Sérgio Cavalheiro Filho

3D printing as a novel method for pharmaceutical products design & formulation

Monografia realizada no âmbito da unidade Estágio Curricular do Mestrado Integrado em Ciências Farmacêuticas, orientada pela Professora Doutora Eliana B. Souto e apresentada à Faculdade de Farmácia da Universidade de Coimbra

Setembro de 2016

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UNIVERSIDADE DE COIMBRA

Monografia realizada no âmbito do Mestrado Integrado em Ciências Farmacêuticas da Faculdade de Farmácia da Universidade de Coimbra

Coimbra, 16 de setembro de 2016

O tutor da monografia,

(Professora Doutora Eliana B. Souto)

O aluno,

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(Sérgio Cavalheiro Filho)

Aos meus pais, por toda a compreensão, ajuda e paciência.

Por abdicarem de tanto para que nunca me faltasse nada. Por todos os dias se derramarem em carinho, amor e dedicação. Por fazerem de mim o que sou hoje.

Ao meu irmão, meu companheiro em *multiplayer*, pela sua paciência, cumplicidade e amizade.

São vocês o meu maior orgulho e inspiração.

Aos meus amigos, que fizeram de Coimbra a minha segunda casa.

Que cresceram comigo deixando parte de si gravada em mim. Que me ensinaram tanto em tão pouco tempo. Que me moldaram e contruíram.

Passei convosco momentos que recordarei sempre como alguns dos melhores da minha vida. Foi uma jornada hilariante, do início ao fim. Nada teria sido o mesmo sem vocês, e não trocava a vossa amizade por nada.

À minha orientadora, a Professora Doutora Eliana B. Souto, por toda a disponibilidade demonstrada e por me acompanhar e apoiar neste último ano de mestrado.

A todos vós, muito obrigado.

"O que cada um de nós deve fazer em primeiro lugar, pois não temos outro remédio, é respeitar as nossas próprias convicções, não calar, seja onde for, seja como for, conscientes de que isso não muda nada, mas que ao fazê-lo, pelo menos temos a certeza de que não estamos a mudar."

- José Saramago

ABBREVIATIONS

3D – Three Dimensional

API – Active Pharmaceutical Ingredient

CLIP – Continuous Liquid Interface Production

FDA – Food and Drug Administration

FFF – Fused Filament Fabrication

DDCP – Drug-Device Combination Product

HME – Hot Melt Extrusion

HPMC – Hydroxypropyl Methylcellulose

MD – Medical Device

PAM – Pressure-Assisted Microsyringes

PB – Powder-Based

SLA - Stereolithography Apparatus

SLS – Selective Layer Sintering

SODF – Solid Oral Dosage Form

USA – United States of America

RESUMO

As tecnologias de impressão tridimensional (3D) são um tipo de produção com uso já estabelecido em várias áreas, como a indústria automóvel e aeroespacial. No que diz respeito à indústria farmacêutica, esta tecnologia tem vindo a demonstrar o seu valor devido à possibilidade que traz no que diz respeito à produção de produtos farmacêuticos personalizados, nomeadamente dispositivos médicos como é o caso dos implantes. No entanto, com a aprovação em 2015 do primeiro fármaco produzido por impressão 3D, surge uma nova perspetiva sobre esta tecnologia: a sua utilização para a produção de formas orais solidas com perfis de libertação complexos e com a possibilidade de doseamento individual. Ainda assim, existem limitações tecnológicas e questões regulamentares que devem ser resolvidas para fazer esta tecnologia avançar verdadeiramente na área da saúde e do medicamento, onde ainda pode contribuir com muito mais para uma prestação de cuidados, cada vez mais personalizada e centrada no doente.

ABSTRACT

Three-dimensional (3D) printing technologies are a manufacturing method with widespread usage amongst various areas such as the automotive and automobile industry. With regards to the pharmaceutical industry, this technology has been proving its value due to the possibility of printing tailored pharmaceutical products, namely personalized medical devices, such as implants. However, with the approval of the first 3D-printed drug-product in 2015, a new perspective over this technology arises: 3D-printing solid oral dosage forms exhibiting complex drug release profiles and allowing for individual dosing. Still, technological hurdles and regulatory issues must be overcome before this technology can truly find its place in the healthcare sector, where it can certainly contribute to a personalized and patient-centered healthcare system.

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1. INTRODUCTION

Three Dimensional (3D) Printing is an umbrella term for a broad range of manufacturing techniques designed to produce three dimensional objects using several different materials. Regardless of their differences, they all function in a similar way – they all produce objects in a layer-by-layer fashion under digital control [1]. In practical terms, this means users can produce practically anything that can be designed using Computer-Aided Design (CAD) software in a digital platform. The facility in changing each object's design, even during the same manufacturing run, allied to the simplicity, low cost and reduced size of the equipment used, allow the design of personalized prosthetics and implants, but also, more recently, Solid Oral Dosage Forms (SODF) at the end of the supply chain [2]. This approach has opened the door to a new era in personalized medicine, which has been gaining more and more relevance in the last few years due to recent developments in molecular biology and gene-profiling. Another promising concept is 3D bioprinting of tissues and organs, using the patient's own stem cells. However, bioprinting is out of the scope of this review.

These innovative production methods have a wide range of applications and extensive usage in a few specific areas, such as the automotive industry [3], but their applications in the pharmaceutical industry are still limited and in their early stages of development. In spite of the extensive research being done in this area and all the experimental drug delivery systems designed and described in numerous papers over the past few years [4-7], there is still some difficulty in transposing this to the pharmaceutical market and gaining market access. Until Food and Drugs Administration's (FDA) approval of Spritam® (levetiracetam) on August 2015 [8], there were no SODFs on the market manufactured by 3D printing. Due to the methods' versatility, an array of technologies has been developed for the production of 3D objects, each with their own specifications. Being a matchless process in the way each layer is constructed individually, SODFs produced using these printing systems demonstrate distinct pharmacokinetic proprieties, owing to their ability to create products with increased complexity. In this review, a comprehensive analysis of the most extensively used methods of 3D Printing will be carried out, giving special emphasis on those used in the pharmaceutical field. 3D printed SODFs and Medical Devices (MD) being developed or already being marketed will be discussed later, alongside with what these innovative production methods can bring to the table in the healthcare sector. Following that, a few considerations on the limitations and challenges of this technology will be made, focusing on the future perspectives for 3D Printing.

