Universidade de Lisboa

Faculdade de Farmácia

3D printing of medicines. Current challenges.

Carolina Ferraz Marques Chaves

Monografia orientada pelo Professor Doutor Luís Gouveia, Professor Auxiliar.

Mestrado Integrado em Ciências Farmacêuticas

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

A impressão tridimensional tem vindo a ganhar relevância no desenvolvimento científico e, inevitavelmente, na área farmacêutica. Esta tecnologia permite o desenvolvimento de formulações individualizadas, ajustadas às necessidades do doente e, por isso, pode vir a tornar-se uma ajuda valiosa na área dos medicamentos órfãos. Para além disto, também permite o desenvolvimento de formas farmacêuticas com várias substâncias ativas e/ou diferentes perfis de libertação de fármaco, que poderá vir a permitir um aumento da adesão à terapêutica por parte dos doentes polimedicados.

Apesar de atualmente já haver um fármaco impresso aprovado pela FDA desde 2015, o Spritam®, ainda há várias limitações associadas a esta tecnologia, nomeadamente a regulamentação, matérias-primas, controlo do processo e validação do mesmo, controlo de qualidade, estabilidade e a localização na cadeia de fabrico.

Quanto à regulamentação, não havendo diretivas regulamentares específicas para esta tecnologia na área farmacêutica, acaba por se adaptar a regulamentação existente. A escolha das matérias-primas é limitada pela capacidade de impressão e a estabilidade físico-química, reduzindo a panóplia de materiais adequados para esta técnica. Para o controlo do processo seria benéfico adaptar um controlo em tempo real optando, preferencialmente, por métodos não destrutivos, pois não sendo esta tecnologia a ideal para produção em larga escala, a perda de qualquer unidade teria um peso negativo significativo no balanço geral do processo.

A validação do processo deve ser elaborada de forma a garantir a qualidade, segurança e eficácia do medicamento. Para isso, é necessário validar não só o software, como todo o processo. No controlo de qualidade, mais uma vez, deve-se optar por métodos não destrutivos e selecionar, pelo menos, um para avaliar o sucesso da impressão, sendo que pode ser utilizada o *Quality by Design* como uma ferramenta para otimizar o processo. A estabilidade, tal como nos outros processos, também deve ser testada e a localização da impressão tridimensional no ciclo do medicamento é outra questão levantada, uma vez que tanto poderá ter um papel na farmácia hospitalar ou comunitária, como na indústria farmacêutica ou, já numa hipótese remota, na casa do doente.

Palavras-chave: Impressão 3D; regulamentação; qualidade; eficácia, segurança.

Abstract

Three-dimensional printing is a technique that has been drawing attention recently in the scientific community and, inevitably, in the pharmaceutical field. As allows the development of personalized medicine, adapted to the patient's needs, it can be a valuable tool for orphan drugs. On the other hand, it also allows the development of dosage forms with various active pharmaceutical ingredients and/or with different drug release profiles, which can improve patient compliance.

Although there is a printed medicine approved by FDA since 2015, Spritam®, there are still a few limitations in this methodology, as regulation, raw materials, process controls and validation, quality control, stability, and even location.

In terms of regulation, there are no specific regulatory guidelines regarding this technology in the pharmaceutical area, however, a 3D printed drug product should be produced following the existing guidelines that can be adapted. In terms of raw materials, the range available is limited by printability and physicochemical stability, reducing the suitable materials. For process control, it would be advantageous to adopt a real-time control and, favour non-destructive techniques, as the loss of any unit would harm the overall balance of the process.

Process validation should be designed to ensure the quality, safety, and efficacy of the drug product. Taking this into account is necessary to validate the software to the process itself. In terms of quality control, should go for non-destructive methods, once again, and is going to be needed to assess the success of the print. Quality by design can be used as a tool to optimize the process. As in other methodologies, stability test must be conducted and the location of the three-dimensional impression on the drug cycle is another issue that arises, as it may play a role in the hospital or community pharmacies, as in the pharmaceutical industry or, in a more remote hypothesis, at the patient's home.

Keywords: 3D printing; regulation; quality; efficacy; security.

Acronyms

3D	Three-dimensional
ABS	Acrylonitrile Butadiene Styrene
AMF	Additive Manufacturing File Format
API	Active Pharmaceutical Ingredients
CAD	Computer-aided Design
CMA	Critical Process Attributes
CMC	Chemistry, Manufacturing and Control
CO_2	Carbon Dioxide
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
CTD	Common Technical Document
DoD	Drop-on-demand
DoE	Design of Experiments
DSC	Differential Scanning Calorimetry
EC	Ethylcellulose
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDM	Fused Deposition Modelling
FLE	First Layer Effect
FTIR	Fourier-Transform Infrared
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HME	Hot-melt Extrusion
HPC	Hydroxypropyl Cellulose
HPLC	High-performance Liquid Chromatography

HPMC	Hydroxypropyl Methylcellulose
ICH	International Council Harmonization
ISO	International Organization for Standardization
Laser	Light amplification by stimulated emission of radiation
Micro-CT	X-ray Micro Computed Tomography
MSPC	Multivariate Statistical Process Control
NIR	Near-infrared
ODTs	Orally Disintegrating Tablets
PAT	Process Analytical Technology
PCL	Polycaprolactone
Ph. Eur.	European Pharmacopoeia
PLA	Poly(lactic acid)
PMMA	Poly(methyl methacrylate)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PU	Polyurethane
PVA	Poly(vinyl alcohol)
PVP	Poly(vinyl pyrrolidone)
QbD	Quality by Design
QTPP	Quality Target Product Profile
RTR	Real-time Release
SEM	Scanning Electron Microscopy
SLA	Stereolithography
SLS	Selective Laser Sintering
STL	Standardized Triangular Language
TGA	Thermogravimetric Analysis
UV	Ultraviolet

UV-VIS	Ultraviolet-visible
XRPD	X-ray Powder Diffraction

Index

Figures Index

Tables Index

1 Introduction

Three-dimensional (3D) printing is a manufacturing process that has been launched in the pharmaceutical field in the 90s and allows the production of three-dimensional solid objects of essentially any shape from a 3D model file. The 3D models can be created by computer-aided design (CAD) software or taken from 3D scanners that capture images and distance information of real objects and then transfer the data to a computer (1,2).

In general terms, the 3D printing process consists of modelling a solid part in a computer with CAD software, converting the CAD file into Standardized Triangular Language (STL) file, creating a volumetric mesh and the supporting structure, slicing the volumetric-meshed model layer by layer and producing SLC file. The file is then exported to the 3D printer, building the structure layer by layer. The supporting structure is removed to get the green part and it goes to post-processing (3).

3D printing methods may support the development of personalized medicine and therapy, dosage forms with tailored release profiles and adjust the drug dose to the needs of each patient. Most of the current pharmaceutical manufacturing processes are meant to allow mass production of significant numbers of unit dosage forms of fixed doses, with the advantage of reducing the cost of production of large numbers of unit dosage forms of fixed-dose. On the other hand, the dose personalization takes into account factors like gender, age, weight, pharmacodynamic and pharmacokinetic, state of the disease and the genetic profile to maximises the therapeutic efficacy of drugs and to reduce the incidence of undesirable effects and risk of overdose, which are critical for drugs with a low therapeutic index. 3D printing can also be used to produce drug products with multiple active pharmaceutical ingredients in numerous sections, which can be helpful to develop formulations that reduce multiple daily dosing and, consequently, improve patient compliance and therapeutic efficiency (2,4–8).

3D printing can be economically viable, not only because personalized medicines usually only require small batches, but it can also be cost-effective to manufacture the personalized medicines. This technique can also be helpful in low-stability drugs because is possible to print only when is necessary (9).

