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Abstract: 3D printing, and particularly fused deposition modeling (FDM), has rapidly brought the possibility of personalizing drug therapies to the forefront of pharmaceutical research and media attention. Applications for this technology, described in published articles, are expected to grow significantly in 2020. Where are we on this path, and what needs to be done to develop a FDM 2.0 process and make personalized medicines available to patients? Based on literature analysis, this manuscript aims to answer these questions and highlight the critical technical aspects of FDM as an emerging technology for manufacturing safe, high-quality personalized oral drug products. In this collaborative paper, experts from different fields contribute strategies for ensuring the quality of starting materials and discuss the design phase, printer hardware and software, the process, the environment and the resulting products, from the perspectives of both patients and operators.

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Sarah Trenfield
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Guest Editors
International Journal of Pharmaceutics

Milan, July 21st 2020

Subject: manuscript submission

Dear Editors,

on behalf of co-authors and following your kind invitation, we are pleased to submit for publication in the Special Issue "Innovations in 2D and 3D printed pharmaceuticals" of International Journal of Pharmaceutics our review article entitled "Quality considerations on the pharmaceutical applications of fused deposition modeling 3D printing" by Alice Melocchi, Francesco Briatico-Vangosa, Marco Uboldi, Federico Parietti, Maximilian Turchi, Didier von Zeppelin, Alessandra Maroni, Lucia Zema, Andrea Gazzaniga, Ahmed Zidan.

The present manuscript, covering over 200 literature references, is the result of a collaborative work involving researchers from academy, industry and regulatory agency (CDER-FDA), who in-depth discuss the critical aspects of 3D printing by fused deposition modeling (FDM) as an emerging technology for manufacturing safe, high-quality personalized drug products. Indeed, 3D printing provided the tool for

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implementing precision medicine, bringing it to the forefront of pharmaceutical research.

In this review article, we made an effort to carry out comprehensive literature analysis of the quality aspects involved by the FDM technique. Sections of the Manuscript were purposely dedicated to the challenges that should be addressed to implement FDM in the fabrication of personalized drug products suitable for oral administration, including geometric design of the dosage form, equipment, raw materials, controls, environment, risks to the operator and regulatory engagement.

Also on behalf of co-authors, we hereby declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere, it does not report on any animal or human *in vivo* experiment, there are no known conflicts of interest associated with publication and the contents have been read and approved by all named authors.

Sincerely Yours,

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Quality considerations on the pharmaceutical applications of fused deposition modeling 3D printing

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Guest Editors International Journal of Pharmaceutics

We would like to thank the Reviewers for appreciating our work and providing helpful comments. Please find below a point-by-point outline of how the manuscript has been modified accordingly.

Reviewer #1:

The manuscript is timely and well written. The structure of the review is very good. The vast majority of the references from the groups that are active in the field are covered and are well represented. The authors set the stage with the case for needing precision medicine which can be materialized by means of 3D printing technology.

Then provide a very good discussion for the technological challenges of FDM, regulatory landscape and the potential health risks for the operators. I particularly like the later as it is rather neglected as a topic although of great importance for the health of the operators. As such I have minor comments to make this a more rounded manuscript.

Typo error line 55 'challenges" instead of challanges

Please improve the quality of the figures.

Following the Reviewer's suggestions, we have checked the Manuscript for typos and improved the quality of the Figures by increasing their resolution.

Reviewer #2:

Overall comments:

The manuscript is well-written and provides a comprehensive overview of attempts to prepare 3DP of pharmaceutical dosages forms and characterisation techniques. It also describes some of the limitations and challenges experienced so far and provides suggestions for approaches to overcome these. As such it is suitable for publication however, a number of comments are provided that the authors should consider addressing:

- Line 164 - clarify what is meant by: "extend patency on the drugs involved"

  We made an effort to improve the text.
- Lines 166 and 167 - this statement doesn't make sense and further clarification should be provided.

  Following the Reviewer's suggestion, we changed the text in order to better clarify the concept.
- Comments on section 1.2 - while Spritam is a 3D printed medicine, it is not considered as a personalised medicine (precision medicine) as all dosage forms prepared during the manufacture contain the same quantity of drug. This should be highlighted by the authors. Rather than being used to prepare a personalised medicine 3DP was leveraged to achieve a niche critical quality attribute (an extremely rapidly disintegration ODT) which meets the requirement of the need to rapidly administer of levetiracetam to epileptic patients suffering from seizures.

  We agree with the Reviewer that the description of Spritam as the first 3D printed drug product on the market was neither comprehensive nor effective. We made an effort to include all the suggestions provided in the text.
- Lines 210-212 the authors intimate that photocuring of polymers with UV light would result in difficulty of preparing safe and efficacious dosage forms but do not provide an explanation which should be provided.

  We have amended the text in order to improve the relevant clarity.
- Lines 252-253 - the authors should also mention the risk to the physical stability of the API including the polymorphic form; e.g. change in polymorphic form at higher temperature, or formation of an amorphous form which then recrystalises over time. Physical stability of the API is of key importance for OSDs and this should be addressed.

  We agree with the Reviewer about the importance of the physical stability of drugs and we have modified the text accordingly.
- Lines 289 - 300 - supply chain and pricing should also be considered - good to see abuse and counterfeiting are mentioned.

The text was implemented following the Reviewer's suggestion.

- Lines 301-302 - In terms of multidisciplinary collaborations, the authors should provide examples of the key disciplines that would be required (e.g. regulatory, pharm sci, manufacturing, analytical, QA, supply chain, community health care professionals)

  The text was implemented following the Reviewer's suggestion.
- Lines 403 - is it really fair to say that benchtop 3D FDM printers have reduced the quality of printed objects e.g. by lowering resolution compared to industrial printers? Maybe the initial FDM desktop printers were not producing high quality printed parts but the technology is evolving and desktop printers are improving all the time?

  We agree with the Reviewer that FDM printers have improved over time, leading to better quality of the resulting products, at least in terms of physical appearance. However, the improvements achieved are still far away from the characteristics that industrial equipment would be able to provide the final object with, especially with respect to printing reproducibility when small details are involved. By way of example, the Arburg droplet-based deposition process enables fine-control of the pressure on the material within the extruder, the dimensions of each single molten drop to be deposited and the frequency with which these are layered down. We made an effort to highlight progresses undergone over time by desktop 3D printers and emphasize the above mentioned concepts in the text.
- Table 1 - this is a helpful table - the authors could consider adding an additional column indicating how the issues identified could adversely impact the critical quality attributes of the printed dosage form.