2. 3D PRINTING TECHNOLOGIES

3D printing is a form of additive manufacturing, which means it creates objects from scratch instead of molding them out of a solid block of starting-material. Most authors use both these terms interchangeably and consider them synonyms [1, 9, 10], but there is still some debate over what truly distinguishes 3D printing from additive manufacturing and even from rapid prototyping [11]. The American Society of Mechanical Engineers is adopting the umbrella term "Additive Manufacturing" for all these technologies, thus considering them equal in their fundament [1]. In this review though, the term "3D printing" will be employed preferentially, due to its widespread usage.

The term 3D Printing was coined by the Massachusetts Institute of Technology (MIT) in the early '90s, when it filled its patent for a powder-based technology used for the production of 3D objects [12]. However, other additive manufacturing techniques were already being developed at that time, and even patented, such as a laser based system, which was designed and patented in 1986 by Charles Hull [13]. Even though Hull did not employ the term "3D Printing", he is credited with the development of the ".stl" file format, which comprises all the coordinates of triangles that make up the surface of the project designed using a CAD software, and can then be uploaded to the SLA for production [14]. Since then, 3D printing has evolved significantly, revolutionizing production methods in many areas, and showing promising developments in many others, such as the pharmaceutical industry.

2.1 LASER-BASED PRINTING SYSTEMS

Being the first of these technologies to be patented [15], Hull's Stereolithography Apparatus (SLA) is one of the most widely used and reviewed 3D printing techniques, useful in many areas. SLA 3D printing relies on radiation to trigger the polymerization of photo-sensitive materials and thus producing 3D objects [14]. Curing of these polymers is usually done using a digitally-controlled UV-light emitter, which scans the surface of a photopolymerizable liquid polymer plastic resin, creating a layer of solid resin which is then lowered to a depth equivalent to the thickness of the layer previously formed [2]. Because UV-light penetrates further than each layer's thickness, when the following layer is being cured, the surface of the previously formed layer is being simultaneously overcured, fusing both layers. This process is repeated as many times as needed to achieve the intended design. Figure 1 shows an illustration of a SLA 3D printing process, in a simplified manner. Due to the nature of this process and the materials used, SLA 3D printing produces glassy and brittle materials with high level of accuracy

and resolution. On the other hand, resins available to be employed in this production method are very limited [14], and are often carcinogenic, hindering their approval for the production of SODFs. Besides, support structures attached to the elevator platform need to be printed along with the 3D object to avoid its deflection, which means more resin needs to be used. This technology has been used for the production of implantable devices [16] and hydrogels [17], but one of its most promising capabilities lies in the production of micro-structures such as micro-needles, which seems to be much more difficult when using other 3D printing methods. This will be discussed later in this review.

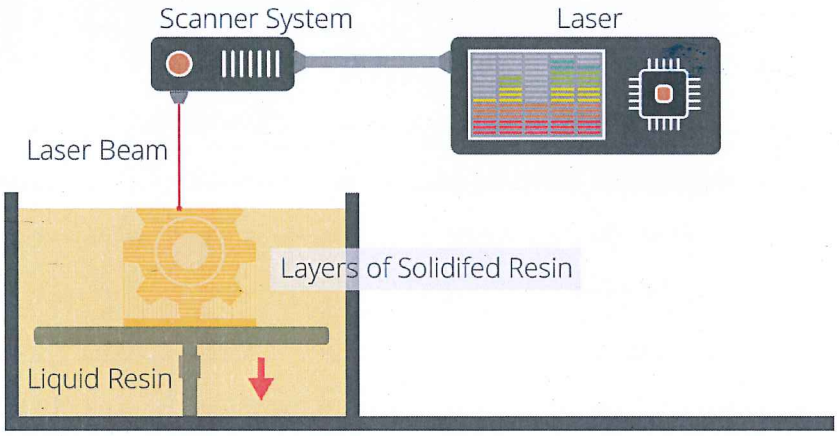

Fig. 1 –Schematic of a Stereolithography Apparatus (SLA) 3D printing process *(Adapted from www.3dprintingindustry.com)* [18].

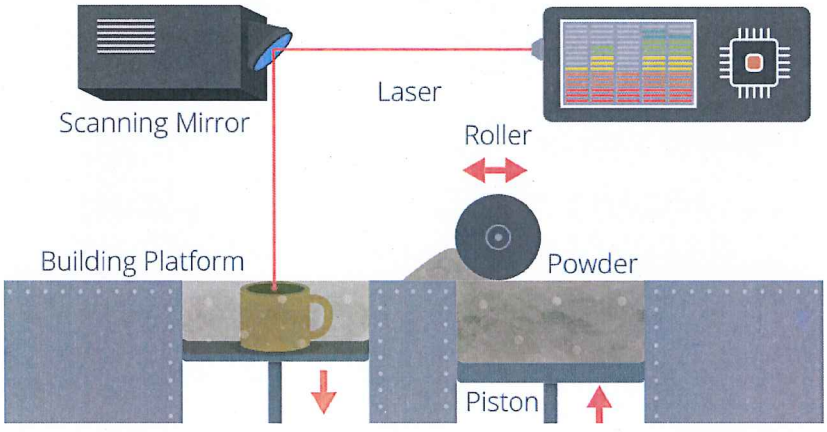

Fig. 2 –Schematic of a selective layer sintering (SLS) 3D printing process *(Adapted from www.3dprintingindustry.com)* [18].

Other laser-based printing systems worth mentioning include Continuous Liquid Interface Production (CLIP) and Selective Layer Sintering (SLS). CLIP is a novel variation of the SLA 3D printing technique with a considerably increased printing speed, higher resolution and without the need to make micrometer-level changes in fluid height during processing. This is because polymerization in this process is done in a continuous manner, meaning that it does not produce objects in a layer-by-layer fashion. This is only possible due to the existence of an oxygen-containing "dead-zone", where polymerization does not occur, so the laser can emit radiation continuously into the liquid polymer as the printed object is pulled out of the pool [19]. SLS 3D printing, on the other hand, is similar to SLA 3D printing but instead of a liquid polymer, a powder bed is used as starting material and a laser is used to liquefy and fuse these powders together (Fig.2). This technology however is mostly used for the production of 3D metal structures, and no pharmaceutical applications other than the production of MDs are known, due to the high energy input from the laser [9].

