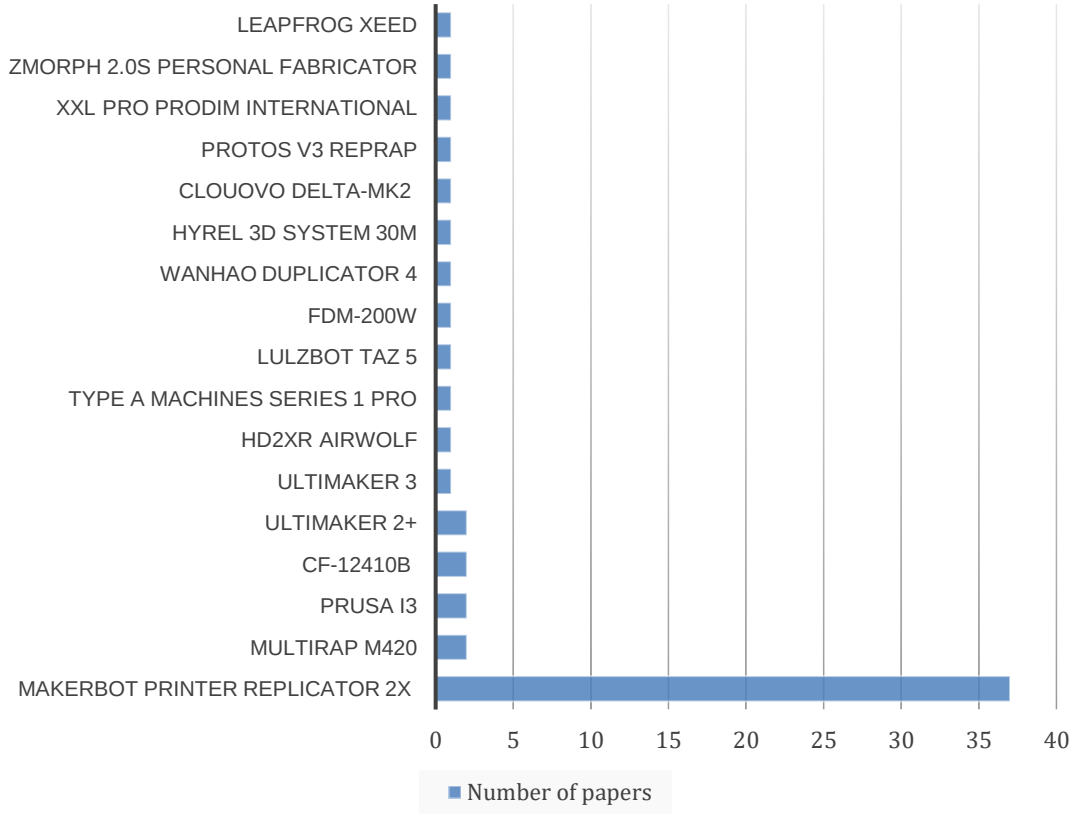
Fillers and plasticizers	Triethyl citrate (TEC), tricalcium phosphate (TCP), tribasic phosphate (TBP), triacetin, talc, spray-dried lactose (SD), directly compressible lactose (DC), microcrystalline cellulose (MMC), polyethylene glycol (PEG), polysorbate, polyethylene oxide (PEO), methylparaben, mannitol, stearic acid, sodium polyacrylate
Lubricants	Castor oil, oleic acid, glycerol, glycerin, magnesium carbonate, magnesium stearate
Disintegrants	Sodium starch glycolate, croscarmellose sodium, crospovidone
Active pharmaceutical ingredients	Theophylline, 5-ASA, 4-ASA, captopril, prednisolone, budesonide, paracetamol, caffeine, salicylic acid, dipyridamole, felodipine, acetaminophen, furosemide, fluorescein sodium salt, quinine, indomethacin, nitrofurantoin monohydrate, nitrofurantoin anhydrate, hydroxyapatite, glipizide, curcumin, disulfiram, zinc, copper, silver, gentamicin, methotrexate, deflazacort, sodium warfarin, hydrochlorothiazide, fluorodeoxyglucose, ramipril, metformin hydrochloride, haloperidol, riboflavin, progesterone, domperidone, rifampicin, isoniazid, carbamazepine, saquinavir, halofantrine, pantoprazole sodium, aripiprazole, clobetasol propionate.

FDM: Fused deposition modeling; HME: Hot melt extrusion.

1.13.2 COMPLEMENTARY DATA



Complementary Figure 1. Number of published papers (research and review) related to fused deposition modeling 3D printing of drug-delivery systems along the years.



Complementary Figure 2. Fused deposition modeling 3D printers used on research papers.

1.13.3 COMPLEMENTARY REFERENCES

Arafat B, Qinna N, Cieszynska M, Forbes RT, Alhnan MA. Tailored on demand anti-coagulant dosing: An in vitro and in vivo evaluation of 3D printed purpose-designed oral dosage forms. *Eur. J. Pharm. Biopharm.* 128, 282-289 (2018).

Arafat B, Wojsz M, Isreb A *et al*. Tablet fragmentation without a disintegrant: A novel design approach for accelerating disintegration and drug release from 3D printed cellulosic tablets. *Eur. J. Pharm. Sci.* 118, 191-199 (2018).

Boetker J, Water JJ, Aho J, Arnfast L, Bohr A, Rantanen J. Modifying release characteristics from 3D printed drug-eluting products. *Eur. J. Pharm. Sci.* 90, 47-52 (2016).

Chai X, Chai H, Wang X *et al*. Fused Deposition Modeling (FDM) 3D Printed Tablets for Intragastric Floating Delivery of Domperidone. *Sci. Rep.* 7(1), 2829 (2017).

Feuerbach T, Kock S, Thommes M. Characterisation of fused deposition modeling 3D printers for pharmaceutical and medical applications. *Pharm. Dev. Technol.* 1-10 (2018).

Fu J, Yin H, Yu X *et al*. Combination of 3D printing technologies and compressed tablets for preparation of riboflavin floating tablet-in-device (TiD) systems. *Int. J. Pharm.* 549(1-2), 370-379 (2018).

Fu J, Yu X, Jin Y. 3D printing of vaginal rings with personalized shapes for controlled release of progesterone. *Int. J. Pharm.* 539(1-2), 75-82 (2018).

Genina N, Boetker JP, Colombo S, Harmankaya N, Rantanen J, Bohr A. Anti-tuberculosis drug combination for controlled oral delivery using

3D printed compartmental dosage forms: From drug product design to in vivo testing. *J. Control. Release.* 268, 40-48 (2017).

Gioumouxouzis CI, Katsamenis OL, Bouropoulos N, Fatouros DG. 3D printed oral solid dosage forms containing hydrochlorothiazide for controlled drug delivery. *J. Drug. Deliv. Sci. Technol.*164-171 (2017).

Goyanes A, Scarpa M, Kamlow M, Gaisford S, Basit A, Orlu M. Patient acceptability of 3D printed medicines. *Int. J. Pharm.* 530(1-2), 71-78 (2017).

Goyanes A, Fernández-Ferreiro A, Majeed A *et al*. PET/CT imaging of 3D printed devices in the gastrointestinal tract of rodents. *Int. J. Pharm.* 536(1), 158-164 (2018).

Jamróz W, Kurek M, Łyszczarz E *et al*. 3D printed orodispersible films with Aripiprazole. *Int. J. Pharm.* 533(2), 413-420 (2017).

Kempin W, Domsta V, Grathoff G *et al*. Immediate Release 3D-Printed Tablets Produced Via Fused Deposition Modeling of a Thermo-Sensitive Drug. *Pharm. Res.* 35(6), 124 (2018).