  We implemented Table 1 with the additional information requested by the Reviewer. This was introduced in the third column, previously entitled as "Issues" and currently named as "Issues and relevant impact on the product".
- Line 440 - "plasticate" is not a real word. Suggest "plasticise" instead?

  We amended the text substituting the word plasticate with plasticize.
- Line 443 - the authors state that the Freeformer equipment was developed from Injection Moulding technology, however, the process described does not relate to injection moulding whereby a semi solid or liquid material is injected into a mould and allowed to cool. The authors should highlight and clarify in the manuscript precisely how the Freeformer equipment works differently from an injection moulding process.

  Following the Reviewer's comments, we made an effort to highlight and clarify in the text similarities and differences between the working mechanism of the Freeformer equipment and

that of an injection molding press. In particular, we highlighted how the new additive manufacturing process is based on the deposition of droplets directly within the build chamber.

- Table 2. the authors should consider the polymer composition and its propensity to exhibit either thermal expansion or contraction post extrusion - in the table this is more simply described as "must keep their shape". DSC, PXRD and IR are listed in the commentary but should also be included in the table which is quite broad and non-specific. Chemical analysis (e.g. by HPLC) should also be included to confirm assay and related substances are not impacted by the filament forming and/or printing processes.

  Following the Reviewer's comment, in Table 2 we clarified what we meant writing that the "deposited layers should keep their shape". Actually, Table 2 was built on purpose around filament thermo-mechanical requirements only, as a comprehensive summary of the latter characteristics was lacking in the literature available. Such a choice was better highlighted in the text introducing the Table itself. For this reason, we preferred to discuss the specific use of DSC, PXRD and IR and chemical analyses in the text of Section 2.3, which was improved in agreement with the Reviewer's comments.

- Line 616 check reference - Goyantes et al 2018 (should be Goyanes et al?)

  The Reviewer is right and we corrected the text accordingly.

- Lines 631-634 - the use of mathematical models to predict quality attributes may have some value as a theoretical derisking exercise but analytical testing would be required in order to ensure that the dosage forms manufactured possess the attributes required to support release.

  We agree with the Reviewer that analytical testing of the final dosage forms will be always needed to ensure their quality. In this respect, mathematical models can help in decreasing the number of analyses to be performed, especially when dealing with pre-validated products, thus limiting costs and time for batch releasing. We made an effort to improve the clarity of the text and to highlight the merely derisking capabilities of mathematical models.

- Line 648 - generation of a library of critical quality attributes is not required - the critical quality attributes of oral solid dosage forms are already defined and very well understood. The key to the success of 3DP will be identifying the relevant critical process parameters which impact the CQAs and ensuring that these parameters remain within defined ranges which have been agreed with the regulators.

  We agree with the Reviewer's comment on critical quality attributes and critical process parameters and we modified the text accordingly.

- Section 2.5 - Environment

In general there is not enough information provided in this section with respect to where 3D printers could be employed to fabricate oral solid dosage forms. There is no business case for constructing new "facilities" for 3DP when GMP manufacturing areas are already well established and 3DP could simply be brought in as an alternative manufacturing process. There is no mention of the doctor's surgery, or community and hospital pharmacies or even the patient's home as alternative locations which would also require separate bespoke solutions for 3DP of medicines.

In this manuscript, we discussed in a critical way the scientific literature available and we presented our point on the future of 3D printing by fused deposition modeling, also hypothesizing where fabrication of personalized medicines will occur. In this respect, we described the environment in which 3D printing of high-quality and safe dosage forms would be desirable to be performed. This was envisaged to be an industrial-like environment characterized by a quality-oriented mindset.

Resorting to compounding/galenical practice and extemporaneous formulations within compounding/hospital pharmacies was initially proposed in the literature as a suitable alternative for regulating 3D printing of personalized drug products. However, this choice would currently result in poor quality control, in view of the limited resources/instrumentations available within these facilities. Moreover, the chance to decentralize printing infrastructures, i.e. availability of printers at home and in small clinics to be operated either by the patients themselves or remotely/in person by healthcare professionals, would raise too many issues not only in terms of quality but also of responsibilities.

From our point of view, 3D printing could be simply brought into GMP manufacturing areas, but these would also need to be improved to fulfill specific safety requirements (e.g. presence of filters dedicated to the 3D printing environment). For this reason, we discussed the possible scenario of more widespread dedicated 3D printing facilities on the territory, thus easing production on demand and distribution of personalized drug products with respect to centralized GMP production sites.

- Section 3 - the authors should mention that appropriate cleaning methods would need to be developed for 3DP in order to ensure that cleaning verification could be completed (in combination with the use of appropriately validated analytical methods) after manufacture of batches of 3DP tablets have been completed. This would be particularly important if the same printer was required to be used to print multiple different formulations with different drug substances. The other points raised are valid and could be managed within a GMP

manufacturing environment. How this would translate to the pharmacy / community setting would be more challenging.

Following the Reviewer's suggestions, we mentioned in the text the need for implementation of purposely-developed cleaning procedures.

- Lines 779 - 780: "FDA is a member of America Makes and participates in research, standards…" - this sentence does not make sense.