In the development of a 3D printed product, there are some aspects to be considered. The drug product design needs to match the target patient; the specific patient needs; type of the molecule to be delivered and its indication; target dose and the level of precision; level of personalization; target delivery route; target in vitro drug release and matching pharmacokinetic

characteristic to be achieved; target quality attributes; target packaging configuration, and target shelf life (10). On the other hand, the printing resolution is directly proportional to the printing time, which means that the higher the printing resolution, the longer is the printing time (11).

Despite the advantages, some challenges arise with this technology. Difficulties as speed and limited availability of suitable blinders are such a few examples (12,13).

3D printing methods vary from each other in various aspects like the type of material used, the technology of deposition, the mechanism of formation of the layers or the characteristics of the final product. The main 3D printing techniques that are used in the pharmaceutical field, briefly described in Table 1, are Inkjet Printing, Fused Deposition Modelling (FDM), Stereolithography (SLA) and Selective Laser Sintering (SLS) (14–17).

Table 1: Summary of the main techniques used in the Pharmaceutical Field, adapted from (12,17,18).

Technique	Substrate	Mechanism of Layering	Process
Inkjet Printing	Solid particles	Liquid binding agent is deposited to join powder materials	Chemical/mechanical
Fused Deposition Modelling (FDM)	Filament (thermoplastic polymer)	Melting by a heated nozzle	Extrusion
Stereolithography (SLA)	Liquid (photopolymer)	Binding by UV ray	Photopolymerization
Selective Laser Sintering (SLS)	Solid particles	Melting by laser	Solidification of powder

1.1 Inkjet Printing

Binder jet printing or inkjet printing was one of the first 3D printing technologies to be used in the preparation of drug delivery devices and one of the most studied (15).

Binder jet printing is a technology that fuses powdered material with a layer-by-layer approach. A printer nozzle containing a binder, or the drug liquid is instructed to go through an

x-y axis and spray the liquid onto a flowing powder bed. Then, the powder particles are soaked by the droplet which results in local hardening and layer solidification (17).

Inkjet printing can require the continuous jetting of droplets or with a drop-on-demand (DoD) mechanism. To control droplet deposition, the printers use two different kinds of DoD heads: piezoelectric and thermal heads. A current is pulsed through a resisting element in the print head, causing an increase of the internal temperature and subsequent vaporisation, nucleation and expansion of a bubble which imparts sufficient energy to eject a droplet. The particles are joined by the formation of binder bridges or the dissolution and re-crystallisation of particles (17,19).

The fabrication build plate is moved down along the z-axis, with the powder delivery platform moving upwards and the next layer is distributed on the top of the previous bound layer and the process is repeated. The final pharmaceutical product is extracted from the powder bed with the excess powder being removed. The process is drafted in figure 1 (17).

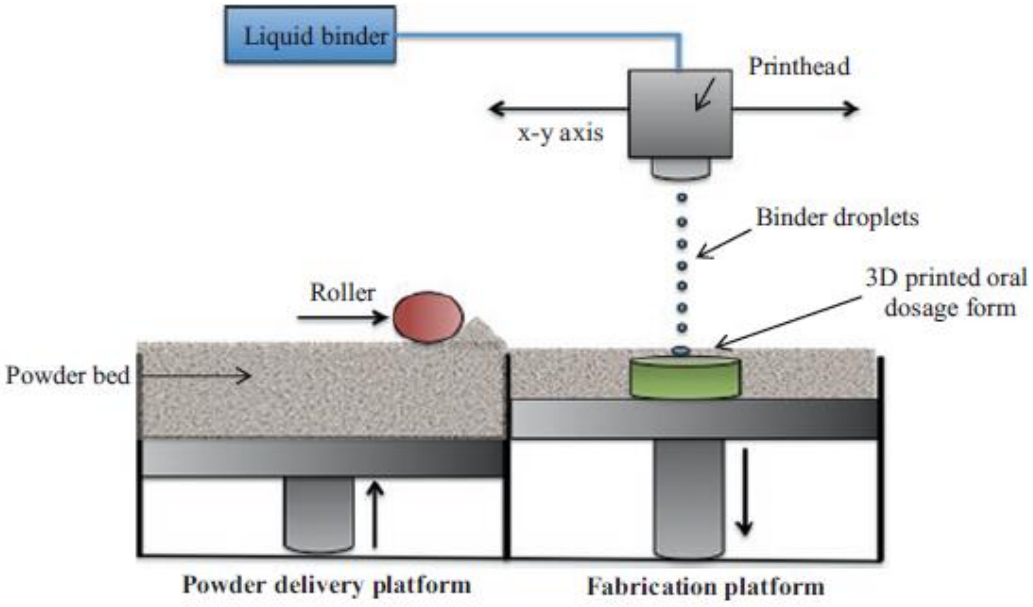

Figure 1: schematic of the inkjet printing process, adapted from (17)**.**

The inkjet printing offers excellent precision and can produce low bulk density and highly porous. The fact that active ingredients can be in the amorphous phase, can be valuable for drugs with poor solubility (17).

This technology was used to produce the Spritam® (figure 2), an oro-dispersible levetiracetam tablet, developed by Aprecia Pharmaceuticals, that is, currently, the only approved 3D printed medicinal product, by the Food and Drug Administration, FDA, since 2015. Spritam® has four dose strengths with a dose range from 250 to 1000mg and is capable

of rapidly dissolving in the mouth with an average disintegration time of 11 seconds, providing the intake of a small sip of liquid. The printing process itself, Zipdose®, has been optimized for bulk manufacture, with the process including the powder bed being transported on a conveyor belt and numerous printers being used to deposit the solution as the belt progresses, gradually building up the tablet thickness. This drug product was developed to overcome the poor adherence of this therapy in specific groups, like the paediatrics and geriatric patients (6,7,17).

Figure 2: The Spritam® tablets, adapted from (20)**.**

1.2 Fused deposition modelling

Fused deposition modelling, FDM, is a 3D-printing method, developed in the late 1980s, where the feed material enters the heated printer nozzle as a filament. The drug pre-loaded filament melts as it enters the liquefier, and the yet solid part acts as a piston forcing the melted material through the liquefier cavity. The print head moves in the *x*, *y*-plane at an established velocity, whereas the build platform moves in *z*-direction allowing the addition of the material, layer by layer, to produce the structure instructed by the CAD drawing file input (1,5,15,21).

In the FDM technique, the choice of the polymer must take into account thermoplasticity as the application of high temperatures for relatively long periods, can result in drug degradation and modification of the polymer characteristics. Thereby, the materials should be thermostable, non-volatile, and non-aerosolizing. Polymer materials are typically amorphous or semicrystalline. In the case of amorphous materials, the extrusion is done at a temperature above the melting temperature of the crystalline portion of the polymer. The filament has to be flexible enough to allow some bending in the supply system and hard enough to tolerate the compression forces applied by the pulling wheels without major deformation (5,15,21). The printer and the feeding system are represented in figure 3 (21).

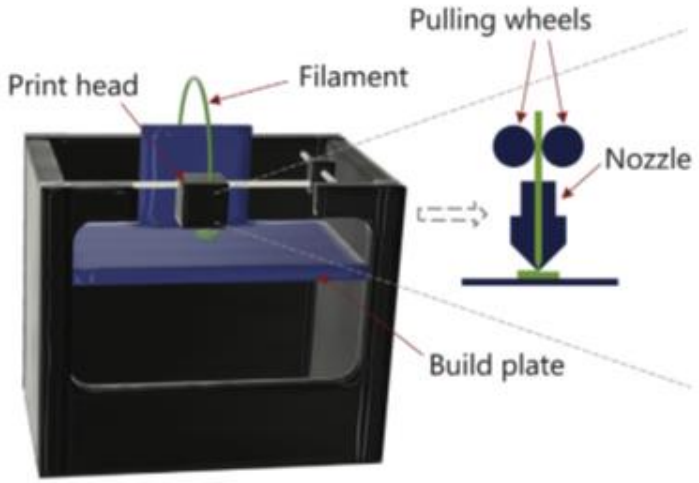

Figure 3: simplified model of an FDM 3D printer and the filament feeding system, adapted from (21)**.**

There are different ways to prepare filaments for this technique. Premanufactured filaments can be soaked in an Active Pharmaceutical Ingredients (API) solution, or filaments can be coated with a layer of API with excipients, or the polymer filaments can be manufactured with hot-melt extrusion (HME). This methodology simplifies the incorporation of the drugs into the filaments because the process automatically involves a mixing and blending step at elevated temperatures before being extruded through a die to produce a strand of uniform characteristics. HME is a continuous, efficient, and simple procedure, who has a specific requirement for a carrier polymer since exceptional high temperatures are used in the process. However, the addition of a plasticizer can boost the extrusion capability of the carrier polymer (7,18,22–24).