2.2. INKJET-BASED PRINTING SYSTEMS

3D printing techniques can be considered printing-based inkjet systems if they operate by placing liquid droplets onto a substrate in a well-organized manner. If these droplets are the actual building material, this system is called Drop-on-Drop (DoD) deposition. On the other hand, if the droplets are a binder solution/suspension/polymer or other liquid used to bind the substrate together, then this system is called Drop-on-Powder (DoP) deposition [20].

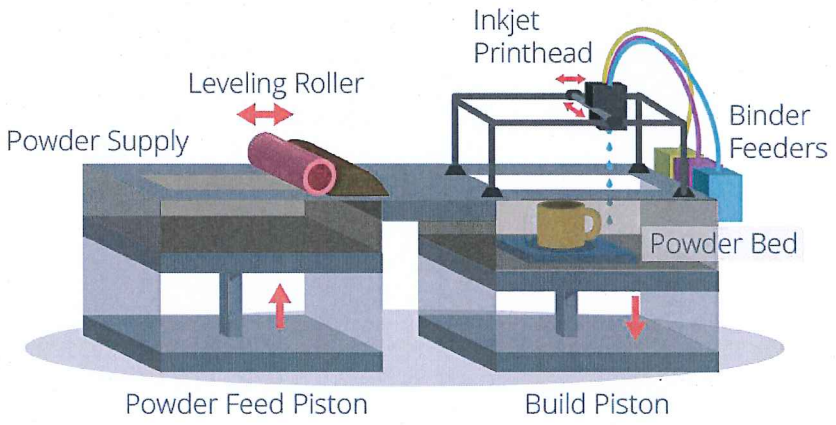

Fig. 3 – Drop-on-powder (DoP) inkjet 3D printing process, using a powder bed *(Adapted from www.3dprintingindustry.com)* [18].

DoP is usually done either on a powder bed, covered with unbound powder, or with a powder jetting mechanism, that serves as the powder supply. In figure 3, a DoP 3D printing process using a powder bed is shown. As the inkjet printhead sprays the binder formulation onto the powder bed, moving in the longitudinal and transversal axis, the platform onto which the object is being built moves down, giving space for a new layer to be formed. The leveling roller then replenishes the powder bed with powder and this cycle is repeated until the object is fully-formed. The active pharmaceutical ingredients (API), may be formulated into the liquid used as binder, or it may be formulated into the powder that makes up the powder bed. The interactions that occur between binder solutions and dry powders in 3D printing processes are the same that occur in traditional methods for wetting granulation, and are well described in the literature [21]. This production method was developed by the MIT, and it was patented in 1993 [12], the first time the term 3D Printing was employed.

DoP is considered by many as the primary 3D printing technology used for pharmaceutical production [1], and is the technology behind the development of the first FDA approved 3D-printed SODF, Aprecia's Spritam® [8], which will be discussed later in this review. This technology's main advantage lies on the fact that many of the materials used (powders and binder solutions) are already used for the production of SODF, making it easier for formulators to transition from current production methods to 3D printing. Also, if using a piezoelectric printer head (whose mechanism of printing relies on the deformation of a crystal that creates a pressure pulse to shoot out the ink [22]), there is no need for submitting any of the materials used to high temperatures. This reduces the chances of API/excipients degradation to a minimum, unless additional post-printing processes are carried out (i.e. drying or sintering), usually carried out in order remove any residual solvents or to improve mechanical resistance [9].

As a result of the production method itself, objects produced using DoP present high porosity and high friability, physical features which correlate directly with these SODF's dissolution profiles [23]. Nevertheless, these properties can be controlled to some extent during production. For instance, optimization of each layer's thickness will determine how compact the printed object will turn out. Also the flow rate of the binder ink and the printer's head speed in the fast-axis, both interfere with the amount of binder that is deposited per unit line length [2]. So, a faster deposition speed allied to a slower flow rate will lead to the production of objects with smaller amounts of binder, thus presenting higher friability. This is only true, however to a certain point, as excessive amounts of binder will produce uneven oozing structures.

DoD is in many ways similar to DoP. The main difference is that a powder bed with solid material is not used here. Instead, the starting materials being printed are the same that compose the building structure. A formulation containing both the API and the excipients is contained in the in liquid or molten state, and they can be polymers, waxes, curable resins, solutions, suspensions or other multi-component formulations [1]. After being jetted through the printhead, the droplet is exposed to some form of thermal stimulus that causes the solvent to evaporate, consequently solidifying and enabling it to serve as support for the next droplet to be jetted [2]. In figure 4, a DoD 3D printing process using a powder bed is shown.

This production method has had a more challenging implementation than DoP, as it's much more critical in this method to control droplet size, by optimizing the rheology of the liquid, as well as all the droplet flight path and all ejection conditions [22]. On the other hand, objects produced using this method are of a much higher-resolution than those produced by DoP processes, because droplets in DoD are about 100 μm in diameter (creating layers even thinner than this due to surface wetting, solvent evaporation or shrinkage) [1].

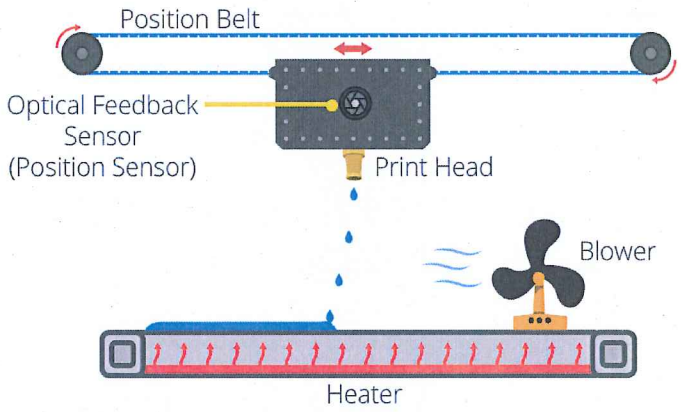

Fig. 4 - Drop-on-drop (DoD) inkjet 3D printing process *(Adapted from www.3dprintingindustry.com)* [18].

2.3. EXTRUSION-BASED PRINTING SYSTEMS

Methods based on extrusion are by far the most used methods for 3D printing, due to their versatility and simplicity. Extrusion-based printing systems are characterized by the employment of a nozzle through which semi-solid material is ejected. In a much similar style as laser-based and inkjet-based 3D printing systems, these printing systems deposit layers of material in successive layers, enabling the construction of objects bottom-up. These systems

can be divided based on their need for a heating/melting step to liquefy the material to be extruded. Although a standardized nomenclature for these methods is yet to be adopted, for the purpose of this review, these printing systems will be categorized either as Pressure-Assisted Microsyringes (PAM) Printing Systems or as Fused Filament Fabrication (FFF).