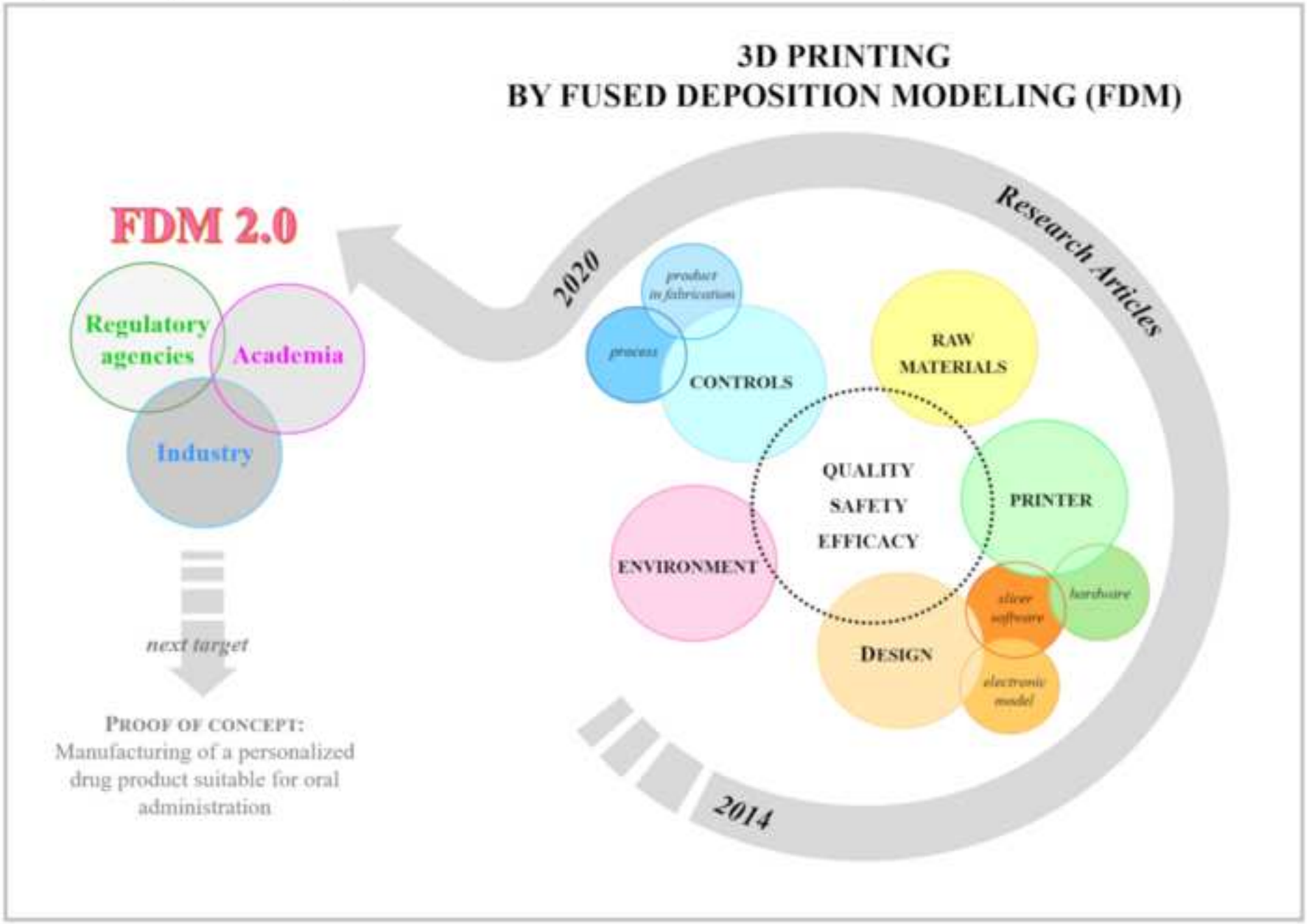
  The Reviewer is right and we corrected the sentence.

- Line 806 - the question mark is not needed.

  The Reviewer is right and we removed the question mark.

*Graphical Abstract (for review)

…portrait of the state of the art



Quality considerations on the pharmaceutical applications of fused deposition modeling 3D printing

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DISCLAIMER

This presentation reflects the views of the authors and should not be construed to represent the FDA's views or policies.

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Abstract

3D printing, and particularly fused deposition modeling (FDM), has rapidly brought the possibility of personalizing drug therapies to the forefront of pharmaceutical research and media attention. Applications for this technology, described in published articles, are expected to grow significantly in 2020. Where are we on this path, and what needs to be done to develop a FDM 2.0 process and make personalized medicines available to patients? Based on literature analysis, this manuscript aims to answer these questions and highlight the critical technical aspects of FDM as an emerging technology for manufacturing safe, high-quality personalized oral drug products. In this collaborative paper, experts from different fields contribute strategies for ensuring the quality of starting materials and discuss the design phase, printer hardware and software, the process, the environment and the resulting products, from the perspectives of both patients and operators.

Keywords: 3D printing, fused deposition modeling, drug product fabrication, quality, safety.

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1. Introduction

1.1 Overview of 3D printing through 2020

3D printing began officially in 1984, with the approval of the first stereolithography patent (Hull, 1986). However, this technology did not achieve widespread adoption for more than 10 years, as its use was limited by numerous other patents (https://www.wipo.int/edocs/pubdocs/en/wipo_pub_944_2015.pdf). Only after the patents' expiration did desktop 3D printers become easily available on the market, resulting in the birth of the consumer 3D printing community. Thereafter, the 3D printing industry, encompassing not only companies employing printers but also those building them, grew very quickly. It is likely to reach a market size of more than $17 B in 2020 and is expected to increase to $34.8 B by 2024 (https://www2.deloitte.com/content/dam/Deloitte/de/Documents/operations/Deloitte_Challenges_of_Additive_Manufacturing.pdf; https://downloads.3dhubs.com/3D_printing_trends_report_2020.pdf; https://www.grandviewresearch.com/industry-analysis/3d-printing-industry-analysis; https://www.marketsandmarkets.com/Market-Reports/3d-printing-market-1276.html; https://www.marketresearch.com/Expeditious-Research-v4071/3D-Printing-Outlook-9903905/). This expected continuous growth spurred venture capital funding of 3D printing-related startups, which exceeded $300 M in 2019.

In its evolution, 3D printing has shifted from being considered just a prototyping tool, to being employed as the additive manufacturing (AM) method of choice for low-volume batches of high-value products. For such products, the upfront investment in tooling required by subtractive methods would not be cost-effective (Ford and Despeisse, 2016; https://nvlpubs.nist.gov/nistpubs/SpecialPublications/NIST.SP.1176.pdf). Moreover, novel interesting applications have been identified. These include printing of metals and electronics to reduce assembly time and human labor in the manufacturing of sensors; generative design in the fields of art, architecture, communication and product design (*i.e.*, a fast method to explore design

possibilities providing physical prototypes to simplify visualization); and 4D printing (*i.e.*, the fabrication of objects capable of changing their shape in response to an external non-mechanical stimulus) (Lukin et al., 2019; Maroni et al., 2019; Mehrpouya et al., 2019; Melocchi et al., 2019a; Savolainen et al., 2020; Trenfield et al., 2019a).

Given the improvement of 3D printing and the widespread awareness that it can help connect marginalized and difficult-to-reach populations with essential products, several industries (including automotive, defense and healthcare) have begun to experience 3D printing-related production, business and supply-chain transformations (Chan et al., 2018; Despeisse et al., 2017; Ghobadian et al., 2020). In this respect, the percentage of companies using AM for specific production purposes increased from 24% to 65% in 2019 (https://assets.ey.com/content/dam/ey-sites/ey-com/en_gl/topics/advisory/ey-3d-printing-game-changer.pdf; https://cdn2.hubspot.net/hubfs/5154612/downloads/Sculpteo_The%20State%20of%203D%20Printing_2019.pdf). At the same time, the news media started to pay great attention to 3D printing and to incorporate it into the concepts of the fourth industrial revolution and a new manufacturing renaissance (Baines et al., 2019; Berman, 2012; Garret 2014; Prince, 2014).