Kollamaram G, Croker DM, Walker GM, Goyanes A, Basit AW, Gaisford S. Low temperature fused deposition modeling (FDM) 3D printing of thermolabile drugs. *Int. J. Pharm.* 545(1-2), 144-152 (2018).

Korte C, Quodbach J. Formulation development and process analysis of drug-loaded filaments manufactured via hot-melt extrusion for 3D-printing of medicines. *Pharm. Dev. Technol.* 1-11 (2018).

Liang K, Carmone S, Brambilla D, Leroux JC. 3D printing of a wearable personalized oral delivery device: A first-in-human study. *Sci. Adv.* 4(5), eaat2544 (2018).

Luzuriaga MA, Berry DR, Reagan JC, Smaldone RA, Gassensmith JJ. Biodegradable 3D printed polymer microneedles for transdermal drug delivery. *Lab. Chip.* 18(8), 1223-1230 (2018).

Markl D, Zeitler JA, Rasch C *et al*. Analysis of 3D Prints by X-ray Computed Microtomography and Terahertz Pulsed Imaging. *Pharm. Res.* 34(5), 1037-1052 (2017).

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

Melocchi A, Parietti F, Maccagnan S *et al*. Industrial Development of a 3D-Printed Nutraceutical Delivery Platform in the Form of a Multicompartment HPC Capsule. *AAPS. PharmSciTech.* (2018).

Okwuosa TC, Soares C, Gollwitzer V, Habashy R, Timmins P, Alhnan MA. On demand manufacturing of patient-specific liquid capsules via co-ordinated 3D printing and liquid dispensing. *Eur. J. Pharm. Sci.*118, 134-143 (2018).

Sadia M, Arafat B, Ahmed W, Forbes RT, Alhnan MA. Channelled tablets: An innovative approach to accelerating drug release from 3D printed tablets. *J. Control. Release.* 269, 355-363 (2018).

Scoutaris N, Ross SA, Douroumis D. 3D Printed "Starmix" Drug Loaded Dosage Forms for Paediatric Applications. *Pharm. Res.* 35(2), 34 (2018).

Smith DM, Kapoor Y, Klinzing GR, Procopio AT. Pharmaceutical 3D printing: Design and qualification of a single step print and fill capsule. *Int. J. Pharm.* 544(1), 21-30 (2018).

Solanki NG, Tahsin M, Shah AV, Serajuddin ATM. Formulation of 3D Printed Tablet for Rapid Drug Release by Fused Deposition Modeling (FDM): Screening Polymers for Drug Release, Drug-Polymer Miscibility and Printability. *J. Pharm. Sci*. 107(1), 390-401 (2018).

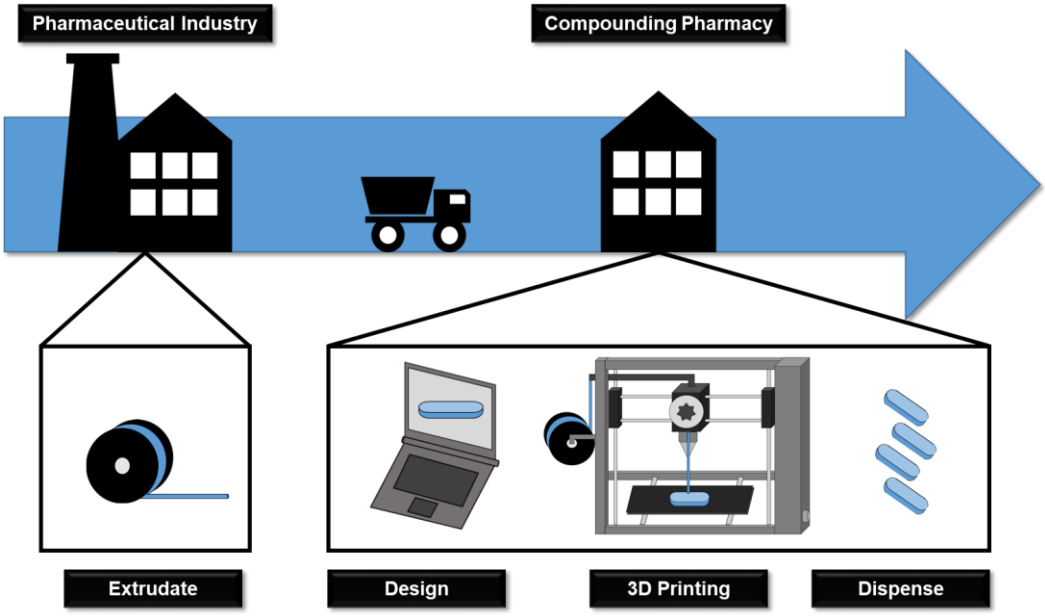
Verstraete G, Samaro A, Grymonpré W *et al*. 3D printing of high drug loaded dosage forms using thermoplastic polyurethanes. *Int. J. Pharm.* 536(1), 318-325 (2018).

Zhang J, Yang W, Vo AQ *et al.* Hydroxypropyl methylcellulose-based controlled release dosage by melt extrusion and 3D printing: Structure and drug release correlation. *Carbohydr. Polym.* 177, 49-57 (2017).

2. CHAPTER 2

Pathway to the market of fused deposition modeling 3D printed drug delivery devices: co-participation between pharmaceutical industry and compounding pharmacy.

2.1 GRAPHICAL ABSTRACT



2.2 ABSTRACT

Fused deposition modeling 3D printing has currently been explored in the research field for the elaboration of multiple drug products. The extruded drug loaded filaments melted and placed layer by layer are capable of producing complex pharmaceutical forms with different dosage, shapes and release kinetics, giving place to customized medicines. This work aimed to present an up-to-date on FDM 3D printing of drug delivery devices based on data published between 2014 and 2018. A co-participation between pharmaceutical industries and compounding pharmacies in a complementary production chain is also proposed. We suggested that the hot-melt extruded filaments, loaded with the active pharmaceutical ingredient and different pharmaceutical grade polymers, should be fabricated industrially and

purchased by compounding pharmacies. Then, an adapted pharmaceutical 3D printer with prescriptioner's friendly software need to be developed and the drug devices designed according to the patient's specific prescription would be printed and dispensed at local sites. In the end, this new technology revealed to be highly versatile and with an undeniable capability to produce personalized drug products. The partnership between pharmaceutical industries and compounding pharmacies demonstrated to be a viable pathway to market, but for this process to become a reality, regulatory and patent agencies should work side-by-side with companies.

Keywords: Modified drug release, Fused deposition modeling 3D printing, Pharmaceutical industry, Compounding pharmacy

2.3 EXECUTIVE SUMMARY

Fused deposition modeling three-dimensional (3D) printing of drug products:

- 3D printing is a technique used to produce an object layer by layer in the x, y and z-axes.
- Fused deposition modeling (FDM) is the most popular 3D printing technique to produce drug delivery devices that use heat to melt polymeric filaments and deposit them layer by layer to create 3D products.
- Multiple drug delivery devices (DDD) were developed using FDM 3D printing, such as oral, dermal and implant dosage forms. Complex pharmaceutical products with different dosages, shapes and release kinetics can be produced using this technology.

Pharmaceutical Industry:

- The pharmaceutical industry would be responsible for the filament production and quality assurance in large scale.
- The filament production process consists on only three steps: (1) active pharmaceutical ingredients (API) and excipients (polymer) blend; (2) extrusion of filaments by hot-melt extrusion (HME); and (3) filament packing preventing degradation.