After the deposition, the filament must be accurately fused into the formerly deposited layer before it is solidified. However, the cooling must be sufficiently quickly and the viscosity of the layer high enough so that the printed structure will keep its shape without crumbling under the increasing number of layers (21).

Shear viscosity is the most important rheological property in FDM and is reliant on both the internal factors such as the molecular structure, molecular weight, molecular weight distribution of the polymer and the solid form of the drug, as well as the external factors such as the temperature and the shear rate (21).

Since after a few hours, could be required a nozzle cleaning, the printers offer precise indications on timing and mode of nozzle cleaning, to simplify this process (25).

In summary, FDM can generate solid dosage forms of appropriate mechanical strength and dosing accuracy, although there is only a limited selection of thermoplastic materials approved for human use (5).

FDM has been studied, for example, to print a bilayer dosage form containing two drugs with different daily dose regimens of metformin and glimepiride. It has also been studied the possibility to print pregabalin tablets for intra-gastric floating and controlled release. Both studies have proven the possibility to use this technology to prepare those dosage forms, although the articles do not describe the batch size (15,26).

1.3 Stereolithography

Stereolithography, SLA, is a production technique based on the solidification of a liquid resin by photopolymerisation. This process has three general stages: initiation, propagation, and termination. In the initiation, a photoinitiator undergoes a reaction upon exposure to light-producing initiating species, such as free radicals. The reactive species can attack monomer units and propagate between the monomers/oligomers and the functional groups and crosslinking occurs. Covalent bonds are then formed between the crosslinked networks. The requirement for reactive groups is, however, a disadvantage of this process (17).

The localized polymerization is caused by a laser (light amplification by stimulated emission of radiation) beam leading to the solidification of photocrosslinkable polymers to form a solid layer. The platform is moved down alongside the *z*-axis, the built layer is recoated with resin and the process is repeated layer-by-layer until the solid 3D object is produced. SLA printers operate lasers combined with galvanometers to cure the resin (1,17,27). The process is drafted in figure 4 (17).

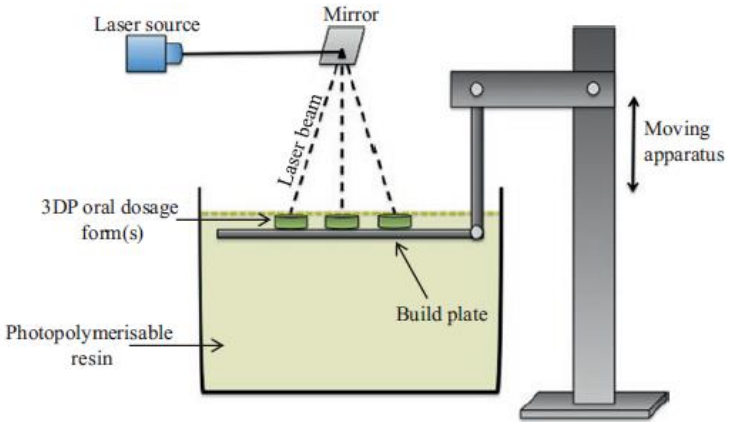

Figure 4: schematic of the SLA printing process, adapted from (17)**.**

The avoidance of thermal degradation, improved resolution, higher accuracy, and the fact that is a faster method, are some of the advantages that SLA has over other 3D technologies. However, the fact that the process depends on ultraviolet curing can create problems on drug stability and safety (3,28,29).

This method has been studied, for example, for the possibility to print a polypill tablet (printlet) containing six different model drugs: paracetamol, naproxen, caffeine, aspirin, prednisolone, and chloramphenicol, although the article does not describe the batch size. This study has demonstrated the potential of the SLA to produce multi-layered pills, increasing the personalisation for patients (28).

1.4 Selective Laser Sintering

Selective Laser Sintering (SLS) is one of the most recent and most innovative technologies proposed for the preparation of solid dosage forms. SLS is a one-step, solvent-free fabrication process containing a laser to selectively sinter powder particles in a layered method to form 3D structures. This printer comprises a powder bed, a powder pool, a roller, and a laser source. Most of the SLS printers available employ carbon dioxide (CO_2) lasers, which provide higher power at a lower cost (11,16,30).

The powder for printing is equally distributed on the powder bed by the roller. Depending on the 3D design of the object, the laser is determined to draw specific patterns on the powder surface sintering and agglomerating the powder particles. Once the first layer is sintered, the powder bed moves down while the pool bed moves up to allow for the delivery of a new layer of powder on top of the previous one (16,30). The process is drafted in figure 5 (31).

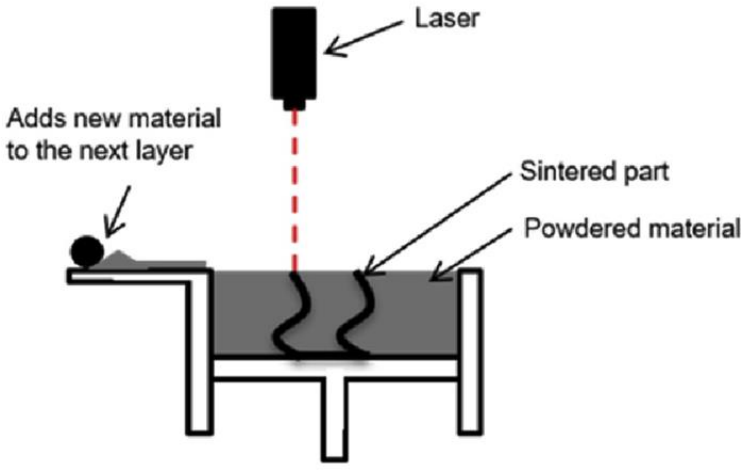

Figure 5: schematic of the SLS printing process, adapted from (31)**.**

It has been thought that SLS was not suitable for the preparation of medicines due to the potential degradation of the drugs caused by the high energy of the CO_2 lasers that work in the Infrared region of the spectra. Currently, the use of SLS printers that use lower intensity diode lasers allowed the production of novel drug products with no drug degradation (16).

An advantage of this technology is the laser sintering process, which blends the drug and polymer particles, producing a strong coherence between the particles and supporting the drug release from the molten matrix. Additionally, the high resolution of the laser bean facilitates the printing of very small and detailed units (30).

This technology has been studied, for example, to print orally disintegrating tablets (ODTs) of ondansetron. This dosage form increases the bioavailability and absorption of drugs, being more suitable for patients with dysphagia or those who have difficulties in swallowing. In this study, the batch size is six. It has also been studied to print paracetamol-loaded miniprintlets with sustained drug release, where for each batch were printed 100 miniprintlets at a time. Both studies have shown the potential of SLS to print those dosage forms (16,30).

2 Objective

This monograph has the main objective to make a bibliographic review, describing aspects related to the 3D printing of medicines, such as the printing types that can be used to print medicines, the advantages and benefits that printing can bring to the drug production and patient acceptability.

Throughout this monograph, will also be discussed the regulatory aspects, the raw materials necessary to print, process control and validation, as well as the quality controls, stability studies and the location which are currently described as the challenges that this technology entails.