Despite the initial enthusiasm about 3D printing technology, its actual application potential in different industries is only now beginning to be tested in depth (Achillas et al., 2015; Anton et al., 2014; Bogers et al., 2016; Culot et al., 2019; Garmulewicz et al., 2018; Huang et al., 2013; Kleer et al., 2019; Mir and Nakamura, 2017; Petrick and Simpson, 2013; Rehnberg and Ponte, 2016; Tran 2017; Yao and Lin, 2015). In particular, due to a few technological bottlenecks such as production speed, as well as cost and labor associated with pre- and post-printing operations, 3D printing currently is filling a niche as a complement to other existing manufacturing processes. In this context, the unique capabilities of 3D printing in terms of on-demand and delocalized production, product customization and realization of complex designs might find their full application.

1.2. 3D printing for precision medicine

In parallel with the increasing attention to 3D printing in many different areas, scientists have been investigating its suitability for the manufacturing of drug products enabling precision medicine, for the treatment of subpopulations with specific needs even of a single patient (*i.e.* personalized drug products) (Alhnan et al., 2016; Economidou et al., 2018; Jamróz et al., 2018a; Kjar and Huang, 2019; Musazzi et al., 2020; Trenfield et al., 2018a, b; Zhang et al., 2018). Indeed, the concept of precision medicine, an emerging approach regarding treatment and prevention of illness that accounts for each individual's genes, environment and lifestyle, is completely transforming the healthcare field (Collins et al., 2016; https://ghr.nlm.nih.gov/primer/precisionmedicine/definition; https://www.fda.gov/drugs/precision-dosing-defining-need-and-approaches-deliver-individualized-drug-dosing-real-world-setting; https://www.fda.gov/Drugs/NewsEvents/ucm132703.htm; Lamichhane et al., 2019; Mirza and Iqbal, 2018; Rahman et al., 2018). For instance, the importance of genomics has been highlighted in clinical decision making and for identifying optimal pharmacological treatments (Alomari et al., 2015; Kaae et al., 2018; Menditto et al., 2020; Radhakrishnan et al., 2020). However, an unmet need exists in the caring cycle for drug products tailored to the variables identified as crucial for a specific subject. In this respect, 3D printing is described as one of the most cost-effective alternatives for moving from mass production (*i.e.*, a one-size-fits-all approach) to fabrication of small batches that are not all the same (Aquino et al., 2018; Awad et al., 2018; Chandekar et al., 2019; Fastø et al., 2019; Goole and Amighi, 2016; Goyanes et al., 2017; Kjar and Huang, 2019; Liang et al., 2019). Indeed, 3D printing would enable: *i)* personalization of the amount of active ingredient in a drug product, *ii)* achievement of high drug loads, *iii)* co-administration of drugs in the same dosage form, *iv)* avoidance of the use of specific excipients in cases of intolerance, *v)* modulation of the release kinetics of drugs, and *vi)* definition of the flavor and other aspects of drug products in order to improve patient compliance, for instance favoring swallowability, especially from a psychological point of view. Adjustments and modifications needed would be made possible by real-time changes in the digital models of

products and process parameters (*e.g.*, number of shells, infill percentage, layer overlap), as discussed extensively in the recent literature (Trenfield et al., 2018a, b, 2019; Joo et al., 2020; Norman et al., 2017; Zema et al., 2017). A new and exciting possibility with AM is the manufacturing of medicines on demand and at the point of care, thus removing the need for long-term storage and stability studies. In addition, 3D printing can easily be adapted to fulfill the need for continuous manufacturing, taking advantage of the limited space required to set up a production facility (Cunha-Filho et al., 2017; Desai et al., 2017; Mascia et al., 2013; Melocchi et al., 2015a; Puri et al., 2017; Zhang et al., 2017a). In this respect, it may be possible to implement an innovative AM-based approach to larger-scale production.

The availability of customized drug products not only would decrease healthcare system expenses associated with side effects and hospitalization, but it also may be of utmost importance for patients with special needs (Norman et al., 2017; Hsiao et al., 2018). These patients include, in particular, those affected by rare diseases, children, the elderly, the poor or the high metabolizers, individuals with illnesses affecting elimination organs and people taking multiple medicines. Indeed, concomitant use of numerous prescription drugs, or polypharmacy, has largely increased in recent years. Combination products, in addition to enhancing patient adherence, also have the potential to extend commercial interest in specific drug molecules after the expiration of the relevant patents and improve cost-effectiveness by creating a single product pipeline. This would reduce the costs associated with packaging, prescribing and dispensing. Moreover, the design versatility of 3D printed products makes it possible to formulate non-compatible molecules within separated compartments of the same dosage unit.

Finally, 3D printing may become an effective tool in the near future for developing telemedicine (Araújo et al., 2019; Johnson and Brownlee, 2018; Wang and Kricka, 2018; Wen, 2017). This is defined as the remote delivery of healthcare services (*i.e.*, consultation, diagnosis, intervention, monitoring and education) by taking advantage of communication technologies whenever physicians and patients are not physically close. Telemedicine could advantageously be integrated

with other technological advancements, such as smart health monitors, mobile applications and cloud-based computing, which would allow physicians to evaluate patient health in real-time and to collect any data about modifications of the status quo. Telemedicine could also provide a tool to enable the adjustment of the pharmacological treatment when needed. In this respect, an FDM printer, supplied with the necessary raw materials and remotely controlled, may become a crucial element in making home therapy possible.

Despite the great potential for 3D printing to change current treatment strategies, one 3D-printed drug product is on the market, *i.e.* Spritam. It consists of fast-dissolving tablets containing levetiracetam, manufactured by the binder jetting technology initially developed in the late 1980s in the labs of the Massachusetts Institute of Technology and then fully redesigned by Aprecia Pharmaceuticals (Alhnan et al., 2016; https://www.spritam.com/#/hcp/zipdose-technology/what-is-zipdose-technology). This 3D printing technique was selected to give a specific quality attribute to the product, *i.e.* an extremely rapid disintegration, which increases the dissolution rate and improves the bioavailability of the drug, enabling better treatment of epileptic patients suffering from seizures. Although Spritam is available on the market in few different dosages, all the units belonging to a single batch contain the same drug strength. Therefore, it may not be considered a personalized medicine. Indeed, it was approved by the U.S. Food and Drug Administration (FDA) in 2015 through a traditional regulatory pathway, after years of research aimed at making the technology suitable for mass manufacturing (Goole and Amighi, 2016; Boudriau et al., 2016; Preis and Öblom, 2017). Some of the challenges of producing 3D-printed personalized drug products include difficulties in generating real-world evidence during the new drug development process to support precision dosing and the application of individualized dosing regimens in clinical practice.