Compounding pharmacy:

- The compounding pharmacy is responsible for the drug delivery device production and quality assurance at local site.
- The drug delivery device dispensing process consists on three steps: (1) drug delivery device design according to patient specific prescription; (2) drug printing by an adapted pharmaceutical FDM 3D printer using industrially produced filaments; and (3) dispensing of the drug product to the patient.

2.4 INTRODUCTION

3D printing, a technique used to produce an object layer by layer in the x, y and z-axes, is recently gaining space in the pharmaceutical field [1]. This technology poses major benefits when compared to traditional production methods, such as, the ability to develop, in a practical way, personalized complex pharmaceutical forms with flexible dosage, different shapes, multiple active pharmaceutical ingredients (even incompatible one's) and variable release kinetics [2]. Moreover, drug delivery devices for oral, dermal and implantable administration have been successfully produced using 3D printing machines [3].

Fused deposition modeling (FDM), a type of 3D printing technology, is the most quoted one when dealing with drug delivery devices production. The amount of research using this technology has consistenly increased in the last years all over the world [4]. The FDM 3D printer uses heat to melt a polymeric filament and deposit it layer by layer creating a three-dimensional product [5,6]. The filament used to feed the printer is produced by hot-melt extrusion, using mainly active pharmaceutical ingredients and pharmaceutical grade polymers [7].

But competing against the drug mass production implemented by the pharmaceutical industry after the industrial revolution is no simple task. FDM 3D printers cannot match the industrial tablet machines velocity, but they certainly represent a cost-effective method to develop individual complex pharmaceutical dosage [8]. That is why this technology is ideal for production

of personalized drugs products prescribed specifically to each patient at compounding pharmacies [9]. The artisanal processes used until today at local pharmacies are subjected to failures that may put in danger the patient security and hinder some drugs extemporaneous production, such as antibiotics, hormones and cytostatic, that need additional care [10]. The printing process is safer and may prevent these quality issues meeting the necessary requirements to raise the drug personalization to another level [3,11,12].

The co-participation of both pharmaceutical industry and compounding pharmacy seems to be the best way to cross the barrier of research and finally reach patients. The FDM 3D printer is portable and relatively simple to operate, making it eligible for implementation at compounding pharmacies. On the other hand, the hot-melt extruded drug loaded filaments can be produced by the industry on a large-scale as an intermediate product. These filaments can be transformed into personalized medicines according to the medical prescriptions at local pharmacies [13]. Quality control tests would be required at both sites, especially rheological tests and thermal analyses. Despite the fast development in this field and the release of the first 3D printed drug product, Spritam® (levetiracetam), there are still technical and regulatory issues to be addressed [14].

This work aimed to present an up-to-date on FDM 3D printing use for drug delivery devices and propose a new production pathway to make these products a market reality. 85 research and review papers were found in PubMed® and SciFinder® databases, between the years 2014 and 2018, using “3D PRINTING” AND “FDM” AND “DRUG” as key words and had their data used on this revision.

2.5 VERSATILITY OF FDM 3D PRINTING FOR DRUG-DELIVERY DEVICES

FDM 3D printers can produce a wide range of different drug delivery devices. Articles published in the last five years have revealed a still incomplete picture of the therapeutic potential of this technology. Figure 1 displays the percentage of these devices according to published research papers on FDM 3D printing (reviews not included).

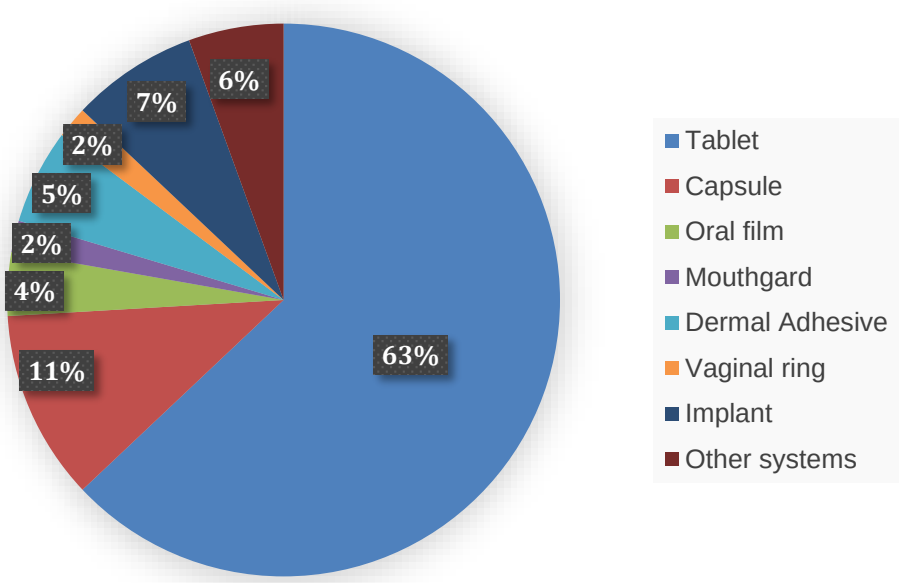


Figure 1. Percentage of drug-delivery devices (n = 54) in fused deposition modeling 3D printing published research papers, between years 2014 and 2018.

As expected, the majority of studies explored the development of oral dosage forms, with tablets being the most studied (63%), followed by the capsules (11%). Oral pharmaceutical presentations represent more than 40% of drug products in the market [15]. The simple control of printing variables can offer interesting therapeutic advantages to printed 3D drug products. The precision in the personalization of dosage is undoubtedly one of the great benefits of the FDM 3D printing technology, as opportunely explored in the case of warfarin tablets. This narrow window API was printed in tailored doses safely administered to rats, eliminating the need to split and facilitating the progression and regression of doses, usually employed in treatments with this drug [16].

Another interesting approach was obtained printing domperidone disks with low infill that increased the drug time in stomach through flotation, decreasing the tablet intake [17]. Moreover, it is possible to easily associate several drugs in the same pharmaceutical unit, such as in the case of a “polypill” printed with intercalated layers of paracetamol and caffeine leading to a simultaneous release of both drugs [18]. FDM 3D printing could also produce immediate release tablets from distinct pharmaceutical grade

polymers [19] or by adding gaps to the tablet design, called “gaplets”, increasing the porosity of the tablets by printing configuration [20].

Moreover, 3D printing can be useful to create innovative geometries that can increase patient compliance. Indeed, tests performed *in vivo* revealed that patients were open to new geometries, such as donut (torus) [21]. Pediatric dosage forms imitating candy may improve children administration of oral forms and the extrusion and printing processes using polymers help to mask bitter active pharmaceutical ingredient flavor [22]. Besides the aesthetic aspect, the control of the tablet can be used to modulate the drug-released rate, which is dependent on surface area/ volume of the tablet [23].

Some works habe been dedicated to explore the 3D printing of capsules as well. A capsule combining two different polymer compartments produced a two-pulse release kinetic [24] and the dual release was studied for caffeine [25]. Hollow printed capsules containing complex compartments filled with liquid metformin, where the liquid formulation was not exposed to heating, lead to a controlled drug release by the capsule dissolution rate [26]. Printed capsules may also create different release rates of drug solutions by changing the shell thickness and the core volume [27], whereas for the printed cores, the infill and the polymeric matrix helped to achieve even a zero order release rate [28]. Zero order release was also reached in a three-part donut shape tablet composed of polymeric water insoluble outside layers and a soluble polymeric drug loaded center [29]. Figure 2 shows several different FDM printed tablets and capsules.

Other oral forms printed using FDM are oral films (4%) and even medicinal mouthgards (2%). Hot-melt extrusion and 3D printing processes together have improved aripiprazole oral films dissolution rate by amorphization of the active pharmaceutical ingredient and formation of a porous polymeric matrix [30]. FDM 3D printing also allowed the production of a new personalized drug delivery device, shaped as a mouthgard, containing clobetasol propionate to treat mouth inflammation [31].