3 Methodology

This monograph was made following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A bibliographic search was performed in books and electronic databases, such as PubMed, using the keywords “3D printing”, “3D printing of medicines”, “pharmaceutical 3D printing”, “3D printed novel dosage forms”, “3D printed polypill”, “3D printing regulation”, “filaments 3D printing medicines”, “3D printing raw materials”, “process controls 3D printing”, “validation 3D printing”, “3D printing medicines quality assurance”, “3D printing quality by design”, “quality by design” and “pharmaceutical 3D printing stability”.

A selection of criteria was assigned for defining which articles were going to be included. The articles must contain quality information about 3D printing, its techniques, and its advantages, as well as its limitations. Articles that use the 3D printing technology to produce medicines, as well as their evaluation, were also selected. Additionally, other publications with these thematic such as conference papers, review articles, etc. were excluded. The themed specific bibliography published over seven years ago were also excluded. Another bibliography, as the regulation, were also consulted, which was consulted the most recent one available.

4 3D printing of medicines

Being 3D printing a flexible manufacturing process, aspects like dose strength, release properties, drug combinations and personal preferences as size, shape or colour can be taken into account, leading to pharmaceutical care tailored according to the patient needs (18).

4.1 Novel Dosage Forms and Drug Delivery Systems

Numerous studies have been done to demonstrate the suitability of printing technology to create different dosage forms with variable drug release profiles since 3D printing can offer a new way to modify the release profile from dosage forms, as shown in figure 6 (15,18).

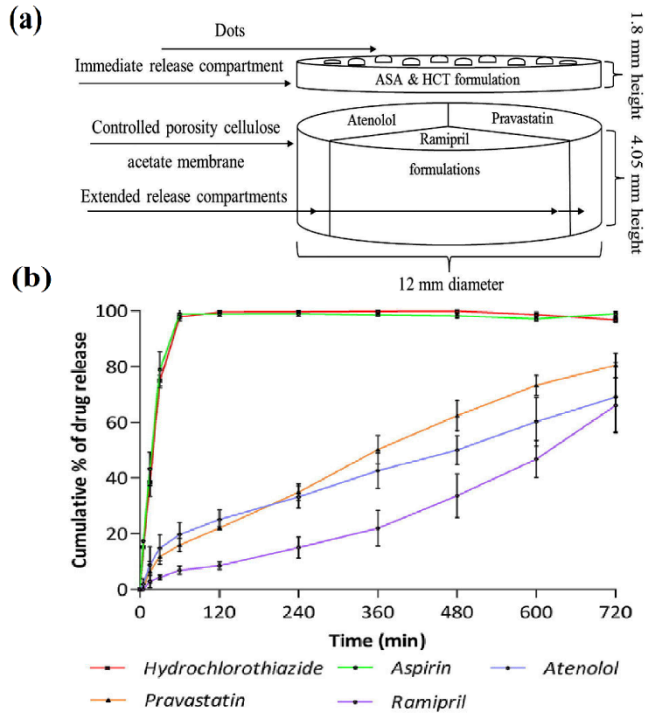

Figure 6: schematic structural diagram of a polypill (a) and in vitro cumulative drug release profile of each drug (b), adapted from (32)**.**

The basic approach to modify the release profile is to change the formulation by, for example, modifying excipients (18).

In the specific case of the 3D printing, the same drug filament can print controlled, immediate or combined release kinetics, modifying a few printing parameters, as the geometric shape of the printed drug product; the infill density that can modify the porosity; or the infill pattern which affects the hardness and, consequently, the disintegration time (33).

Infill density, %infill or fill density is a print parameter that monitors the per cent of the printed region in the walls, and the top and bottom layers of the design. This parameter can be controlled through the slicing step of the process and has been proven that has a significant impact on the release kinetics of the drug from the polymer. That is, the drug dosage with a higher infill had a more sustainable release while the one with the least infill has the fastest release (34).

Changing the geometry of the dosage form, as the surface area accessible to the dissolution medium, can also be a way to modify the drug release profile, which can be done in the design process without changing the dosage. The Noyes-Whitney equation, modified by Nernst and Brunner (equation 1) is an equation that explains the relation between dissolution behaviour and surface area (18).

Equation 1: the Noyes-Whitney equation, modified by Nernst and Brunner (18).

$$\frac{dc}{dt} = \frac{A * D * (C_s - C_t)}{\delta * V}$$

In this equation, dc/dt signifies the change in concentration over time $t_x - t_{x-1}$, A the surface area available to dissolution, D the diffusion coefficient of the substance in the solvent, δ the thickness of the diffusive layer, V the volume of the solution, c_s the saturation concentration, and c_t the concentration in the solvent at time t. This equation can be utilized in many immediate releases and unmodified dosage forms (18).

Starting printing with 3D printers with multiple nozzles also allowed the fabrication of dosage forms, that could modify and regulate the release of the incorporated APIs, depending on their detailed design (26).

With 3D printing technology, can be manufacture, for example, an immediate-release drug dosage without the use of disintegrant or filling agents, by making physical structure changes as thickness or creating holes in them (35).

In research papers, HME and FDM have been successfully studied for the possibility of printing a novel gastroretentive floating pulsatile drug delivery system. Pulsatile drug delivery systems offer a timely pharmacological effect to the patient, although preventing unwanted sustained drug exposure. These delivery systems are not beneficial in all disease conditions, however, when suitable, can prevent harmful drug-drug interactions without adjusting the administration schedule of drugs and can improve patient compliance. In the study was developed a floating pulsatile tablet with desired lag time for pulse release of the API. A floating

tablet is a low-density system with adequate resilience to stay afloat above the gastric content in the stomach for a long and pre-determined period without intervention from the normal peristalsis of the gastrointestinal (GI) tract (36,37).

4.1.1 Polypill

Polypharmacy defined as the coadministration of multiple medications in patients with probably multiple comorbidities, which is one of the most crucial prescribing issues, associated with increased non-adherence and patient confusion due to the high pill load and complicated administration requirements. Reducing the number of dosage units could help to solve the problem, that is, the solution to this problem can be polypills, as it simplifies complex therapies and dose regimens (18,28,38).

The polypill, as shown in figure 7, is a tablet that comprises a combination of medicines for chronic diseases, such as hypertension, that intends to reduce the number of pills taken by the patient to increase adherence to the therapeutic regimen (32,39).

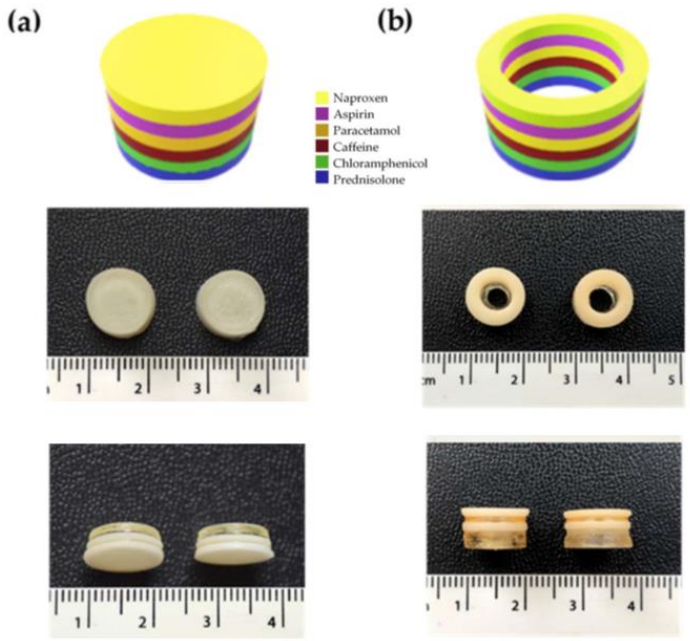

Figure 7: 3D designs of the *printlets* (top) and polypill *printlet* (bottom) in a cylinder shape (a) and a ring shape (b), adapted from (28). The scale is in cm.