In addition, a specific regulatory framework for assessing the quality and safety of personalized medicine is lacking. Indeed, the conventional approach of quality assurance would hardly apply in this respect (Khairuzzaman, 2018). For example, quality controls (*e.g.*, content uniformity, weight uniformity, dissolution rate) established in traditional manufacturing based on sampling units from

each batch and evaluating them for critical parameters, while retaining at least twice the quantity necessary to perform all the required tests, would be difficult to apply to personalized products. In this case, the result would be numerous batches, each consisting of a few units and each differing from the others. Therefore, new strategies to ensure quality of the starting materials, robustness of the printing process, and specification of finished product should be developed by the pharmaceutical industry and assessed by regulators for suitability. In this context, newly-on-the-market startups involved in the manufacturing of 3D printed products could play a pivotal role because they benefit from greater flexibility, cutting-edge approaches and an application-specific focus.

In recent years, the research community has focused their interest on investigating the feasibility of 3D printing in manufacturing a range of customizable dosage forms and drug delivery systems (DDSs). They considered not only binder jetting, but also extrusion printing, encompassing gel deposition and fused deposition modeling (FDM), selective laser sintering and stereolithography techniques. Among those technologies, the last probably was the most challenging, as evidenced by the limited number of applications proposed in the scientific literature. This could be associated with the need for using photosensitive polymers, which have to be cured upon irradiation with UV light, to build up the item structure layer by layer. The polymers currently used for this process are smelly and potentially toxic, which would hardly fulfill the safety and quality requirements of drug products.

Based on the analyses of the scientific literature published so far, FDM was found to be the most studied 3D printing technique (Lamichhane et al., 2019; Gioumouxouzis et al., 2019). Indeed, the number of research articles increased from fewer than five in 2014 to almost forty in 2019, with a growth trend confirmed for 2020 and an evident focus on the oral route of administration (Figure 1). This phenomenon could be explained by the similarity of FDM to other hot processing techniques already known in the pharmaceutical industry, for example hot melt extrusion (HME), and the possibility of using thermoplastic polymers commonly employed in the formulation of drug

products (Norman et al., 2017; Thakkar et al., 2020; Zema et al., 2012, 2017). Moreover, the cost-accessibility of desktop FDM equipment and the possibility of modifying it were key factors favoring its adoption. Analyzing the available scientific literature, in the following sections we made an effort in this critical overview to highlight all aspects that should be addressed before implementing FDM in the fabrication of personalized drug products for human use, which could correspond with the beginning of a new FDM era we named FDM 2.0. Notably, we purposely focused solely on the oral route, which allows us to circumvent at least those issues associated with sterility.

2. Technology implementation challenges of FDM

The FDM process involves deposition of softened/molten material layers that are fused together in a controlled pattern to create a 3D object, following its digital model. The material is generally fed into the FDM equipment in the form of a filament, with defined size and thermo-mechanical characteristics, fabricated by HME starting from a thermoplastic polymer (Araújo et al., 2019; Aho et al., 2019; Azad et al., 2020; Long et al., 2017; Palo et al., 2017; Konta et al., 2017; Zema et al., 2017). The filament is then heated in the 3D printer and extruded onto the build plate through the nozzle. Objects produced by FDM are generally characterized by good mechanical resistance, except for highly porous structures that may be friable. On the other hand, surface smoothness often needs to be enhanced eventually through post-processing operations, as the layer deposition pattern often can be evident and might affect user compliance. Resolution of details also can be an issue, particularly when these are geometric features critical to the printed item's performance (*e.g,*. thickness of a release-modifying coating layer, overlapping parts of capsule closure).

According to the analyzed literature, FDM was initially investigated for its intrinsic suitability for low-volume production of traditional orally-administered dosage forms such as tablets, capsules and matrices). This was translated to the fabrication of personalized medicines (Algahtani et al., 2018;

Awad et al., 2018; Cunha-Filho et al., 2017; Tan et al., 2018). In this respect, the main advantages of FDM resemble those already identified for other hot-processing techniques, such as the lack of solvents, which both reduces overall time and cost of the manufacturing process and is beneficial to product stability (Zema et al., 2017). Moreover, the operating temperatures limit microbial contamination and promote drug-polymer interaction with the formation of solid dispersions, possibly leading to better bioavailability of the active pharmaceutical ingredient (API).

On the other hand, temperature could impact the chemical as well as physical stability of drug and excipients, leading for instance to changes in the solid state. As a consequence, the finished item itself could be affected by the presence of byproducts, shrinkage/warpage and recrystallization phenomena. In a narrow and more advanced set of applications, FDM also was tested as a rapid prototyping tool with respect to other processes that are more suitable for mass manufacturing, for example injection molding (IM) (Melocchi et al., 2015b; Maroni et al., 2017; Shin et al., 2019). Currently, FDM is undergoing a reevaluation for the fabrication of DDSs with increasing design complexity (*e.g.*, coated, hollow, pierced, multilayered and with gradient composition) and performance (*e.g.*, combined-release kinetics, shape memory response), using the same equipment, possibly in a single production step (Genina et al., 2017; Joo et al., 2020; Matijašić et al., 2019a; Melocchi et al., 2020a,b). Indeed, this would hardly be achievable by employing other production methods. In addition, some of the new proposed systems target either novel or uncommon therapeutic needs (*e.g.*, microneedles for transdermal drug delivery, biodegradable prolonged-release projectiles for administration of contraceptives to wildlife) as well as administration routes (*e.g.*, topical, vaginal, rectal, intraauricular, intragastric and intravesical) (Fu et al., 2018; Liang et al., 2018; Lim et al., 2018; Long et al., 2018; Luzuriaga et al., 2018; Melocchi et al., 2019b; Tagami et al., 2019).

Extemporaneous 3D printing by FDM within pharmacies was initially described in the scientific literature as a way to make personalized drug products available (Araújo et al., 2019; Jamróz et al., 2018a; Lind et al., 2016; Prasad and Smyth, 2016; Rautamo et al., 2020)]. In this environment,

FDM would increase not only the variety of products that could be prepared (*e.g.*, controlled-release DDSs), but also their reproducibility, thanks to the intrinsic automation of the 3D printing process. This approach was proposed as it could in principle take advantage of *i)* the presence of educated staff, *ii)* the already-regulated possibility of preparing extemporaneous medicines tailored to single patients, and *iii)* the well-established system for dispensing drug products. However, it could result in poor quality control for these more complex finished products, in view of the limited resources/instrumentations available within compounding and hospital pharmacies.