In PAM printing systems, semi-solid materials are extruded using a pressured air piston (pressure around 3-5 bars). The printed object will only fully solidify upon light exposure or drying, in a way much similar to the DoD processes mentioned before [4], which implies that there is always a risk of deformation, excessive droplet shrinkage, or even collapsing of the structure if it does not harden enough between each layer deposition. Also, this technique presents low resolution, as nozzles with large orifices are used (0.4 - 0.8 mm) [9]. Being performed in a continuous flow at room temperature, this process requires the use of solvents, which are essential for promoting layer to layer adhesion after evaporation. These solvents are often toxic and may interfere with the API's stability during the manufacturing process or upon drying [2]. On the other hand, drying temperatures are never as high as temperatures employed in FFF methods, so the risk of API degradation by temperature is much lower in PAM printing systems.

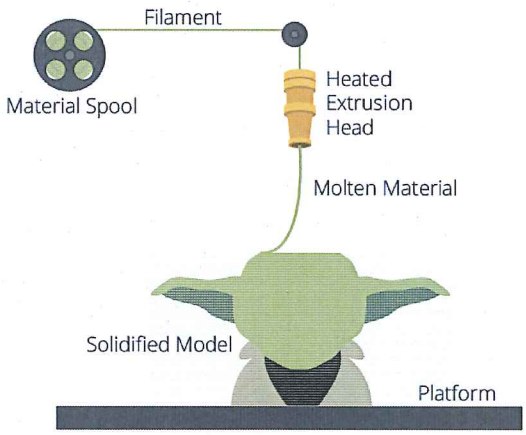

Fig. 5 – Fused Filament Fabrication (FFF) 3D printing process *(Adapted from www.3dprintingindustry.com)* [18].

FFF (also known as fused deposition modeling or FDM®, it's trademarked name) is a very common type of extrusion-based printing method whose wide range of applications are well established in the non-pharmaceutical industry. Equipment used for FFF is simple and inexpensive, and many low-cost user-friendly FFF printers are already available on the market

[9]. This method uses thermoplastic starting materials in the form of solid filaments, which are driven into the printhead by a gear system, where they are molten or softened prior to extrusion, solidifying almost instantly upon deposition (Fig. 5). Rheological proprieties of the material to be extruded are critical, and must be analyzed prior to extrusion as well as other parameters such as nozzle diameter, feed rate, printhead speed and nozzle temperature [13]. Figure 5 displays a schematic of a FFF 3D orienting process.

For pharmaceutical application, filaments used must either be impregnated with API or reprocessed by Hot Melt Extrusion (HME) to incorporate it. Either way, these filaments cannot contain high concentrations of API, or their rheological proprieties may be altered, making them inappropriate for extrusion [2]. This requirement for upstream processing alongside with its slow printing speed and the need for heating the filaments are the most relevant drawbacks of this technology. While impregnation does not require for APIs to be exposed to the high temperatures necessary for the reprocessing of these filaments, it often uses organic solvents which may be toxic and difficult to remove. Besides, yields of drug loading in impregnation processes are usually low (usually around 1 - 2% w/w), limiting this process to low-dosage forms. It's advantages in comparison to other printing systems include the wider range of starting-materials available for use in extrusion methods, its simplicity and versatility and the low cost of the equipment needed [1].

3. 3D PRINTED SOLID ORAL DOSAGE FORMS

3.1. 3D-PRINTED APPROVED SOLID ORAL DOSAGE FORMS

Currently, there is only one 3D-printed SODF available on the market, which is Aprecia Pharmaceutical's Spritam®. These are fast-disintegrating tablets containing levetiracetam at 4 different strengths (250 mg, 500 mg, 750 mg and 1000 mg). This SODF has gained FDA's approval in August 2015, but it was only on March 2016 that Spritam® hit the market in the United States of America (USA). Levetiracetam is an anticonvulsant, whose 3D-printed immediate release formulation (Spirtam®) is indicated for adjunctive therapy in the treatment of myoclonic and tonic-clonic seizures in different types of epilepsy syndromes. Patients are advised to take this medication with a sip of liquid, as no more than a few milliliters (15 mL or less) are needed for the tablet to almost instantly dissolve (5 s, as opposed to traditional dissolving times of around 60 s), exhibiting a T_{max} at around 9 minutes [8].

At this time, the alternative to Spritam® is Keppra® (brand name) or levetiracetam's generic formulations, existing both in oral solutions or in SODF, making Spritam® the only fast-disintegrating formulation for this drug. From a patient's perspective, the 3D printed formulation's main benefit over the regular SODF of levetiracetam is the ease of administration [24]. As with most high-dosage SODFs, levetiracetam tablets' dimension may cause difficulty in swallowing, especially in pediatric and geriatric populations. This becomes of particular importance considering that these drug is indicated for use in both of these age groups. The oral solution of levetiracetam has been formulated as an alternative, but dosing liquid formulations can be challenging and inconvenient for patients and care givers [13].

Spritam® is produced using an inkjet-based printing technology, namely a DoP type of production that was patented by Aprecia Pharmaceuticals as ZipDose®. Because this technology produces highly porous objects, water penetration in the tablet occurs at a much faster pace, which explains the fast disintegration times of Spritam® [9]. Another characteristic of this technology is its ability to easily incorporate taste masking agents, which is particularly relevant for a SODF meant to be orally dispersed. High friability and poor mechanical resistance, characteristic of DoP printing systems are a barrier yet to be overcome, and that is evidenced by the information listed on Spritam's® Highlight of Prescribing Information, which states that patients should be instructed not to push the tablet through the packaging's aluminum foil, but to peel it from the blister by bending and lifting the peel tab around the blister seal [8]. Despite all the benefits listed above, being the first 3D-printed SODF, Spritam® does not take advantage of some of the most promising characteristics associated with 3D

printing, like the ability to create complex formulations with distinct pharmacokinetic profiles and diverse shapes (the tablet is shaped in a circular flat cylinder, like most fast-dissolving tablets) or the ability to print individual doses, directed to each patient's needs.