Merging multiple APIs will probably boost the potential for adverse effects. As so, the composition of the dose combination should ideally be individualised to offer the best possible

solution for each patient to meet the treatment goals, the response, preferences and unwanted adverse effects (40).

The biggest challenge to produce a polypill is to minimize the chemical instability, incompatibility, or physical interactions between the different components of the formulation. However, 3D printing can accurately distribute materials, leading to the fact that drugs can be designed to be physically separated, making it possible to adjust doses and release profiles individually as well as to co-formulated drugs that may potentially interact (18,28,30).

Some strategies can be followed to guarantee the physical separation of the components of the formulation. An example is the segmented tablet strategy, which gives flexibility in production, altering the drug loading and excipient composition in the individual parts of the formulation. The manufacturing process can be designed to be divided into steps, that is, every layer is printed in turns, first is printed the first layer, then the second and so on (32,41).

In a research paper where stability tests for the polypills were conducted, more specifically accelerated stability, neither physical change nor considerable changes in the drug content have been detected. The integrity of the polypills stayed intact even in stress conditions and the release profiles remain the same after the tests. The Differential Scanning Calorimetry (DSC) thermogram also suggested that no interaction occurred between drugs and excipients (42).

5 Current challenges of 3D printing of medicines

Despite the advantages that have been pointed out for 3D printing, there are some challenges associated with this technology. The low printing speed, the lack of quality control procedures for printed systems manufactured at hospitals or pharmacy, or even the possible risk of cyber-attacks on the computer which controls the printing process, threatening the formulation, are just a few examples (2).

On the other hand, some questions can be raised about the printing process, for example, while more traditional methods can produce a tablet in milliseconds, a 3D printer may require a few minutes to print the drug product. Whether the 3D printing will be suitable for mass production; if it will be possible to scale up; how to prevent nozzle clogging; if the manufacturing speed will be acceptable to meet up the market demand; if the process will be prepared to reproduce each unit dose consistently and has flexibility; will the process be compliant with the qualification and validation in Good Manufacturing Practice (GMP); if the process could be well controlled by the software or, even, if the software could be validated are a few examples of questions that this technology raises (10,33,43). Table 2 is a summary of a few advantages and disadvantages of both "traditional manufacturing" and 3D printing (18).

Table 2: Advantages and disadvantages of 3D printing, compared with "traditional manufacturing", adapted from (18).

	"Traditional manufacturing"	**3D printing**
Advantages	• Large scale; • Known products; • Recognized.	• Small to medium scale; • Proper for orphan drugs.
Disadvantages and limitations	• Fixed doses; • Sized dosage forms; • Lack of orphan drugs; • No individualization.	• Brand-new control systems and directives; • Higher risk due to greater flexibility; • Available equipment.

A rising concern that has come with this technology is the fact that 3D printing has given an increase to a do-it-yourself culture, which can trigger significant damage in the case of self-

treatment. Articles regarding how to print are available online and it can be catastrophic if the patients are unaware of proper procedures to be followed (44).

The number of regulatory approved 3D printed drug products remains limited due to the number of printers available to comply with GMP, high variability of 3D printers, and end-product quality (6).

5.1 Regulation

Currently, there are no regulatory guidelines specific for the 3D printing of drug products but, like any other dosage form, a 3D printed drug product should be produced following current chemistry, manufacturing and control (CMC) standards (10,45,46).

Medicines prepared by 3D printing technology are subordinate to regulatory requirements like others made by another manufacturing process. In 2017, the FDA released guidelines for producing medical devices and implants, that have subjects that can also be applied in 3D printing medicines. However, currently, the European Medicines Agency (EMA) has not released a statement, an opinion, or a guideline about this topic (10,45,46).

All four International Council for Harmonization (ICH) subjects and their beliefs, Quality, Safety, Efficacy and Multidisciplinary guidelines, can be similarly applied to the 3D printing technology for pharmaceutical products. In terms of Quality, the manufacturer can follow the ICH Q8(R2)[1], Q9[2], Q10[3] and Q11[4] ICH guidelines. All other CMC aspects of a 3D printed drug product such as stability, impurities, drug substance and drug product specification, and GMP can stick to the ICH guidelines as delineated in Q1[5], Q2[6], Q3[7], Q6[8] and Q7[9] (10).

The EMA quality guidelines for active substances, manufacturing, impurities, specifications (analytical process and validations), excipients, packaging, stability, pharmaceutical development, the specific type of product and lifecycle management, can be suitable for any 3D printed drug products with additional features that are specific to the 3D

[1] ICH Q8(R2) on Pharmaceutical Development.
[2] ICH Q9 on Quality Risk Management.
[3] ICH Q10 on Pharmaceutical Quality System.
[4] ICH Q11 on Development and Manufacture of Drug Substances.
[5] ICH Q1 on Stability Testing.
[6] ICH Q2 on Analytical Validation.
[7] ICH Q3 on Impurities.
[8] ICH Q6 on Specifications.
[9] ICH Q7 on Good Manufacturing Practice.

printed products. 3D printing should also be under their regulatory jurisdiction for mass production and distribution within their respective countries (10).

According to the Technical Considerations for Additive Manufactured Medical Devices by the FDA, the file format must be compatible with the different software applications used. Patient images, design manipulation software for patient-matching, digital point clouds and meshes, and machine-readable files each have their specifications, coordinate systems, default parameters and each package have a different approach for interpreting those specifications. One possibility is the Additive Manufacturing File Format (AMF) described in the ISO/ASTM 52915 Standard specification for AMF (47).

The 3D printer itself can be considered an advanced manufacturing technology, and is eligible as a production tool, falling under the scope of the EU Machinery Directive 2006/42, which establishes conformity obligations assuring standard levels of safety. Keeping correct calibration and performing preventive maintenance have been recognized as key factors to achieve low rejection rates (47,48).

Under the current regulatory framework, it is not clear if the print cartridges should be regulated as a drug-device combination product or as a pharmaceutical raw material manufacturer, taking into account that the cartridges may be produced with the drug-loaded formulation in it (10).

5.2 Raw materials

The selection of APIs and excipients depend on their printability and physicochemical stability, in combination with the type of 3D printer to be used (10).

Understanding the raw material properties and their effect on the printability product has major importance, supporting in a rapid process system, in preventing or mitigating typically occurring processing problems, and in expectation of the output quality. Printability of the raw materials, uniformity of mass, content uniformity and resolution of the printed drug product are examples of factors that could be affected. The main factors that can influence the printability of the raw materials are mechanical resilience and their rheological properties (9,18,21,47,49).

Surface roughness, flexural strength, physical characterization, and toughness are examples of characteristics that can be evaluated in the printing process, which can be done for

both empty and drug-loaded raw materials. Nanoindentation is a process that can be utilized to measure the hardness of the material (5,50).

Mechanical resilience has been described as a key factor considering print viability. The mechanical properties must allow, for example, the precise conduction of the filament across the print head without deformation or breakage, in the case of FDM. The tensile test and three-point bend test have been used to verify the mechanical resilience of filaments. The tensile test applies mechanical stress in a longitudinal direction, while the three-point bend test in a transversal direction (51).

The specifications of the materials are going to depend on the type of materials. If the material is solid, common specifications are particle size, distribution and relevant rheological performance for powders, or filament diameter and diametric tolerances for filaments. In the case of a fluid material, viscosity or viscoelasticity are important or, in the case of a polymer or monomer mixture, the composition, purity, water content, molecular formula, chemical structure, molecular weight, molecular weight distribution, purity information, glass transition temperatures, melting and crystallization point temperatures are a few examples (5,47).

It is necessary to ensure that materials comply with standards created by entities, such as the International Organization for Standardization (ISO). Although a raw material may meet the ISO standards, the 3D printing process could create questions as to the biocompatibility and other materials properties of the finished product, because the materials could undergo polymerization or phase change depending on the 3D printing methodology (52).