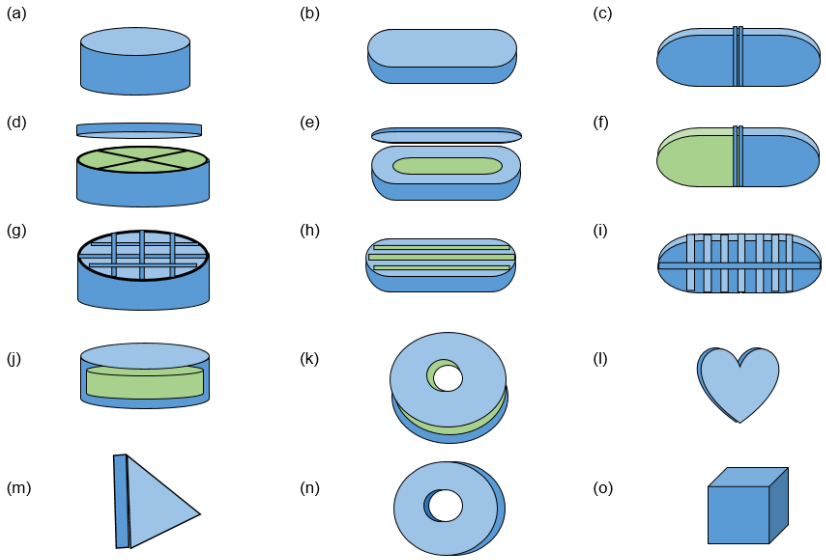


Figure 2. Different shapes of oral drug-delivery devices produced using fused deposition modeling 3D printing (blue = API 1, green = API 2). (a) [17], (b) [16], (c) [25], (d) [26], (e) [27], (f) [24], (g) [19], (h) [18], (i) [20], (j) [28], (k) [29], (l) [22], (m) [18], (n) [21], (o) [21].

Dermal adhesives for cutaneous drug delivery were also produced using the same technique. Printed polylactic acid microneedles devices have showed to be able to pierce porcine skin and deliver a model drug [32]. Vaginal rings and drug implants represented 2% and 7%, respectively, of the printed drug delivery devices. Printed progesterone vaginal rings in different shapes, “O”, “Y”, “M”, have distinct dissolution rates based on surface area/ volume and released the drug over a period of one week [33]. A polylactic acid sub cutaneous implant for prolonged release of disulfiram [34] and even ethylene vinyl acetate intrauterine devices loaded with indomethacin [35] were also printed using FDM.

Other complex delivery systems correspond to 6% of the researched papers, like “tablet-in-devices”, were developed to keep riboflavin tablet floating in stomach acid for a longer period, enhancing drug absorption and keeping a sustained release [36]. A “dual-compartmental dosage unit” combined two incompatible drugs used in tuberculosis treatment: rifampicin and isoniazid has been also developed. In such device the polylactic acid printed units separated the drug filaments and generated distinct dissolution patterns [37].

The 3D printing technology has proved, therefore, to be able to produce very complex anatomical shapes, with multiple active pharmaceutical ingredients and different release kinetics. But despite all research, this topic is not exhausted and, in the future, new pharmaceutical devices could be produced to deliver drugs to other specific body parts. Drug loaded contact lens to treat eye disorders, pharmaceutical polymeric nails to treat fungal infection and drug delivery had caps to treat baldness, are some obvious alternatives that have not yet been tested.

2.6 ADAPTATIONS OF A PHARMACEUTICAL FDM 3D PRINTER

FDM printing represent the most studied technique for drug delivery devices 3D printing in research today when compared to other 3D printing techniques such as selective laser sintering and powder bed. The equipment has an accessible cost, is easy to operate and has different versions available in several countries. MakerBot® (USA), Multirap M420® (Germany) and Prusa i3® (Czech Republic) are printer brands used in several studies and its process variables, such as temperature, speed and infill have been correlated with the pharmaceutical production variables [4,38].

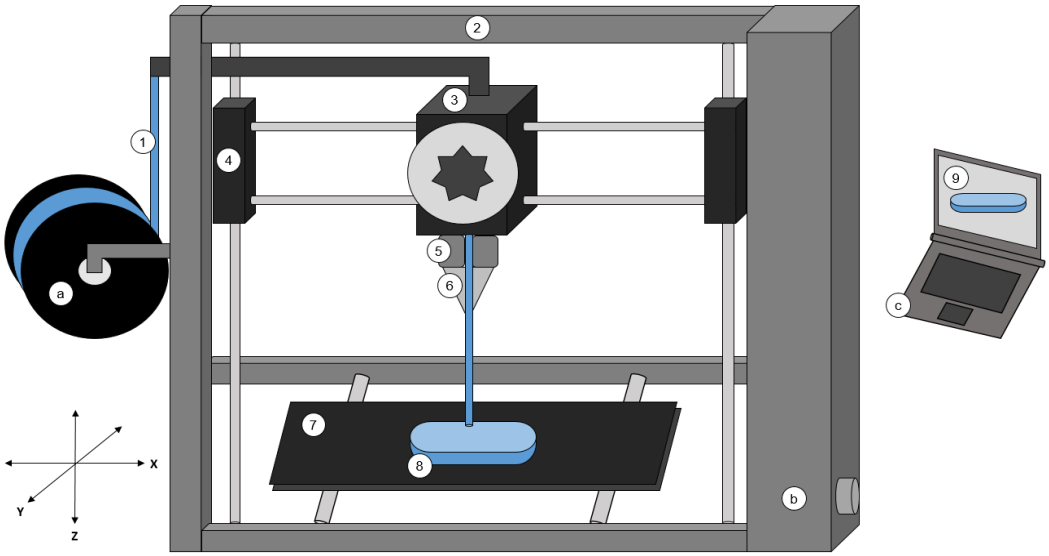


Figure 3. Schematic picture of a pharmaceutical fused deposition modeling 3D printer. (a) Spool, (1) Filament, (b) FDM 3D printer, (2) Printer enclosure, (3) Extruder head, (4) Motor, (5) Heater, (6) Nozzle, (7) Build Platform, (8) Drug delivery device, (c) Computer, (9) 3D design.

Despite this, no commercial model is available for pharmaceutical use. Moreover, as pointed out in recent studies, several adaptations in the commercial machines are needed to meet pharmaceutical production requirements [39]. Figure 3 shows the main FDM printer parts that could suffer adjustments.

The spool containing the extruded drug loaded filament is attached to the printer through a tube from where it reaches the equipment nozzle [40]. The filament coiled in the spool is not protected from particles or humidity during the printing process. This could generate contamination of the produced drug delivery devices by dust or cross contamination by other drug powders. To solve this inconvenient, a closed compartment could be connected to the printer covering the spool attachment, facilitating filament changes. The printer enclosure should also be sealed against contaminants, protecting the printed drug delivery device and eliminating the need of a laminar airflow to avoid particles contamination [25].

In order to meet the Good Manufacturing Practices, all the printer parts that have direct contact with the filament and the printed device (extruder head, nozzle and build platform) should be made of an inert material that is easy to clean, such as stainless steel, or other FDA approved materials. Also the mechanical parts of the FDM printer, such as the motors, need to be completely closed, preventing lubricant oil to spill over the product [25]. Another important point for pharmaceutical use concerns the need of a more precise control of the heater’s temperature. An overheating could lead to modifications of the polymer viscoelasticity compromising the drug control release, and eventually the stability of the drug product.