On the other hand, the chance to decentralize printing infrastructures (*i.e.*, the availability of printers to fabricate medications at home and in small clinics; these printers would be operated either by the patients themselves or remotely/in person by healthcare professionals other than pharmacists) might not be feasible, as it would raise issues not only of quality but also of responsibility (Trenfield et al., 2018a). Currently, such issues can be better addressed in an industrial-like environment, which generally is characterized by a quality-oriented mindset. By way of example, this results in, the enforcement of standard operating procedures, the presence of trained and continuously updated personnel, the possibility of performing an increased number and a wider range of quality control tests. However, even considering this approach to the production of personalized pharmaceuticals, concerns about differing social and/or regulatory impact and relevant questions remain that need to be answered, such as the following (Mirza and Iqbal, 2018; Kaae et al., 2018; Awad et al., 2018; Preis and Öblom, 2017):

i) Should all patients have access to personalized products, or should they be available only to people with identified special needs?

ii) If the 3D printing of drug products were to be implemented within a pharmacy, would this be an optional or a mandatory service?

iii) In the case of at-home printing, what would happen if patients were to unintentionally print in a wrong way, or if they decided to print too many drug products for selling/abuse purposes?

303 *iv)* How could counterfeiting issues be prevented? How supply chain and pricing topics may be
304 addressed?
305 *v)* Who would be responsible for the finished product quality and its evaluation?
306 *vi)* In the case of combination products, how would manufacturers address side effects possibly
307 related to a combination of multiple active ingredients that either were not previously in the
308 same product or have been combined, but in different doses?
309 To find solutions, increasing awareness of these issues among experts in different domains (*e.g.*
310 pharmaceutical technology, process engineering, quality control, regulatory affairs, supply chain
311 and public health) and establishing relevant multidisciplinary collaborations may be necessary.
312 Quality, regardless of where the personalized product ultimately is manufactured, is of paramount
313 importance, both from patients' and operators' perspectives. In this respect, control of all the
314 variables involved in the fabrication of drug products by FDM will play a pivotal role (Figure 2).
315 Indeed, the quality of the final product will depend on the design phase of the dosage form, slicing
316 parameters, starting materials and software settings, as well as mechanical performance achievable
317 by the printers and on the environmental conditions at the production site. Based on these
318 considerations, all abovementioned aspects will be discussed in depth in the following sections.
319

320 **2.1. Geometric design of the product**

321 Product design and all iterations needed to fabricate customized medicines should be carried out
322 through an appropriate computer aided design (CAD) suite enabling the 3D representation of
323 objects in a file format, which can then be transformed into instructions for the printer (*i.e.*, .stl file)
324 (Zhang et al., 2018; Heikkinen et al., 2018; Junk and Kuen, 2016). Currently, a large variety of
325 commercial and non-commercial CAD systems with a range of licensing features and computing
326 requirements are available. The selection of the CAD software generally is a trade-off between ease
327 of use (*i.e.* easy and intuitive operability) and scope of function (*i.e.*, range of available geometric

features and the possibility of modifying them afterwards). Most high-performance CAD systems also allow simulations, enabling the reduction of prototyping needs and physical testing costs by identifying and correcting possible issues during the core design phase. Some of these software suites are tailored for use in specific fields, such as automotive and aerospace (Cicconi et al., 2018; Hirz et al., 2017). However, users need to complete comprehensive training and accumulate years of experience before being able to fully benefit from and master all of the functionalities (Chester, 2007; Ye et al., 2004). Actual printing then requires a .stl file, generally written in a binary format, which specifies the x, y and z coordinates of the vertices of the triangular elements adapted to approximate the surface of the object in the so-called tessellation process (Adhikary and Gurumoorthy, 2018; Leong et al., 1996a,b; Liu et al., 2009; Livesu et al., 2017; Ma et al., 2001; Manmadhachary et al., 2016; Rypl and Bittnar, 2006). Notably, the more detailed and complex the digital model, and the higher the accuracy sought for fabrication, the more triangular elements the program will use to create its representation. The main advantages associated with the .stl file are its simplicity and independence from the 3D software and the AM process employed. For many shapes, this file format can provide an effective and accurate model.

This approach, however, is very limited in the functionality it supports. For example, duplicating vertices and edges results in a high degree of redundancy. In the case of electronic models with smooth curves, thousands of triangles may be required to represent the shapes with sufficient accuracy/precision. Moreover, complex geometries, as for example pierced or encompassing hollow parts, often have led to defective .stl files that are time-consuming to fix. Similarly, the tessellation process can be challenging, leading to the formation of gaps and holes in the cross-sections of the model, which impair the deposition of continuous layers. Many repair tools have been developed to improve the generation of .stl files and reduce errors, although their use always entails a trial-and-error approach.

Finally, the file encoding the entire surface geometry of the object is processed by slicer software to convert the model into a series of thin layers and produce the associated G-code, *i.e.,* a series of

instructions written in a numerical control programming language that should, in principle, be tailored to a specific printer (Leong et al., 1996a,b). Indeed, the FDM equipment follows the G-code to fabricate successive layers of material and additively build the item through a series of cross-sections from the CAD model. Currently, a variety of available slicing tools, both open-source and proprietary, are available. Evaluating their advantages and disadvantages when used with specific equipment and materials is ongoing in the desktop 3D printing community. Such an approach also would be worth implementing in the pharmaceutical field, considering the possible impact of the thermomechanical characteristics of the formulation on the selection of slicing parameters.

2.2 FDM equipment

FDM printers, like any other machine used in pharmaceutical manufacturing, should comply with current good manufacturing practices (cGMP) (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211). Indeed, as per CFR 21 Part 211 Section 211.63 "equipment used in the manufacturing, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance." Moreover, these machines should be built so that the surfaces that contact components, in-process materials, or finished products should not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements. Currently, commercially available 3D printers, which generally are those used in research applications, hardly meet the cGMP regulations, and thus may render the 3D printed drug products unsafe for human consumption. Consequently, a limited number of publications have focused on the *in vivo* performance of 3D printed medicines, mainly on those orally administered (Arafat et al., 2018; Charoenying et al., 2020; Genina et al., 2017; Goyanes et al., 2018; Scoutaris et al., 2018; Shin et al., 2019). To overcome such limitations, preliminary attempts to attain equipment

compliance recently have been described (Araújo et al., 2019; https://www.fabrx.co.uk/technologies/?utm_term=0_13f427b78b-78b91812b1-41694769; Melocchi et al., 2018). Many involved with 3D printing of medicines are still developing their knowledge base on this topic. Most manufacturers that currently design and build 3D printers have relatively limited experience in pharmaceutical manufacturing and need to deepen their knowledge of specific strategies in this area (Lamichhane et al., 2019)]. Collaboration among engineers with different backgrounds, overseen by regulators, could be helpful in this regard.