A variety of materials can be used for 3D printing, as cellulosic derivatives, polymethacrylates, polyurethanes and polyvinyl alcohols (25,53–56). Ethylcellulose (EC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), poly(vinyl alcohol) (PVA), poly(lactic-co-glycolic acid), poly(methyl methacrylate) (PMMA), poly(methacrylates) (Eudragit®), polyurethane (PU), poly(ethylene glycol) diacrylate, poly(lactic acid) (PLA), polycaprolactone (PCL), poly(vinyl pyrrolidone) (PVP or Kollidon®), and acrylonitrile butadiene styrene (ABS) are a few examples of polymers that can be used in medical applications of 3D printing (25,53–56).

5.3 Process Validation

The validation plan and organization should ensure product quality, safety and efficacy all through its life cycle (57).

According to EMA guidelines on process validation for finished products, process validation is defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes. Process validation can be made following the ICH Q7[10], conducted under GMP and data should be held at the manufacturing location and made available for inspection if not required in the marketing authorization dossier. The process validation scheme to be followed must be incorporated in the dossier, where the scheme includes the description of the manufacturing process, the tests to be performed and acceptance criteria, a description of the additional controls in place and the data to be collected. The justification of the process validation scheme should be in Common Technical Document (CTD) Module 3. Data from a minimum of 3 production scale batches should be submitted unless otherwise justified (58).

As so, validation and verification systems are important, especially, in the case of custom designs, that have further potential for error or weakness, being vital to minimize the potential for error and contributing to assuring drug quality. Note that during process validation and qualification, the critical process parameters should be monitored (52,59,60).

Process validation can be made in traditional process validation, performed when the pharmaceutical development and/or process development is concluded, or it can be made in continuous process validation. In the case of continuous validation, Process Analytical Technology (PAT) applications as NIR spectroscopy, and Multivariate Statistical Process Control (MSPC) can be considered as enablers for continuous process verification. The validation can also be in a Hybrid approach, where is necessary to use either the traditional process validation or the continuous process verification approach for different steps within the manufacturing process (58,60).

According to process validation: general principles and practices by FDA, all parameters and attributes must be assessed in terms of their roles in the process and impact on the product or in-process material and revaluated as new information becomes available. The level of

[10] ICH Q7 on Good Manufacturing Practice.

control over those attributes or parameters should be proportionate with their risk to the process and process output, which means that a high degree of control is appropriate for attributes or parameters that pose a higher risk (59).

Software must be validated for its expected usage according to an established protocol because the software also has an important level in preserving a high level of accuracy. FDA defines software validation as the confirmation by examination and provision of objective evidence that software specifications fit in the user needs and intended uses, and that the requirements implemented through software can be consistently fulfilled. According to the general principles of software validation by the FDA, software validation can occur during and at the end of the software development life cycle to guarantee that all the requirements have been achieved (25,47,61).

Quality might change when using different printers (printing devices), even when the same model, parameters, process steps, and raw materials are used. Thus, the process must be validated with a high degree of confidence and certified according to established procedures to certify and sustain the quality of the products built in a single build cycle, between build cycles, and between printers. Factors as the temperature at the beam focus, melt pool data, environmental conditions as temperature, pressure and humidity, the power of the energy delivery system and the status of mechanical elements of the printing system should be considered when performing process validation (18,47).

Test methods used for procedure monitoring and control must also be validated. For instance, the analysis should be done to confirm that the test sample used is representative (47).

The individual dosage forms obtained by 3D printing, assessed with non-destructive methods, may be tested for compliance specifications. A single failed component in a build cycle may not require the elimination of all other components within that building cycle. The principles for deciding whether to reject a single component or the entire batch should be established before testing (47).

5.4 Process controls

The 3D printing process could be adjusted in a way that quality control is integrated into the manufacturing process itself. The quality systems should be able to take measurements at a

rate that is suitable to the specific type of printing and the length of the manufacturing process (10,44).

In research studies, it has been noted a phenomenon called the First Layer Effect (FLE), that when the first layer is deposited on the build plate, the fluid melt spreads sideways, increasing in width and decreasing the thickness. In summary, the first deposited layer tended to have different morphology to the layer above (29).

Printing medicines combined with suitable online, in-line or at-line measurement of critical quality attributes and proper feedback loops can improve the production efficiency by allowing real-time release testing. Typically, spectroscopic tools as near-infrared (NIR) spectroscopy, X-ray, Raman and Fourier-Transform Infrared (FTIR), are used for real-time measurement of API content, polymorphism, degradation, air entrapment and other properties. Temperature sensors, image sensors, ultrasound, hyperspectral imaging and lasers can also be used for real-time measurement (10,43).

3D printing requires a reference trajectory, which is defined as a set of points for the axes to follow to trace the as-designed shape, but currently, there are no printers available with closed-loop process control monitoring the material placement. To solve this issue, sensors, as x-ray imaging, diffraction and optical microscopy, can be used to monitor the material placement (62).

Image analysis is also being studied to be used to process control, in a way that can be incorporated into the 3D printing process, leading to multiple images of the process that can be, in real-time, compared with the virtual model (CAD model) of the 3D-printed geometry through a proper image software analysis. This leads to the interruption of the printing when an error occurs, followed by an investigation of the error source and for performing corrective actions. Thermal imaging can be as well used as a process control to check for potential hotspots and provide an early alert for potential degradation (21).

Taking, for example, the case of FDM, to monitor in real-time mode the homogeneity of drug distribution during the extrusion process, it would be beneficial to use non-destructive analytical techniques. Near-infrared spectroscopy has been used to detect the variation in drug load in extruded FDM filament feedstock and films, although Raman spectroscopy has been used for drug load quantification in hot-melt extrudates during processing (21).

There are a few examples of possible process controls, for each technique, described in table 3 (17).

Table 3: Examples of manufacturing risks, process and raw material controls and typical quality defects, adapted from (17).

Type of 3D printer	Manufacturing risk	Process control	Raw material control and intermediate material properties	Typical quality defect
Inkjet printing	Variable layer thickness	• Software control; • PAT; • Material feed rate; • Base plate speed and powder roll speed.	• Particle size and shape; • Porosity; • Surface charge; • Moisturise content.	Friable tablets, banding (ripples on the product side).
	Inconsistent print droplet formation	• PAT; • Parametric control as drop velocity, voltage gap or temperature.	• Binder/fluid viscosity; • Binder surface tension; • Dynamic viscosity.	Friable tablets, disintegration, and dissolution.
Fused Deposition Modelling	Clog, uniformity problem due to undesired melt viscosity.	• PAT; • Parametric control as nozzle diameter, pressure, temperature, and head speed; • Cooling rate and temperature.	• Filament uniformity; • Glass transition temperature; • Viscoelastic properties; • Polymer mechanical properties.	Dissolution, content uniformity, degradation.
Stereolithography and Selective Laser Sintering	Variable layer thickness, degradation.	• Power and speed of the laser; • Beam diameter and powder deposition rate.	• Particle size; • Polymer miscibility with API; • Amorphousness.	Laser-induced degradation, content uniformity.

5.5 Quality assurance

Quality assurance could be a more challenging issue for 3D printing than it is for traditional methods of manufacturing (52).

Even performing the proper quality controls through the printing process, variations in the final printed drug product can still appear (both intra-batch as well as inter-batch). Therefore, the 3D printing manufacturing process should preserve a state of control to offer assurance of product quality. Unexpected software malfunction, uncontrolled modification in process variables, such as print head voltage gap, print head clog, roller speed, powder bed alignment, print head alignment, laser power and temperature, are examples of situations that could happen and is necessary to understand so that the manufactured product meets the predefined quality attributes (10,18).