Another operational problem with regular FDM 3D printers is the lack of flexibility in the size of the nozzle, since commercial filaments have standard 1.75 mm diameter. However, for pharmaceutical use, a wide range of polymeric materials is extruded generating small diameter oscillations due their viscoelastic characteristics. It will be necessary to design nozzles that can adjust to these oscillations [41]. Furthermore, an optimized FDM printer with multiple nozzles could improve the printing time of a batch or even

produce devices with multiple APIs without the need to change filaments during process [18].

For drugs that require a liquid formulation, instead of stopping the process to fill the printed capsule with the liquid drug manually [42], an extra syringe dispenser could be added to automate the process [27].

The software used to control the printer should be compatible with the most common operating systems, so that any computer already available at pharmacies could operate the FDM printer, thus reducing equipment costs. The software interface need to be adapted for health prescriptioner's use, making it simpler to enter relevant information, such as dose, shape and quantity. The more complex information such as, nozzle and platform temperature, speed, layer height and infill would be supplied by the pharmacy technicians based on the filament manufacturer information. After a rapid training, the professional should be qualified to operate the machine. The 3D design of devices would be preferably pre-selected from a database, thus saving time when defining the device shape. At last, the system may connect with mobile devices making it possible for on-line prescriptions to arrive from different sites [43, 44].

2.7 DRUG DELIVERY DEVICE PRODUCTION PROCESS

FDM 3D printing of drugs has become a great hype in the last few years, with multiple research groups developing the technique for several different drug delivery devices, as pointes before. Despite this current movement and the commercially printing of Spritam®, the FDM technology was unsuccessful in reaching the pharmaceutical market until now [45].

In the light of previous works and considering the extrusion process steps already used by the pharmaceutical industry, this work proposes a partnership between pharmaceutical industries and compounding pharmacies in a complementary production chain to create a new pathway to market.

The production of drug-loaded filaments, consisting on three steps, would occur in a large scale in pharmaceutical industry sites: (1) Blending of APIs, polymers and other fillers, (2) Extrusion of drug loaded filaments via industrial hot-melt extruders and (3) Storage of filaments hermetically packed

in spools. The extruded filaments purchased by compounding pharmacies would serve as an intermediate pharmaceutical product in the FDM printing process divided in three steps: (1) Printer parameters setting and drug design by trained professionals according to prescription, (2) 3D printing of the required drug delivery device and (3) Storage, labeling and dispensing to patient. Quality control tests would be required at both sites. Figure 4 outlines the steps required for filament production in pharmaceutical industries and drug delivery device production in compounding pharmacies.

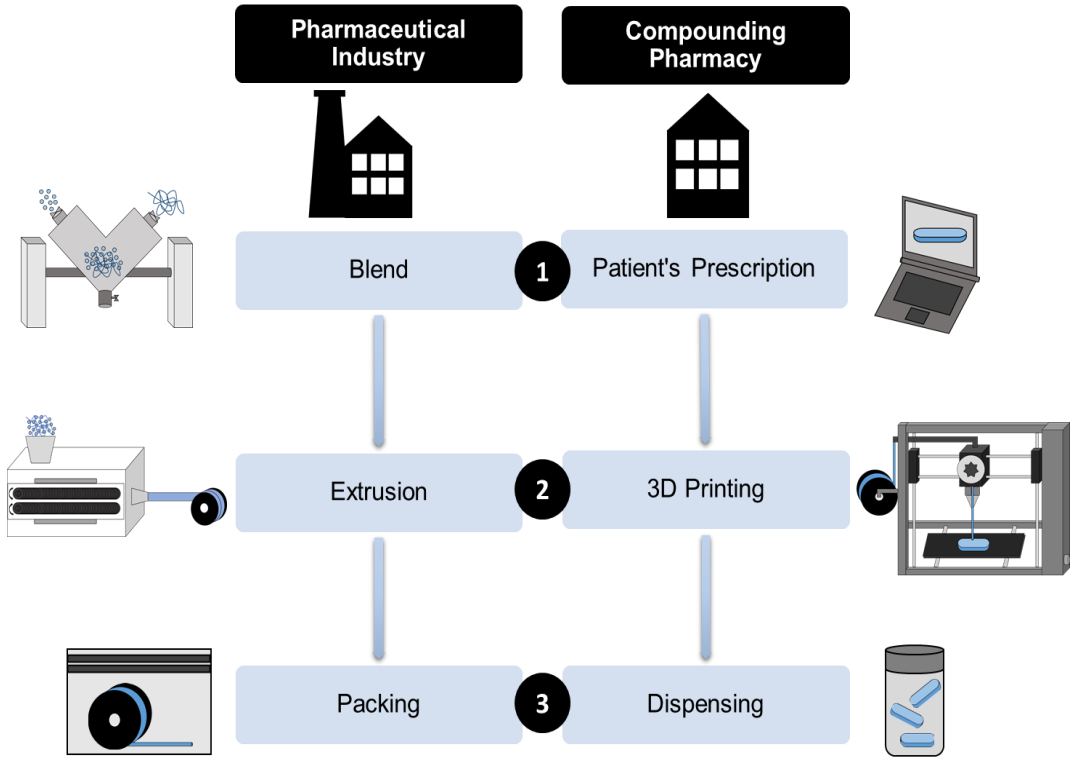


Figure 4. Schematic steps required for: filament production in pharmaceutical industries and drug delivery device production in compounding pharmacies.

2.7.1 FILAMENT PRODUCTION AT PHARMACEUTICAL INDUSTRY

Initially, the industry dedicated to produce the filaments should conduct the development for each product based on the selected drug and release kinetics chosen. At this stage, the formulation composition, as well as the extrusion process, will be defined following a quality-by-design planning [46]. Thermal and rheological studies should be performed to determine the compatibility between the components and their suitability for the HME

processing and for the 3D FDM printing. Then, stability studies should be conducted to find the shelf life of the product.

The filament diameter is crucial for the printing process, in face of an improper size the extruder may clog or lead to a lower feeding rate [47]. Some hygroscopic polymers can cause a diameter enlargement, compromising the filament passage through the printer mechanism [29]. In addition, the heating process could cause diameter deformities, which is why an external pulley with a cooling system should be attached to the extruder dye end in some cases [41].

HME is an already stablished industrial production process for drugs, but the nuances for printable filaments fabrication still need to be better studied. A routine filament production is extremely simple following just three major steps. First, the components of the batch are mixed, for example in an industrial V-blender. In the next step, a production area with multiple lines of industrial hot-melt extruders would be required; the equipment fed with the components mixture would produce the drug-loaded filaments desired. Finally, the third step consists on filament bulk packaging in smaller spools. This intermediate pharmaceutical product should be hermetically packed to prevent product deterioration until it reaches the local compounding pharmacies.

Routine quality control tests should include: organoleptic characteristics, dimensions, rheological properties, tensile strength, thermal behavior and drug content. In addition, the drug release should be performed normally using dissolution apparatus or Franz cells [48,49].

2.7.2 DRUG PRODUCT PRODUCTION AT COMPOUNDING PHARMACY

The current compounding pharmacies have the ideal conditions to produce 3D printed drug delivery devices. In fact, the usual layout of that site is already proper for the FDM pharmaceutical printer installation [15]. At the compounding site, the equipment could be set over already existing benches in the solid preparation room, requiring only a power source to operate. Additional printers could also be installed at cytostatic, hormone and antibiotic room if necessary that requires additional care, preventing cross

contamination [50]. The purchased hermetically packed filaments would be placed for use in storage room. No additional costs for room renovations would be necessary, making it simple for every pharmacy to add this technology in its facilities. Figure 5 shows the layout of a hypothetical compounding pharmacy with installed FDM 3D printers.