3.2. 3D-PRINTED TRIAL SOLID ORAL DOSAGE FORMS

Many studies have been carried out in order to develop novel SODFs using a 3D-printer-based technology. In order to evidence these delivery systems' benefits over traditional ones, three different experimental SODFs that have been developed in recent years will be analyzed and described.

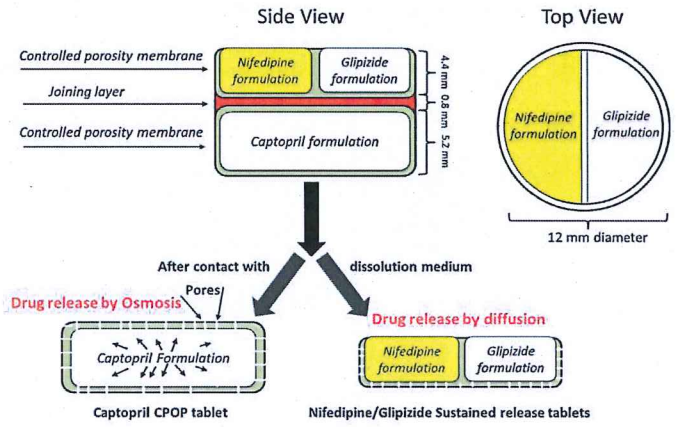

Fig. 6 – Schematic structural diagram of a 3D-printed SODF containing captopril, glipizide and nifedipine *(Adapted from Khaled et. al., 2015)* [4].

Khaled and coworkers developed an extrusion-based method, namely a PAM printing system, to produce a SODF combining 3 different APIs which exhibit different release-profiles: glipizide, nifedipine and captopril (Fig. 6). These drugs are frequently used in hypertensive patients with type II diabetes, but no multi-active dosage form for these 3 APIs exists, as they require different formulations to achieve their ideal release-profiles [4]. Using hydroxypropyl methylcellulose (HPMC), both glipizide and nifedipine were dispersed in a hydrophilic matrix in two different compartments. This allowed for the formulation of a sustained release tablet due to HPMC's ability to form a gel through which the APIs can diffuse. Both of these compartments displayed a first-order drug-release profile. As for captopril, a semi-permeable membrane was prepared using polyethylene glycol 6000 and cellulose acetate, which, in

contact with water, creates a controlled porosity shell through which the API can be released due to osmotic diffusion exhibiting a zero-order release-profile. However, these tablets have a diameter of 12 mm, which can cause difficulties in swallowing, and reducing its size has proven to be challenging because of the large amount of excipients that have to be used in order to achieve these release-profiles [2].

Using FFF to produce theophylline immediate and sustained release tablets, Pietrzak et al. developed a method whose flexibility allows for the development of tablets of different strengths using the same tools, materials and software. Their technique used HME for the production of drug-loaded filaments also containing, either polymethacrylate-based copolymer and triethyl acetate for immediate-release formulations, or hydroxypropyl cellulose and triacetine for sustained-release formulations. A few alterations were made to a commercial extrusion-based 3D printer and caplet-shaped tablets were produced. By altering the volume of each tablet, tablets of different strengths were produced, namely 60 mg, 125 mg, 200 mg, 250 mg and 300 mg. Printed tablets' drug content was then analyzed and a linear correlation (R^2 = 0,9995) was observed between the targeted dose and the actual dose content of the tablets, confirming this method's suitability for the production of precisely dosed SODFs [25].

This study shows how a FFF 3D printing machine can function as a mini-dispenser unit for tablets. Being an affordable equipment that requires minimal space, these printers could easily be integrated in a patient-centered healthcare system, bringing production closer to the patient [9]. For example, in a near future, physicians could prescribe a tailored dose for their patients and a personalized SODF could be printed in their local pharmacy using this technology. But perhaps it's in the hospital context that this technology could bring greater advantages. Tailored-dosed medication is of particular interest when treating hospitalized patients which are often polymedicated or suffering from comorbidities which require personalized doses. Patients with impaired kidney or liver function could also benefit from this, as well as pediatric and geriatric populations. Another approach to tailored dosing in a hospital context, where patients' biochemical parameters are constantly being controlled, would be the printing of SODFs dosed in accordance to each patients' clinical data, optimizing their therapy.

On another study, Sun and Soh were able to produce SODFs with various release-profiles using an elaborate strategy based on a different approach to 3D-printing. Instead of a printing an SODF using a 3D-printer, a 3D template with an embossed feature of different shapes was printed and used to create SODFs. In summary, after printing the embossed template, a polydimethylsiloxane pre-polymer mix was poured over that same template and cured. This

created a mold with a cavity shaped complimentarily to the 3D-printed template. After that, a mixture containing a degradable polyanhydride polymer and the API was poured into the mold and cured using UV light, thus creating the final API-containing polymer (Fig. 7, structure 1.b). In water, this degradable polyanhydride undergoes surface erosion which means that it erodes much faster at its surface than the API can diffuse through the matrix, as it happens in other polymeric systems such as HPMC. This is essential for achieving the desired drug release profile. The cured structure was then inserted into another 3D-printed container (Fig. 7, structure 1.a), which is made out of polylactic acid, a material compatible with 3D-printing that is practically insoluble in water in comparison to the polyanhydride polymer. Then, the existing empty space was filled with the same polydimethylsiloxane pre-polymer mix used before and placed in a vaccum chamber to extract any air bubbles trapped inside. After curing, a tablet of regular size (11 mm × 7.5 mm × 5.5 mm) was obtained. This SODF exhibits a pulsating release profile (Fig. 7, graph in 2.), but many others can be obtained by changing its design [26].