Drug product specifications should follow the principles of the ICH Q6[11] guidelines. Additional quality attributes for the 3D printed manufactured drug product may apply, supplementing the typical quality attributes that are appropriate to the dosage form, like thickness, mass uniformity, water content and content uniformity. These methods should be performed according to the European Pharmacopoeia monographs (10,16,63,64).

The use of FTIR spectroscopy to characterize the materials has been reported in some research papers. Thermal analysis as the DSC and the Thermogravimetric Analysis (TGA) are methods that have been used to test the raw materials, the physical mixes and the 3D printed dosage forms, that investigates the thermal properties, to obtain information about how the formulation changed during the different processing steps (29,64,65).

A Scanning Electron Microscopy (SEM) has been used to take images of the surface and cross-section of the printlets, giving visual information on the internal structure of the printed dosage forms. X-ray Powder Diffraction (XRPD) has been used to assess the physical properties of the crystallinity of the individual powder, powder mixture, filament and the 3D printed final dosage form (9,16,66).

Raman Spectroscopy has been already used to analyse and map the flat surface of the content of a 50% printed formulation, creating a detailed chemical image. This method can also be used to identify polymorphs, if suitable with the materials of the formulation (19,66).

[11] ICH Q6 on Specifications.

X-ray Micro Computed Tomography, or Micro-CT, has been utilized to analyse the internal structure, density and porosity of the 3D printed dosage forms and is used to calculate their porosities. This method is utilized to confirm that the design of printed objects is properly reconstructed (16,55).

The drug content, as well as impurities, can be assessed by using a High-performance Liquid Chromatography (HPLC). The *printlets* can be dissolved in flasks containing HPLC water, making this method a destructive analytical technique. The analysis is performed according to the regulatory requirements (Pharmacopoeial and/or other), as well as the method validation (16,30).

If applicable, dissolution and disintegration tests can be conducted using, for example, a Ph.Eur./USP-II apparatus and a Ph.Eur./USP disintegration apparatus, respectively. In the dissolution test, can be used an ultraviolet (UV) spectrophotometer to determine the percentage of drug release. Dissolution profiles are visualized by plotting the percentage of dissolved drug dissolution against time. The disintegration tests evaluate the time needed to completely disintegrate the dosage form (16,67).

An alternative method to quality control could be the incorporation of real-time release (RTR) testing, that is, the capability to assess and guarantee the quality in-process and/or final product based on process data. NIR spectroscopy is an example of a technique that can be used, because is a non-destructive technique, unlike most of the methods widely used in quality control, and it can be incorporated at the point of dispensing due to its portability (68).

The properties can also be disturbed by post-processing steps, that is, manufacturing steps occurring after the printing process, for instance, eliminating manufacturing excesses from the printed dosage form, heat treatments to relieve residual stress or final machining. As so, procedures for monitoring and controlling process parameters must be created and preserved for validated processes to certify that the specified requirements continue to be met (47).

The quality control of the final product can be summed up in the characterization of the morphology, as the diameter and visual appreciation, determination of the drug content, *in-vitro* dissolution testing and a method suitable to evaluate the printing accuracy and internal structure. Then, there is also “case-specific” tests that can be necessary according to the specificity of the drug dosage (30).

5.5.1 Quality by Design

The design of experiments (DoE) is a component of the quality by design (QbD), to reach a better process and product understanding through the perception of the relationship between the input factors and response parameters (69).

According to the ICH guideline Q8 (R2) on pharmaceutical development, QbD is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. QbD can lead to a reduction of waste, time and cost through early detection of errors during the design and fabrication processes of the 3D printed products (70,71).

The QbD approach is an eight main steps process that follows in a systematic way that can provide a deep understanding of the product and its manufacturing process, including the identification and control of all variables to ensure the desired quality. These steps are the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA), process flow diagram, Critical Process Parameters (CPP) and attributes (CMA), risk management, design space, design and implement a control strategy and development of strategies for product lifecycle management and continuous improvement (70).

Printing drug products under the framework of quality by design (QbD) can considerably improve product quality and simplify the drug supply chain (43).

5.5.1.1 Quality Target Product Profile (QTPP)

Starting with the Quality Target Product Profile (QTPP), it is described as a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account the safety and efficacy of the drug product (71).

QTPP may be the intended use in a clinical setting, route of administration, dosage form, delivery systems, dosage strength(s), container closure system, therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics as dissolution or aerodynamic performance, suitable to the drug product dosage form being developed. Drug product quality criteria, as sterility, purity, stability, or drug release proper for the intended marketed product can also be included in the QTPP (71).

5.5.1.2 Critical Quality Attribute (CQA)

In terms of Critical Quality Attribute (CQA) and according to ICH Q8(R2) on Pharmaceutical Development, is defined as a physical, chemical, or biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure desired product quality. CQAs are usually associated with the drug substance, excipients, in-process materials, and the drug product (71).

PAT tools can be applied to measure the CQAs in real-time, to guarantee the quality that complements the process control for keeping the CPPs in their defined specifications (72).

In the development of the filaments, the filament diameter, as well as the diameter consistency, are CQAs, affecting the quality of filaments and the printed dosage forms. In the literature, the target diameter is achieved by stretching and cooling the filament on conveyer belts and a winder could be implemented to optimize the filament fabrication (49).

In the printing process itself, the printing accuracy, infill density, drug loading, drug dissolution profile and dimensions are examples of CQAs with the greatest probability of creating a product failure (56,73).

5.5.1.3 Critical Process Parameters (CPP) and Critical Material Attributes (CMA)

For the manufacturing process of a 3D printed product, accurate design and fabrication techniques are needed to keep precise control of their dimensional, mechanical, biological, functional, and physicochemical properties. The identification of Critical Process Parameters (CPP) and Critical Material Attributes (CMA) help to determine process parameters and material attributes whose variability can potentially affect CQA, which should be monitored and controlled to ensure process consistency, repeatability, and accuracy. CPPs can be materials related, operation related, or machine-related, for example (18,70,73).

Parameters as needle size, ink viscosity and deposition speed are examples of parameters that should be monitored during the printing process. In the case of extrusion-based printing, is necessary to understand which polymers are suitable for the process, to determine the interactions between the polymer and the drug substance and their impact on the printing process (73).

An Ishikawa (fishbone) diagram (figure 8) identifies potential variables which can have an impact on the desired quality attribute and allowed the identification of the CQAs that have the

greatest chance of leading to product failure, while also prioritizes the possible risk factors associated with the CMAs and CPPs (71,73).