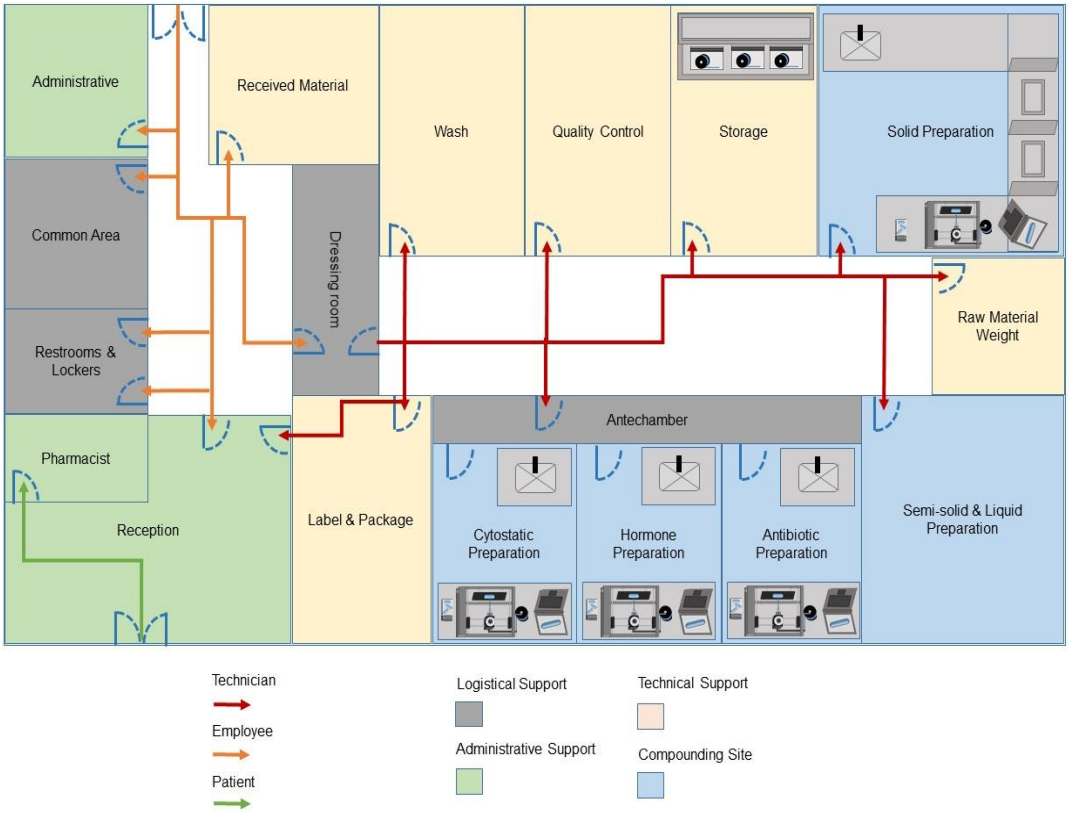


Figure 5. Compounding pharmacy layout containing 3D printing drug products.

The drug delivery device production process should depend on three major steps, all easily executed on compounding pharmacies. First, trained technicians with access to the compounding site would set the printer parameters, such as infill, velocity, resolution, temperature and others using the pharmaceutical printer software [51]. The information provided by the filament manufacturer and the prescriptioner health professional should serve as guidance. In addition, an adequate design (shape) for the drug delivery device need to be selected from the database [23]. It is important that the FDM printer is compatible with the filament manufacturer specifications, so that the intermediate product can be safely used, and validated to guarantee the process reproducibility [39].

After that, the second step should begin with the printer preparation and spool attachment. To avoid wastage and exposure of the entire spool to printing process, the needed amount of filament for the desired batch could be cut and transferred to a smaller spool. The rest of the filament should be hermetically restored using a vacuum device. The FDM adapted pharmaceutical printer with the modifications discussed before would produce the desired drug tailored for a specific patient. After printing, the product batch should be removed and the technician could proceed to step three. At this stage, the drug delivery device produced would be packed and labeled according to the current legislation and dispensed to the patient at the reception room [52]. Before using it again with a different filament, the printer must be cleaned using a validated method. Melocchi et al. suggested disassembling the printer and using specific solvents to release the attached polymers, such as acetone for PLA [53].

The quality control required for the finished drug product would be the same as those currently required for a common solid preparation in compounding pharmacies, which includes average weight and organoleptic characteristics. However, due to the high automation of the 3D printing process and the small number of production steps, there is potentially a lower risk of human error, and consequently a noticeable gain in the safety of printed drug products. Recent studies have shown that there are innumerable cases of intoxication related to the use of medicines produced in compounding pharmacies, resulting, for example, from errors in weighing [10]. This scenario may be part of the past after the introduction of the 3D printing of drug products because of the printer's high precision. Extra tests to determine the drug delivery device characteristics, such as hardness, friability, infrared spectroscopy and drug release could be applied to pilot batches or by sampling in accordance with each country regulatory demand [24, 25, 54].

2.8 PATENT AND REGULATORY LIMITATIONS

In the last years, 3D printing has gained the world's attention especially in the health area with the production of several medical devices. Those products such as, cranial implants, artificial knees and spine prosthesis,

specially made for each patient, were marketed under current FDA regulations following their similarities with already existing medical devices [58].

More recently, in 2015, the American Food and Drugs Administration (FDA) released the first 3D printed drug product, Spritam® (levetiracetam) [2]. This great technological step led to the increase of research using 3D printing technology to produce drug delivery devices, but despite the fast development in this field, there are still legal and regulatory issues to be addressed [55].

Many 3D printing technologies have lost their patents in the last decade, which was decisive to make these machines more accessible to the public and the pharmaceutical field [43]. The patentability process, regarding intellectual property rights, for the production of 3D printed drugs can only be granted to innovative process or products that may be industrially produced. In the past years, few institutions have claimed patent over 3D printed drugs, one of them is Aprecia Pharmaceuticals, the Spritam® manufacturer [56]. Processes to develop the filaments, the 3D printing production and products like the FDM filaments containing active pharmaceutical ingredients, the modified pharmaceutical 3D printer, the printed drug delivery device and the computer program used to control the machine could be patentable. The patent owner has exclusivity over the product or process over the years until the concession expires, in the meantime, other manufactures may not produce, use, or sell without the owner authorization [56]. The extemporaneous formulations produced at compounding pharmacies prescribed by professionals to a specific patient are exempted and do not configure patent violation. In that case, there would not be an industrial production; on the contrary, the drug would be prepared to a particular patient to treat an individual condition, so the pharmacist would not commit an illegal act. That exemption may not apply to all countries and need to be carefully discussed with the legal responsible institutions [56].

The 3D printed medical products also face regulatory limitations regarding the legal pathways available to introduce these products in the market. Most of the medical devices produced using that technology fell into the existing FDA regulations for devices that are similar to already registered existing ones, since the manufacturing process suffers alteration, but the raw

material, indication of use, Good Manufacturing Practices (GMP) and safety remains [57]. The pharmacoprinting process seems more complex and until now the FDA approved only one drug product produced using that technology. In 2014 the FDA hosted a workshop and stated that despite the manufacturing method, industrial drug production should follow the already stablished regulations, since the regularization of each new technology is not viable [58]. The “Technical Considerations for Additive Manufactured Devices-Guidance for Industry and Food and Drug Administration Staff” released by the FDA in 2017 is mainly focused in medical device products, and give some orientation on pre and post process, especially quality control [59].