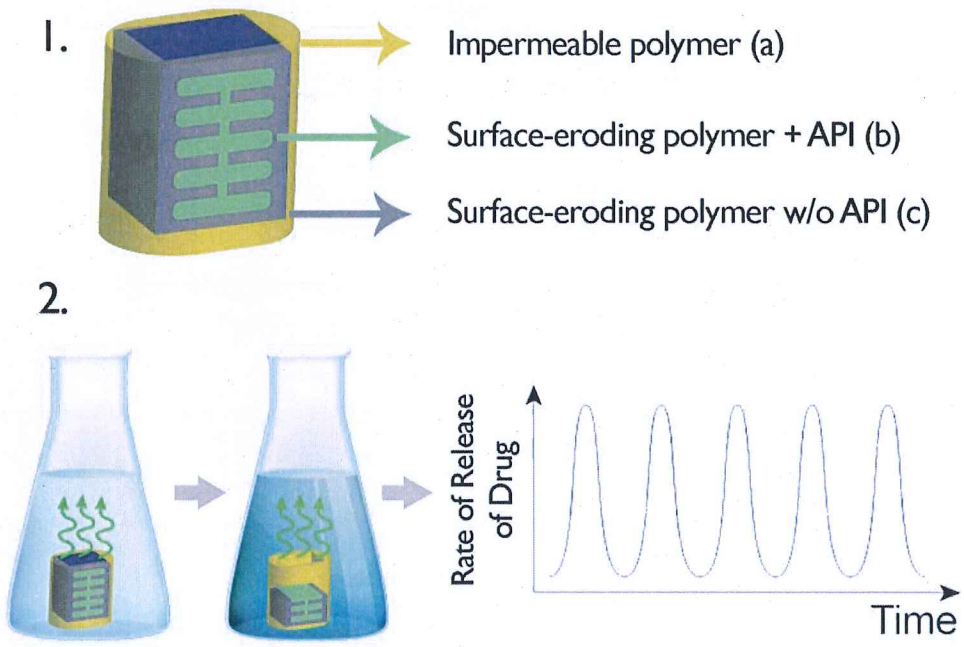

Fig. 7 – Illustration of Sun and Soh's SODF produced using 3D printing to deliver drugs with any desired release profile. 1. Scheme of the SODF – Except for the opening on top, the API containing polymer (b) is surrounded by impermeable polymer (a). 2. This SODF undergoes 1-dimensional degradation, thus explaining the drug release profile displayed above *(Adapted from Sun and Soh, 2015)* [26].

4. 3D-PRINTED MEDICAL DEVICES

4.1. 3D-PRINTED APPROVED MEDICAL DEVICES

According to the FDA, a MD can be defined as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is" [...] "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes." [27]. Even though other regulatory authorities such as the European Medicines Agency have a different definition for MDs, they are similar in its core.

As opposed to what happens with SODFs, there are already many MDs being marketed that are produced using 3D printing methods. As of the end of 2015, FDA had cleared more than 85 3D-printed MDs for marketing in the USA [28]. Most of these devices were granted clearance through the 510(k) process, which means they have provided evidence that they are substantially equivalent to a legally marketed MD. FDA classifies these MDs as "cleared", distinguishing them from those that carry the "approved" status, which means that the latter has had a premarket approval application approved prior to marketing. This approval process is generally reserved for high-risk medical devices and involves a more rigorous premarket review than the 510(k) pathway.

Approved/cleared MDs include surgical instruments, braces, screws, facial implants, hearing aids, dental crowns and many others. As it happens with Spritam®, some of these MDs are mass-produced at a central facility, not taking advantage of 3D-printing methods' ability to print tailored devices, directed to each patient's needs. However, many others make use of this feature and are already showing great results. MDs. For example, the first FDA-cleared polymeric facial implant is designed individually for each patient, and it has obtained FDA's clearance in 2014. Using data from a magnetic resonance imaging or from a computed tomography, patient-specific implants are produced at a central facility and then sent to the hospital for surgical implantation. This is a pioneering technology as up until now there was no process able to treat the highly complex anatomy of these cases. These implants are produced using a trademarked SLS technology, which creates osteoconductive implants, meaning they support bone attachment [29].

4.2. 3D-PRINTED TRIAL MEDICAL DEVICES

3D printing technologies have shown their ability to revolutionize the landscape of MDs mainly due to their ability to print complex patient-specific implants. Using the 510(k) process, these MDs can reach the market in a fairly easy way. On the other hand, MDs classified as being "high-risk MDs" such as implantable devices, or truly innovative MDs such as those containing chemical components responsible for their mechanism of action, cannot use this route as straightforwardly for gaining market access. The latter are considered to be Drug-Device Combination Products (DDCP), more specifically, MD-drug combination products. There are many examples of DDCPs under development described in the literature whose production process involves 3D-printing, usually for the assembly of the MD's structure itself. Two different experimental DDCPs which include a 3D-printing process in their production will be described in this review, evidencing their potential as innovative drug-delivery devices.

An interesting application for high-resolution 3D-printing methods is the production of microneedles. Microneedles are an innovative DDCP for transdermal drug delivery consisting of an array of micron-sized needles that perforate the outer layer of the skin providing a pain-free alternative for the delivery of therapeutics which are difficult to administrate orally. When designing microneedles, many design parameters, are known to be critical to efficacy, but are particularly difficult to alter due to the complex nature of microfabrication techniques. Therefore, Johnson and his team developed a method that uses CLIP for rapid prototyping of microneedles, going back to one of this technologies earliest applications. Rapid prototyping is particularly useful in this case because current microneedle fabrication techniques lead times for new designs are on the order of months, whereas using CLIP, a patch of microneedle arrays of any design can be produced in under than 10 minutes. Nevertheless, CLIP's safety as method for the production of microneedles that can be applied to a clinical scenario is still far from established. Residual unreacted monomers and their degradation products are a cause of concern in terms of toxicity, and the biocompatibility of these systems needs further investigation. The real value of 3D printing in this case lies in the possibility of allowing for the high throughput, systematic investigation of parameters associated with microneedle design, optimizing them, and accelerating translation of microneedle technology into clinical settings. However, CLIP technology is still a promising alternative to traditional micromolding techniques, and with further research, CLIP microneedles could be directly utilized for therapeutic applications [19].

Table I - Summary of the advantages of 3D-printing technologies evidenced by each of the pharmaceutical products discussed in this review.

PHARMACEUTICAL PRODUCT	PRINTING METHOD	BENEFIT
Spritam® (levetiracetam) fast-disintegrating tablet [24]	DoP *Inkjet based*	High porosity, making for a disintegration time of around 5 s
Captopril/Glipizide/Nifedipine tablet [4]	PAM *Extrusion based*	One tablet containing various APIs, displaying different release profiles
Theophylline tablet [25]	FFF *Extrusion based*	Production of on-demand individually dosed tablets
Sustained-release tablet [26]	Use of 3D-printed molds *Indirect method*	Controlled deposition of API within the tablet, creating unique drug release profiles
Polymeric facial implant [29]	SLS *Laser based*	Inexpensive production of individualized implants with complex features
Microneedles [19]	CLIP *Laser based*	Rapid prototyping for optimizing critical parameters
Biodegradable 5-fluoruracil implant [6]	FFF *Extrusion based*	Tailored biodegradable implants that deliver high amounts of API locally.