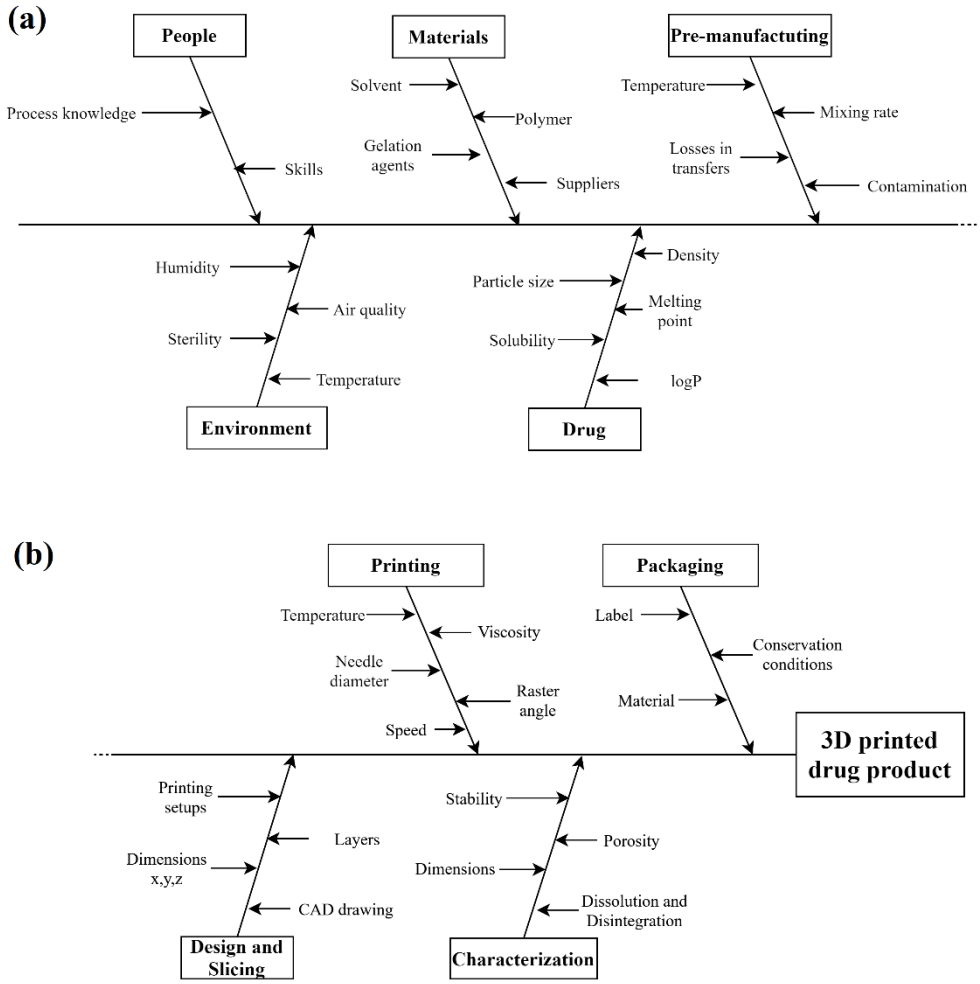

Figure 8: Ishikawa diagram representing the factors that can have an impact on the development of a 3D printed drug product, adapted from (73)**.**

5.6 Stability studies

According to ICH Q1A (R2): stability testing of new drug substance and products, stability tests are performed to give evidence on how the quality of a drug substance or drug product will change with time under the influence of a range of environmental factors as light, humidity and temperature, and to establish a re-test period for the drug substance or to determine the shelf life for the drug product, as well as the recommended storage conditions (74).

The test conditions are defined according to the climatic zone and the study can be accelerated, intermediate or long term, all with different storage conditions and minimum period (74).

As 3D printing can lead to exposure to heat, UV light, water, or free radicals during the process, it can create a risk of affecting the drug stability in the formulation (75).

Some research articles report accelerated stability studies (stability studies performed at higher temperature and relative humidity). Visual inspection, (ultraviolet-visible) UV-VIS spectroscopy for drug content or HPLC, DSC, ATR-FTIR and mechanical analysis are examples of tests performed to assess the stability, however, the articles do not describe the batch size (5,76).

In the articles, the studies performed have a duration of four weeks, since the authors considered it to be enough period for follow-up. However, this period is not in-line with the current regulatory requirements for industrial drug products which state a period of 6 months. The long term stability tests are not commonly performed in these 3D drug products since nowadays they are intended for personalized medicines prepared as extemporaneous formulations, which means that only have to be stable for a few weeks or months after manufacturing (5,74,76).

5.7 Location

Traditional manufacturing methods take place in industrial setups in most cases. In the specific case of 3D printing, it is possible to print innovative products, in small batches and to provide for niche markets (18).

As shown in figure 9, the pharmaceutical industry can supply the starting material and then the printing be in the pharmacy, or both steps could be in the industry, if suitable (18).

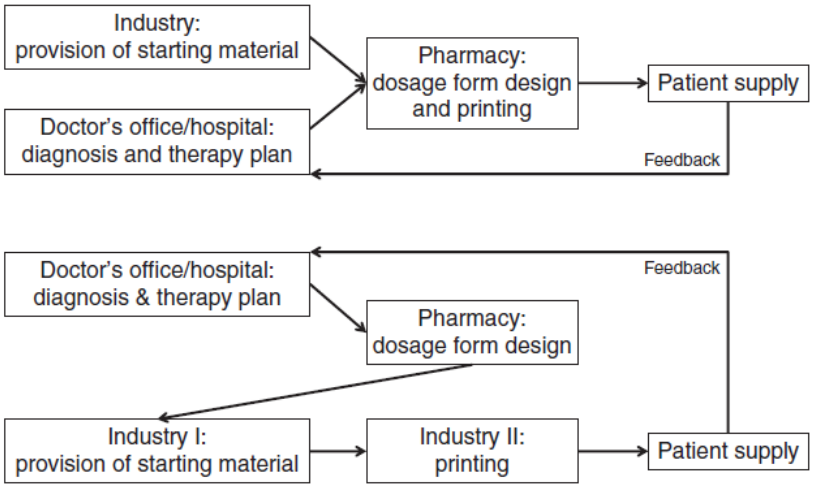

Figure 9: two of the possible scenarios of the location of 3D printing in the healthcare system, adapted from (18).

There is also the hypothesis of printing at the point of care, which has the major advantage to the patient, in terms of convenience, allowing the hospital and pharmacies to manufacture the medications for the patient immediately after consultation, which can be particularly useful in the case of remote areas. In this scenario, the health care professionals could have immediately the patient feedback and the patient will benefit sooner from the tailored dosage form. In short term, it will bring pharmaceutical drug delivery and manufacturing near the patient, facilitating treatment corrections. Investments costs and annual costs for preservation and quality are some factors that will have an influence when selecting the printing method to be implemented in a hospital (9,18,76).

In the literature, is also mentioned that in the future it could be possible to print at home, that is, the patient could print their drug products. According to Maniruzzaman (18), in this situation the printer needs to have security systems, that is going to be operated and controlled by the responsible medical doctor in his office. In my opinion and according to the Portuguese Pharmacists Society, the task of assuring medication safety, as well as guaranteeing good manufacturing practices it's the responsibility of the pharmacist, not for the medical doctor (18,77). Anyway, the process of printing at home would not be considered safe and appropriate, because of the potential issues and risks that this option would bring, for instance, who would be supervising the manufacturing process (17,18).

6 Conclusions

The increased interest in 3D printing is a reality nowadays, as this technology represents a new tool that can be used for personalized therapy, suitable to meet the patient needs.

This technology can be represented as a key solution, that brings so many new hypotheses to solve formulation issues like the possibility to print drug products with various active pharmaceutical ingredients minimizing instability, incompatibility, or physical interactions issues, and/or the opportunity to have a drug product with various release profiles of the drug substances. However, there are not only benefits associated with this technology. There are also some challenges associated with this methodology.

Although there is an approved 3D printed medicine, Spritam® (since 2015 by FDA), nowadays there is still no specific regulation for pharmaceutical 3D printing. As so, it is necessary to adopt the current guidelines.

The raw materials that can be used are also limited because of their printability and physicochemical stability.

Establishing a process control would be advantageous to detect anomalies in the process as soon as it happens. As so, the printing process should adopt a real-time control and ideally with a non-destructive method.

The process validation should be schemed in a way to ensure the quality, safety, and efficacy of the final printed drug product. Quality assurance could also be challenging, because of the variability that can still be present on the final product despite the accurate proper process control. Like in process control, quality testing should be performed by using non-destructive methods. To improve product quality and simplify the drug supply chain, quality by design can be used as a precious tool.

Stability studies should also be performed, bearing in mind that 3D printing can lead to exposure to heat, UV light, water, or free radical, creating a risk of affecting the drug stability in the formulation.

The location in the supply chain is a question that has been arisen, as it could have a place in the pharmaceutical industry, in hospital or community pharmacy or, in a more remote hypothesis, at a patient’s home.

There is still a lot of work to do and things to established. 3D printing could be a reality in our lives and a current practice in the pharmaceutical field, however, these challenges must be taken into account, solve and established the parameters that are pointed out and then, take full advantage of what this technology has to offer.

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