Spritam® is an oral fast disintegrating tablet approved following the existing legislation for a large-scale industrial production. The 3D printing process only improved the disintegrating process, given that the drug contained a known active pharmaceutical ingredient (levetiracetam), in a permitted dosage (up to 1000 mg) to treat a stablished condition (epilepsy) [12,60]. 3D printing in an industrial scale may present benefits, as design of complex geometries, but when compared to other technologies, such as tableting, is not as fast. Another drug mass production technology is no novelty, but using 3D printing at hospitals and compounding pharmacies to improve patient specific dosage forms is a real revolution. Tailored formulations, “polypills” and orphan medications produced in small batches at these sites could reach those who the Pharmaceutical Industry does not contemplate [61].

This scenario is not a reality yet and it is not clear if the existing GMPs for compounding pharmacies would be enough to allow the production of 3D printed drug delivery devices at these sites. Specific pharmaceutical 3D printers and a “pharmaceutical ink” composed of pharmaceutical grade compounds are imperative. The legal requirements may change according to the country, but the basic GMP notion that every process need to allow safety and efficacy of the final product remains the same all over the world [45]. Since it would be impossible to register each customized formulation at the FDA, the professional prescribers and the pharmacist would take responsibility for the safety of the drugs. In that case, the prescribers and pharmacists should first receive proper training.

2.9 CONCLUSION

FDM 3D printing is a versatile technology widely studied for the production of multiple drug delivery devices. Groups all over the world are currently working to decipher the nuances of the production process, and despite the great progress made so far in the research laboratories, a palpable planning to bring these products to people's life is necessary. The potential of 3D printing for development of personalized drug products is undeniable; however, machine adaptations are fundamental for a proper pharmaceutical use. In addition, a viable production process need the co-participation of the pharmaceutical industry, to extrude the filaments in a large-scale, and the compounding pharmacy, to print drugs according to patient's specific prescriptions. Finally, regulatory and patent agencies should work together with companies to stablish the better track to market.

2.10 FUTURE PERSPECTIVE

FDM 3D printing aims to revolutionize production process of medicines bringing it closer to the patient and attending individual needs. With the amount of research developed in the field increasing fast, especially in the last couple of years, it is expected that 3D printing of personalized drug products will gain space quickly. On the other hand, the pharmaceutical industry is very powerful and competing against the traditional mass production model may not be feasible today. Therefore, the best chance to incorporate this new technology is to join forces. The co-participation of both pharmaceutical industry and compounding pharmacy is the best way to make this a reality. In the next few years, after regulatory bases and quality control are better stablished, affordable pharmaceutical FDM 3D printers and extruded filaments may be available for purchase by compounding pharmacies. When this happens, trained health professional must be prepared to operate the machines and to prescribe the printed drug products. The operating knowledge and adapted equipment available at compounding pharmacies may also be explored for nutraceutical supplement production, as a new market trend.

2.11 FINANCIAL DISCLOSURE

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2.12 REFERENCES

1. Norman J, Madurawe RD, Moore CM, Khan MA, Khairuzzaman A. A new chapter in pharmaceutical manufacturing: 3D-printed drug products. *Adv. Drug. Deliv. Rev.* 108, 39–50 (2017).

2. Alhnan MA, Okwuosa TC, Sadia M, Wan KW, Ahmed W, Arafat B. Emergence of 3D printed dosage forms: opportunities and challenges. *Pharm. Res.* 33(8), 1817–1832 (2016).

3. Ventola CL. Medical Applications for 3D Printing: Current and Projected Uses. *P T*. 39(10), 704-11 (2014).

4. Cunha-Filho M, Araújo MRP, Gelfuso GM, Gratieri T. FDM 3D printing of modified drug-delivery systems using hot melt extrusion: a new approach for individualized therapy. *Ther Deliv.* 8(11), 957-966 (2017).

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

6. Prasad LK, Smyth H. 3D Printing technologies for drug delivery: a review. Drug. *Dev. Ind. Pharm.* 42(7), 1019–1031 (2016).

7. Moulton SE, Wallace GG. 3-dimensional (3D) fabricated polymer based drug-delivery systems. *J. Control. Rel.* 193, 27–34 (2014).

8. Hsiao WK, Lorber B, Reitsamer H, Khinast J. 3D printing of oral drugs: a new reality or hype? *Expert Opin Drug Deliv.* 15(1):1-4 (2018).

9. Badhani DC, Raina RS. Novel Concept of Drug Preparation by 3D Printing Technology. *J Rational Pharmacother Res.* 3(1) (2017).

10. James KL, Barlow D, McArtney R, Hiom S, Roberts D, Whittlesea C. Incidence, type and causes of dispensing errors: a review of the literature. *Int J Pharm Pract.* 17(1), 9-30 (2009).

11. Palo M, Holländer J, Suominen J, Yliruusi J, Sandler N. 3D printed drug delivery devices: perspectives and technical challenges. *Expert Rev Med Devices.* 14(9), 685-696 (2017).

12. Lim SH, Kathuria H, Tan JJY, Kang L. 3D printed drug delivery and testing systems - a passing fad or the future? *Adv Drug Deliv Rev*. pii: S0169-409X(18), 30109-1 (2018).

13. Jamróz W, Szafraniec J, Kurek M, Jachowicz R. 3D Printing in Pharmaceutical and Medical Applications - Recent Achievements and Challenges. *Pharm Res*. 35(9), 176 (2018).

14. Pravin S, Sudhir A. Integration of 3D printing with dosage forms: A new perspective for modern healthcare. *Biomed Pharmacother.* 107, 146-154 (2018).

15. Sadia M, Sósnicka A, Arafat B et al. Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets. *Int. J. Pharm.* 513(1–2), 659–668 (2016).

16. Arafat B, Qinna N, Cieszynska M, Forbes RT, Alhnan MA. Tailored on demand anti-coagulant dosing: An in vitro and in vivo evaluation of 3D printed

purpose-designed oral dosage forms. *Eur. J. Pharm. Biopharm.* 128, 282-289 (2018).

17. Chai X, Chai H, Wang X *et al*. Fused Deposition Modeling (FDM) 3D Printed Tablets for Intragastric Floating Delivery of Domperidone. *Sci. Rep.* 7(1), 2829 (2017).

18. Goyanes A, Wang J, Buanz A et al. 3D printing of medicines: engineering novel oral devices with unique design and drug release characteristics. *Mol. Pharm.* 12(11), 4077–4084 (2015).

19. Kempin W, Domsta V, Grathoff G *et al*. Immediate Release 3D-Printed Tablets Produced Via Fused Deposition Modeling of a Thermo-Sensitive Drug. *Pharm. Res.* 35(6), 124 (2018).

20. Arafat B, Wojsz M, Isreb A *et al*. Tablet fragmentation without a disintegrant: A novel design approach for accelerating disintegration and drug release from 3D printed cellulosic tablets. *Eur. J. Pharm. Sci.* 118, 191-199 (2018).

21. Goyanes A, Scarpa M, Kamlow M, Gaisford S, Basit A, Orlu M. Patient acceptability of 3D printed medicines. *Int. J. Pharm.* 530(1-2), 71-78 (2017).

22. Scoutaris N, Ross SA, Douroumis D. 3D Printed "Starmix" Drug Loaded Dosage Forms for Paediatric Applications. *Pharm. Res.* 35(2), 34 (2018).

23. Goyanes A, Robles Martinez P, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. *Int. J. Pharm.* 494(2), 657–663 (2015).

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

25. Melocchi A, Parietti F, Maccagnan S *et al*. Industrial Development of a 3D-Printed Nutraceutical Delivery Platform in the Form of a Multicompartment HPC Capsule. *AAPS. PharmSciTech.* (2018).