On another study, Yi and coworkers developed an extrusion-based method (FFF) for the production on drug-loaded pancreatic implants. Their goal was to create a tailored biodegradable implant that could locally suppress tumor growth by releasing 5- fluorouracil in a sustained manner. In order to achieve that, poly(lactic-co-glycolic acid), polycaprolactone and 5-fluorouracil were used to endow the formulation with both the desired rheological proprieties and drug release profile. After mixing them together, the final formulation was extruded at a temperature of 140°C and left at room temperature to solidify, creating the implantable devices. Four different concentrations of API were tested (10 mg, 50 mg, 100 mg, and 150 mg) and upon conducting Fourier transform infrared spectroscopy on the final 3D-printed implants, it was concluded that no significant molecular degradation had occurred during the extrusion process, despite the high temperatures employed. This study's final results indicate that this strategy was effective in reducing cancerous cells growth, and that the implant released 20% of the API on the first 4 weeks and degraded completely after 4 months. More importantly, a dose 3 times higher than doses achieved with a bolus injection was administered with these implants, but no signs of systemic toxicity were found. This was only possible due to the relatively high dose of API that was successfully incorporated into the polymeric mixture, and because the implant was shaped after the tumor, treating only the affected area and its immediate surroundings. This paves the way for other studies on other types of cancer, as these implants can be printed in any shape as desired [6].

Table 1 lists all the pharmaceutical products which were analyzed in this review, displaying also their advantages and which printing method was utilized in the manufacture of each of these products.

5. LIMITATIONS & CHALLENGES

As it happens with all manufacturing processes, 3D printing has some limitations of its own. Even though in the area of MD-production this technology is already gaining ground, when it comes to drug-products, there is still a long way to go before this technology becomes common-practice in the pharmaceutical industry. Many of this limitations are technical issues related to the state of the art of the technology itself, but perhaps the greatest challenge that this technology will pose to the pharmaceutical industry relates to legal and regulatory issues.

In terms of technological hurdles, the biggest weakness of all 3D-printing methods in comparison to traditional manufacturing methods is its speed. Whereas a conventional tableting process can produce more than 15,000 tablets per minute using one press, times for 3D-printing can vary from an average of 2 minutes up to 2 hours (depending on the process used) to produce just 1 tablet [2]. Even though this hiders industrial production, one may argue that the biggest strength of 3D-printed pharmaceutical products is the possibility of bringing production closer to the patient, which means printing in a small scale locally in pharmacies or hospitals. Other general problems that can be applied to most 3D printing methods are: variability in layer thickness; relatively limited material choices and presence of unreacted starting-material in the final formulation. Other than these, additional more specific obstacles have to be overcome for each printing method. For laser-based systems, it is important to find different starting materials which should be both safer and more diverse in order to provide for different drug-release profiles. Both in DoD and PAM 3D-printing methods, drying processes or the method itself need to be altered because as they are being done, post-treatments extend the manufacturing process, potentiating degradation of the incorporated API. FFF's main disadvantage is the use of high temperatures, which can give rise to stability problems, or polymorphism issues. As for powder-based technologies, poor mechanical resistance of objects printed using this technology continues to be a big concern, even though Spritam® was produced using DoP and it's high porosity gave this formulation a competitive advantage over other fast-disintegrating tablets [1].

Regulatory issues have also to be considered when talking about this technology. For these MDs to gain market access, the strategy most frequently used is the 510(k) route. By providing evidence that they are substantially equivalent to a legally marketed MD, many 3D-printed MDs have reached the general market in the last several years. However, it would be challenging for a manufacturer to submit a truly innovative product, because there are no implemented guidelines that list specific standards which producers are expected to adhere to before submitting products for review. To address this issue, in May 2016 the FDA has

released a draft guidance covering technical considerations for 3D-printed MDs. This draft contains nonbinding recommendations related to the production, testing and characterization of 3D-printed MDs. For instance, it is recommended in this draft that manufacturers clearly explain every step of the printing method employed, from the initial design to any post-printing steps that may be applied, because there are many 3D printing technologies and variations of each method. Another important recommendation stated in this draft is that producers should mention how each production parameter can have upstream effects on a device, for example, "the ratio of recycled to virgin powder can affect melting properties, which affects the energy needed to create consistent bonding between layers, which in turn affects final mechanical properties". Many more recommendations regarding product design, printing, and post-printing validation; printing characteristics and parameters; physical and mechanical; assessment of final devices; and biological considerations of final devices are stated in this guideline, which can be considered the first of its kind in the area of 3D-printing. However, this draft is still the first version of a document that lacks the input from experts from the industry, who are already working with this technology. The FDA strongly encourages experts to make comments and suggestions regarding their considerations, as only working side-by-side with the industry will regulatory agencies be able to standardize the production of 3D-printed pharmaceutical products [30].

Further than market access, other questions arise regarding this technology. For instance, how can regulatory agencies regulate personalized-dose printing? Will pharmacies and hospitals ever be able to produce SODFs locally in a small scale? And if so, would this be considered compounding pharmacy or small-scale production? And in who would lie the liability when a drug causes an adverse reaction? The pharmacist who printed it? The company who produced the starting materials? The company who assembled the 3D-printing machine? These are all questions that need to be answered before 3D-printing can truly claim its part as the lead technology in a tailored-dose pharmaceutical world. Other issue with 3D-printing is that it opens the door for a range of possibilities related to counterfeit drug-products and loss of intellectual rights. Most 3D-printing machines require practically no expertise from the operator, and being inexpensive and small-sized, having a personal 3D-printer will become a standard in a matter of time. The problem with this is that 3D-printing technologies allow users to create practically anything they want with their printer, from counterfeit drugs to machine guns. In a near future, downloadable formulations' designs will be available online, even if illegally, and users will be able to print them at their own risk at home [9].

6. CONCLUSIONS

In recent years the healthcare sector has already started to realize some of the potential benefits that different forms of 3D printing can bring to the table. From the ability to create innovative SODFs with more complex designs and shapes, exhibiting unique release profiles to the possibility of printing personalized implants and other MDs, this technology can truly revolutionize the sector. On the other hand, small-scale local production of personalized-dose formulations is one of the most promising aspect of this technology, and one where pharmacists will play an essential role.