The quality of a final product depends not only on the printing settings but also on the ability of the printer to execute them consistently so that both software and hardware play pivotal roles (Livesu et al., 2017; Feuerbach et al., 2018; Roberson et al., 2013; Šljivic et al., 2019). As was mentioned previously, slicers are responsible for the conversion of the electronic model of the object into elaborated G-code, which serves as instructions for the printer. The latest software suites have setup configurations dedicated to specific printers and can manage many parameters independently, enabling the tuning of many details of the printing process in a way that determines the printing time and the quality of the finished product. Validation of the software *per* the Part 11 and 21 CFR 211.68 would also be key components of meeting the CGMPs requirements (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.68; https://www.fda.gov/media/75414/download). Although developing new slicer software could make it possible to precisely set an even larger variety of parameters, the real limiting step is in the ability of the hardware to precisely execute the settings. In fact, the construction materials, the geometry of different parts and their assembly (including engineering design and tolerance stacks), are responsible for the precision of the response of the FDM machines to software commands. In this respect, there are important differences between printers specifically developed for industrial production and desktop printers for customer use. The former initially were developed in the field of plastics manufacturing as a powerful alternative to IM presses, enabling the fabrication of complicated geometries while maintaining repeatable quality. For these reasons, they were designed

405 from scratch to guarantee a certain level of performance, mainly working with high-quality
406 materials and proprietary closed-source software. These characteristics are impediments to the
407 operator's ability to make adjustment and also make the equipment very expensive and strictly
408 related to specific applications, both in terms of materials employed and its scope of use.
409 As a result of these limitations, desktop FDM printers have drawn a lot of interest. They were
410 derived from the industrial printers by simplifying both the hardware; for instance, in their structure,
411 materials and the internal electronics, with the main objective of making them much more
412 economical. Simplification of the hardware, however, caused a loss of mechanical performance,
413 decreasing the tolerances and lowering the resolution of the objects printed. Initially, such a
414 reduction in the FDM outcome was not considered a big limitation by the consumer community
415 compared to the possibility of making the technology more affordable, and thus available to a wider
416 variety of users. Indeed, the cost reduction played a key role in the widespread adoption of FDM
417 technology, encouraging consumers to also be developers of new materials and products, including
418 pharmaceuticals. Notably, the growing interest in personalized medicine, coupled with the low cost
419 of desktop equipment, created fertile ground for the realization of FDM's potential. However, after
420 a promising initial exploration phase, the limitations became more evident. In this respect, the main
421 issues were associated with the degree of resolution and with the reproducibility of the printing
422 process itself, especially when small details were involved. Being aware of these challenges,
423 different companies tried to improve their desktop 3D printers in the more recent years, thus
424 providing the users with relatively better-performing equipment at limited costs.
425 The requirements for final products are currently pushing standard desktop printers to their limits,
426 demonstrating the drawbacks of the cheaper equipment in meeting the needs of pharmaceutical
427 manufacturing. In fact, when dealing with DDSs, tolerances of tenths/hundreds of microns become
428 crucial to product performance over time (Melocchi et al., 2020a). Some important restrictions need
429 to be addressed in view of the low-budget printer hardware's poor mechanical precision; for
430 instance, by identifying their true achievement potential for a piece of equipment, *i.e.*, the ratio of a

nominal software setting to the real output value. Table 1 is a matrix of the core parts of commercial desktop FDM equipment, analyzing their features, issues and possible improvements/insights.

433 **Table 1:** Function, features, issues and possible improvements/insights relevant to core parts of the FDM equipment currently in use.

	FUNCTION	FEATURES	ISSUES AND RELEVANT IMPACT ON THE PRODUCT	IMPROVEMENTS/INSIGHTS

CHASSIS	- Holds the equipment
	- Determines the shape of the printing chamber
	- Locates the electric motors and control electronics
	- Acts as a guide for all the moving parts
		- Consists of extruded bars of round section made of basic steel (balance between cost, resistance, straightness and weight)
		Equipment examples: makerbot replicator ii, prusa i3, duplicator i3, ultimaker
		- Comprises coupling parts with high tolerances
		Equipment examples: Makerbot replicator II (*e.g.* The building plate position is set manually by screws and springs)
			- Vibrations, deflections and oscillations during the nozzle/printing head movements
			- Loss of uniformity of deposited layers, impacting on
			  - adherence to the electronic model in terms of dimension
			  - mechanical properties
			  - uniformity of composition
			- Unstable printing conditions due to absence of isolation from the external environment
			- Variation in the rheological properties of the material to be deposited impacting on
			  - uniformity of deposited layers
			  - solid state of the formulation components
			  - chemical stability with the formation of byproducts (*e.g.* depolymerization, carbonization, degradation)
			  - physical stability (*e.g.* shrinking, cracking, deflection, fragility, layer detaching)
				- Using more rigid and expensive material (*e.g.* Grounded tempered steel)
				- Implementing an isolated, heated and closed chamber to stabilize the conditions of the printing area
				Equipment examples: Kloner twin, DaVinci series

MOVING PARTS	- Stepper motors connected to a single endless screw for the movement in the z axis
	- Stepper motors connected to pulley-belt transmission for the movement on x and y axes
	Equipment examples: Ninjabot, Zmorph, UP plus, Makerbot replicator
	
	OR
	
	- Stepper motors connected to belts and brackets for the movement on x, y and z axes
	Equipment examples: Kloner twin, Delta wasp
		- Rigidity and straightness
		- Presence of intermediate parts
		  - Mechanical connections to convert force in the actual x- and y-axis translation (belt-mediated transmission)
		- A single mechanical connection coupling moving parts to only one end of the endless screw
		Equipment examples: Printrbot simple metal, Lulzbot taz
			- High tolerances in coupling between transmission components and loose connections
			- Deviations between the pulling value given by the code and the actual movement of the parts
			- Oscillations
			- Non-linear loss of force in the translation of the endless screw movement
			- Loss of uniformity of deposited layers, impacting on
			  - adherence to the electronic model in terms of dimension
			  - mechanical properties
			  - uniformity of composition
			- Uncontrolled cooling of the material due to ventilation phenomena
			- Variation in the rheological properties of the material to be deposited impacting on
			  - uniformity of deposited layers
			  - solid state of the formulation components
			  - formation of byproducts
			  - stability (*e.g.* shrinking, cracking, deflection, fragility, layer detaching)
				- Improving assembly including tighter tolerances
				- Reducing number of intermediate parts
				- Using double joints on the two ends of the endless screw
				- Using backlash for the mechanical connection between the screw and the arm
				- Limiting as much as possible the reciprocal motion of the parts
				- Implementing an isolated, heated and closed chamber to stabilize the conditions of the printing area