26. Smith DM, Kapoor Y, Klinzing GR, Procopio AT. Pharmaceutical 3D printing: Design and qualification of a single step print and fill capsule. *Int. J. Pharm.* 544(1), 21-30 (2018).

27. Okwuosa TC, Soares C, Gollwitzer V, Habashy R, Timmins P, Alhnan MA. On demand manufacturing of patient-specific liquid capsules via co-ordinated 3D printing and liquid dispensing. *Eur. J. Pharm. Sci.*118, 134-143 (2018).

28. Zhang J, Yang W, Vo AQ *et al.* Hydroxypropyl methylcellulose-based controlled release dosage by melt extrusion and 3D printing: Structure and drug release correlation. *Carbohydr. Polym.* 177, 49-57 (2017).

29. Gioumouxouzis CI, Katsamenis OL, Bouropoulos N, Fatouros DG. 3D printed oral solid dosage forms containing hydrochlorothiazide for controlled drug delivery. *J. Drug. Deliv. Sci. Technol.*164-171 (2017).

30. Jamróz W, Kurek M, Łyszczarz E *et al*. 3D printed orodispersible films with Aripiprazole. *Int. J. Pharm.* 533(2), 413-420 (2017).

31. Liang K, Carmone S, Brambilla D, Leroux JC. 3D printing of a wearable personalized oral delivery device: A first-in-human study. *Sci. Adv.* 4(5), eaat2544 (2018).

32. Luzuriaga MA, Berry DR, Reagan JC, Smaldone RA, Gassensmith JJ. Biodegradable 3D printed polymer microneedles for transdermal drug delivery. *Lab. Chip.* 18(8), 1223-1230 (2018).

33. Fu J, Yu X, Jin Y. 3D printing of vaginal rings with personalized shapes for controlled release of progesterone. *Int. J. Pharm.* 539(1-2), 75-82 (2018).

34. Davies MJ, Costley E, Ren J, Gibbons P, Kondor A, Naderi M. On drug base incompatibilities during extrudate manufacture and fused deposition 3D printing. *J. 3D Print. Med.* 1(1), 31–47 (2017).

35. Genina N, Holl¨ander J, Jukarainen H, M¨akil¨a E, Salonen J, Sandler N. Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices. *Eur. J. Pharm. Sci.* 90, 53–63 (2016).

36. Fu J, Yin H, Yu X *et al*. Combination of 3D printing technologies and compressed tablets for preparation of riboflavin floating tablet-in-device (TiD) systems. *Int. J. Pharm.* 549(1-2), 370-379 (2018).

37. Genina N, Boetker JP, Colombo S, Harmankaya N, Rantanen J, Bohr A. Anti-tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage forms: From drug product design to in vivo testing. *J. Control. Release.* 268, 40-48 (2017).

38. Goyanes A, Fernández-Ferreiro A, Majeed A *et al*. PET/CT imaging of 3D printed devices in the gastrointestinal tract of rodents. *Int. J. Pharm.* 536(1), 158-164 (2018).

39. Feuerbach T, Kock S, Thommes M. Characterisation of fused deposition modeling 3D printers for pharmaceutical and medical applications. *Pharm. Dev. Technol.* 1-10 (2018).

40. Alhijjaj M, Belton P, Qi S. An investigation into the use of polymer blends to improve the printability of and regulate drug release from pharmaceutical solid dispersions prepared via fused deposition modeling (FDM) 3D printing. *Eur. J. Pharm. Biopharm.* 108, 111–125 (2016).

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

42. Markl D, Zeitler JA, Rasch C *et al*. Analysis of 3D Prints by X-ray Computed Microtomography and Terahertz Pulsed Imaging. *Pharm. Res.* 34(5), 1037-1052 (2017).

43. Awad A, Trenfield SJ, Gaisford S, Basit AW. 3D printed medicines: A new branch of digital healthcare. *Int J Pharm.* 548(1), 586-596 (2018).

44. Skowyra J, Pietrzak K, Alhnan MA. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. *Eur. J. Pharm. Sci.* 68, 11–17 (2015).

45. Trivedi M, Jee J, Silva S *et al*. Additive manufacturing of pharmaceuticals for precision medicine applications: A review of the promises and perils in implementation. *Additive Manufacturing*. 23, 319-328 (2018).

46. Do Carmo ACM, Cunha-Filho M, Gelfuso GM, Gratieri T. Evolution of quality on pharmaceutical design: regulatory requirement?. *Accreditation and Quality Assurance.* 22(4), 199-205, (2017).

47. Korte C, Quodbach J. Formulation development and process analysis of drug-loaded filaments manufactured via hot-melt extrusion for 3D-printing of medicines. *Pharm. Dev. Technol.* 1-11 (2018).

48. Verstraete G, Samaro A, Grymonpré W *et al*. 3D printing of high drug loaded dosage forms using thermoplastic polyurethanes. *Int. J. Pharm.* 536(1), 318-325 (2018).

49. Sadia M, Arafat B, Ahmed W, Forbes RT, Alhnan MA. Channelled tablets: An innovative approach to accelerating drug release from 3D printed tablets. *J. Control. Release.* 269, 355-363 (2018).

50. Weisman JA, Nicholson JC, Tappa K, Jammalamadaka U, Wilson CG, Mills DK. Antibiotic and chemotherapeutic enhanced three-dimensional printer

filaments and constructs for biomedical applications. *Int J Nanomedicine*. 10, 357-70 (2015).

51. Pietrzak K, Isreb A, Alhnan MA. A flexible-dose dispenser for immediate and extended release 3D printed tablets. *Eur. J. Pharm. Biopharm.* 96, 380–387 (2015).

52. Goyanes A, Kobayashi M, Mart´ınez-Pacheco R, Gaisford S, Basit AW. Fused-filament 3D printing of drug products: microstructure analysis and drug release characteristics of PVA-based caplets. *Int. J. Pharm.* 514(1), 290–295 (2016).

53. Melocchi A, Parietti F, Maroni A, Foppoli A, Gazzaniga A, Zema L. Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling. *Int. J. Pharm.* 509(1–2), 255–263 (2016).

54. Okwuosa TC, Stefaniak D, Arafat B, Isreb A, Wan KW, Alhnan MA. A lower temperature FDM 3D printing for the manufacture of patient-specific immediate release tablets. *Pharm. Res.* 33(11), 2704–2712 (2016).

55. Jose PA, Christoper PGV. 3D printing of pharmaceuticals – a potential technology in developing personalized medicine. *Asian Journal of Pharmaceutical and Development.* 6(3), 46-54 (2018).

56. Stones JA, Jewell CM. 3D printing of pharmaceuticals: patent and regulatory challenges. *Pharm Pat Anal.* 6(4), 145-149 (2017).

57. Liaw CY, Guvendiren M. Current and emerging applications of 3D printing in medicine. *Biofabrication.* 9(2), 024102 (2017).

58. Di Prima M, Coburn J, Hwang D, Kelly J, Khairuzzaman A, Ricles L. Additively manufactured medical products - the FDA perspective. *3D Print Med*. 2. pii: 1 (2016).

59. Economidou SN, Lamprou DA, Douroumis D. 3D printing applications for transdermal drug delivery. *Int J Pharm.* 544(2), 415-424 (2018).

60. Zema L, Melocchi A, Maroni A, Gazzaniga A. Three-Dimensional Printing of Medicinal Products and the Challenge of Personalized Therapy. *J Pharm Sci*. 106(7), 1697-1705 (2017).

61. Awad A, Trenfield SJ, Goyanes A, Gaisford S, Basit AW. Reshaping drug development using 3D printing. *Drug Discov Today*. 23(8):1547-1555 (2018).