However, as opposed to the more than 85 MDs that are already FDA-cleared, only one SODF is already being marketed. Hindering the approval of other pharmaceutical products is the regulatory vacuum that exists in this area and the technological limitations of 3D-printing methods. In the future, efforts must be carried out in order to better regulate this technology, allowing for industries to safely invest in 3D-printing, ameliorating this technology with their own input. All in all, 3D-printing's potential in the healthcare section is undeniable, and the only question yet to be answered is how much time will it need to become common-practice amongst manufacturers and to become properly regulated by the FDA and other regulatory agencies.

7. BIBLIOGRAPHY

1. NORMAN, J., et al., **A new chapter in pharmaceutical manufacturing: 3D-printed drug products**. Adv Drug Deliv Rev, 2016.
2. JONATHAN, G. and A. KARIM, **3D printing in pharmaceutics: A new tool for designing customized drug delivery systems**. Int J Pharm, 2016. 499(1-2): p. 376-94.
3. SAVASTANO, M., et al., **3-D Printing in the Spare Parts Supply Chain: An Explorative Study in the Automotive Industry, in Digitally Supported Innovation: A Multi-Disciplinary View on Enterprise, Public Sector and User Innovation**, L. Caporarello, et al., Editors. 2016, Springer International Publishing: Cham. p. 153-170.
4. KHALED, S.A., et al., **3D printing of tablets containing multiple drugs with defined release profiles**. Int J Pharm, 2015. 494(2): p. 643-50.
5. MELOCCHI, A., et al., **Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling**. Int J Pharm, 2016. 509(1-2): p. 255-63.
6. YI, H.G., et al., **A 3D-printed local drug delivery patch for pancreatic cancer growth suppression**. J Control Release, 2016. 238: p. 231-241.
7. GENINA, N., et al., **Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices**. Eur J Pharm Sci, 2016. 90: p. 53-63.
8. USA FOOD & DRUG ADMINISTRATION, **Highlights of Prescribing Information — Spritam**. 2015 [cited 23/08/2016] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207958s000lbl.pdf
9. ALHNAN, M.A., et al., **Emergence of 3D Printed Dosage Forms: Opportunities and Challenges**. Pharm Res, 2016. 33(8): p. 1817-32.
10. CHOONARA, Y.E., et al., **3D-printing and the effect on medical costs: a new era?** Expert Rev Pharmacoecon Outcomes Res, 2016. 16(1): p. 23-32.
11. CHHAYA, M.P., et al., **Additive manufacturing in biomedical sciences and the need for definitions and norms.** Expert Review of Medical Devices, 2015. 12(5): p. 537-543.
12. SACHS, E.M., et al., **Three-dimensional printing techniques**. 1993, Google Patents [cited 15/08/2016] Available from: http://www.google.pt/patents/US5204055.
13. PRASAD, L.K. and H. SMYTH, **3D Printing technologies for drug delivery: a review**. Drug Development and Industrial Pharmacy, 2016. 42(7): p. 1019-1031.

14. MELCHELS, F.P.W., J. FEIJEN, and D.W. GRIJPMA, **A review on stereolithography and its applications in biomedical engineering.** Biomaterials, 2010. 31(24): p. 6121-6130.

15. HULL, C.W., **Apparatus for production of three-dimensional objects by stereolithography.** 1986, Google Patents [cited 15/08/2016] Available from https://www.google.nl/patents/US4575330.

16. POPOV, V.K., et al., **Laser stereolithography and supercritical fluid processing for custom-designed implant fabrication**. J Mater Sci Mater Med, 2004. 15(2): p. 123-8.

17. XING, J.-F., M.-L. ZHENG, and X.-M. DUAN, **Two-photon polymerization microfabrication of hydrogels: an advanced 3D printing technology for tissue engineering and drug delivery.** Chemical Society Reviews, 2015. 44(15): p. 5031-5039.

18. 3DPI, **3D Printing Processes.** 2016 [cited 12/08/2016]; Available from: http://3dprintingindustry.com/3d-printing-basics-free-beginners-guide/processes/.

19. JOHNSON, A.R., et al., **Single-Step Fabrication of Computationally Designed Microneedles by Continuous Liquid Interface Production**. PLoS One, 2016. 11(9): p. e0162518.

20. DIMITROV, D., K. SCHREVE, and N. de BEER, **Advances in three dimensional printing – state of the art and future perspectives.** Rapid Prototyping Journal, 2006. 12(3): p. 136-147.

21. AULTON, M.E., ***Aulton's Pharmaceutics : The Design And Manufacture Of Medicines.*** 3rd ed. 2007, Edinburgh ; New York: Churchill Livingstone/Elsevier. p. 717

22. DALY, R., et al., **Inkjet printing for pharmaceutics - A review of research and manufacturing**. Int J Pharm, 2015. 494(2): p. 554-67.

23. YU, D.G., et al., **A novel fast disintegrating tablet fabricated by three-dimensional printing.** Drug Dev Ind Pharm, 2009. 35(12): p. 1530-6.

24. APRECIA PHARMACEUTICALS, **About Spritam**. 2015 [cited 19/08/2016]; Available from: https://www.spritam.com/#/hcp/about-spritam/dosing-and-administration.

25. PIETRZAK, K., A. ISREB, and M.A. ALHNAN, **A flexible-dose dispenser for immediate and extended release 3D printed tablets**. Eur J Pharm Biopharm, 2015. 96: p. 380-7.

26. SUN, Y. and S. SOH, **Printing Tablets with Fully Customizable Release Profiles for Personalized Medicine.** Adv Mater, 2015. 27(47): p. 7847-53.

27. USA FOOD & DRUG ADMINISTRATION, **What is a Medical Device?** [cited 05/08/16]; Available from: http://www.fda.gov/AboutFDA/Transparency/Basics/ucm211822.htm.

28. USA FOOD & DRUG ADMINISTRATION, **3D Printing of Medical Devices.** [cited 22/08/2016]; Available from: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/3DPrintingofMedicalDevices/default.htm.

29. OXFORD PERFORMANCE MATERIALS, I., **OPM Receives FDA Clearance for 3D Printed OsteoFab Patient-Specific Facial Device**. 2014. [cited 01/09/2016] Available from: http://www.oxfordpm.com/opm-receives-fda-clearance-3d-printed-osteofab-patient-specific-facial-device

30. USA FOOD & DRUG ADMINISTRATION, **Technical Considerations for Additive Manufactured Device - Draft Guidance for Industry and Food and Drug Administration Staff.** 2016. [cited 29/08/2016] Available from: http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm499809.pdf