ELECTRONICS	- Regulate movements and temperature	- Low-performance and low-budget electronics	- Instability in temperature control	- Increasing processor computing power

			- Variation in the rheological properties of the material to be deposited impacting on - uniformity of deposited layers (*e.g.* due to nozzle clogging and filament erosion/sticking to the gear) - solid state of the formulation components - formation of byproducts - stability (*e.g.* shrinking, cracking, deflection, fragility, layer detaching)	
			- Oscillation in positioning of the moving elements	
			- Loss of uniformity of deposited layers, impacting on - adherence to the electronic model in terms of dimension - mechanical properties - uniformity of composition	
PRINTING HEAD	- Extrusion of the material	- Composed of: - Heating block, containing thermal resistor for increasing the temperature and thermocouple for temperature control; - Nozzle, *i.e.* A metallic channel composed of - A steel or aluminum cold end, where the filament is gripped by a gear placed on a motor and	- Gears with limited ability to generate pressure and to force the material through the nozzle	- Using custom-designed parts - Using compatible materials (in terms of thermal exchange) for interconnected parts - Improving the feeding mechanism to allow the generation of greater pressures
			- Loss of uniformity of deposited layers, impacting on - adherence to the electronic model in terms of dimension - mechanical properties - uniformity of composition	
			- Variable and uncontrollable thermal exchange	

		is pulled down in the hot end - An aluminum or brass hot end directly in touch with the heating block, allowing the thermal exchange needed to soften/melt the material and the relevant extrusion through a calibrated orifice - Parts made of different materials and adapted from existing components coming from other fields (*e.g.* brass nozzles are those used in gas plants)	- Variation in the rheological properties of the material to be deposited impacting on - uniformity of deposited layers (*e.g.* due to nozzle clogging and filament erosion/sticking to the gear) - solid state of the formulation components - formation of byproducts - stability (*e.g.* shrinking, cracking, deflection, fragility, layer detaching)	

434

As we discuss more extensively in the next section, attempts to overcome limitations encountered in the FDM process generally were made by tuning material behavior to adapt to the printer setup instead of empowering the machinery. However, some attempts to use already well-known technologies like piston-based extruders and auger conveyors have been proposed to move FDM printers beyond filament-based processes (Figure 3a, b) (Fanous et al., 2020; Goyanes et al., 2019; Musazzi et al., 2018; Ong et al., 2020). This would enable the machines not only to overcome specific issues related to raw materials, but also to avoid one of the two hot-processing steps required by current FDM printers, removing at least the need for filament production. In particular, the power and robustness of the abovementioned setups might be rapidly adapted to 3D printing hardware, allowing operators to feed the machine with many grades of raw material, in the form either of granules/pellets or powders (Guo et al., 2019). Although skipping the use of filaments represents a significant improvement, in most reviewed cases this was still achieved with custom adjustments to commercial printers. On the other hand, when dealing with pharmaceutical processes, many further improvements are required: for instance, the ability of the device to effectively mix, plasticize and achieve steady flow of the homogeneous melt through the nozzle. In this respect, few researchers have investigated the use of more expensive industrial FDM equipment, comparing the characteristics of the final products with those obtained by other mass manufacturing processes, such as IM (Welsh et al., 2019). By way of example, an open droplet-based printing system was developed by Arburg. This was built starting from the experience gained on IM presses traditionally used in the plastics industry to process polymeric granules/pellets (https://www.arburg.com/products-and-services/additive-manufacturing/; Ceskova and Lenfeld, 2018). As occurs during an IM process, the material is conveyed from the hopper of such a printer into a heated barrel where it melts, as a result of temperature increase and rotation of a never-ending screw. When a sufficient amount of material accumulates in front of the screw, the latter stops rotating and moves forward to inject it into the nozzle. In contrast to IM, there is no mold and the nozzle works directly within the build chamber to fabricate the final object bottom up, thus recalling

an FDM process. The equipment can operate at temperatures and pressures greater than 300 °C and 400 bar, respectively, being particularly suitable for viscous melts (Figure 3c).

The equipment was initially implemented with two separate material preparation units and other specific tools for the fabrication of medical devices in agreement with ISO 13485 standards. It was also provided with precise linear axes for positioning the micrometer of the part carrier, and a closed air/ventilation system for ensuring uniform temperature control in the heated build chamber. One of the main differentiation elements of this new type of printer from desktop FDM ones is the presence of a piezo controlled nozzle to finely control the flow of material as a continuous strand of droplets. As each layer would be composed of a number of these droplets, a higher level of control of shape and morphology as well as density - impacting overall performance of the printed drug product - would be assured. With freedom in adjusting slicing and process parameters an undeniable advantage of new FDM printers, the software was designed as an open system in which the user can fine-tune the conditions to different formulations. Moreover, the extruder assembly can be disassembled for cleaning, and all the parts in contact with the in-process material can be changed. In this respect, it should be stressed that the central problem is still that actual FDM equipment available on the market is generally very far from being standardized for fabricating medicines. Indeed, it lacks many industrial-grade requirements, due to the absence of: *i)* a printing environment well isolated from either the external environment or contaminants, such as lubricants and oils coming from the moving parts; *ii)* the entire assembly made of compliant materials and designed to be safely disassembled for cleaning and maintenance, including parts dedicated to the processing of specific materials; *iii)* the evaluation of any possible contaminants released during a single process and along the entire life of the machine; and *iv)* standards of process-process and printer-printer reproducibility.

2.3 Raw materials

A strict control on the characteristics of raw materials may be applied to ensure the quality of the FDM process and the safety of the printed products (Awad et al., 2018; Joo et al., 2020; Jain et al., 2018). With FDM 3D printing, the most common form for raw materials is currently represented by filaments prepared by HME. Depending on the intended use, filaments may be formulated starting from a thermoplastic polymer either adding only processing adjuvants and release modifiers, or also drugs (Hsiao et al., 2018; Melocchi et al., 2016). While in the latter case monolithic dosage forms (either having immediate or modified release performance) would be printed, in the former case, shells, coatings or separating structures may be fabricated to be combined with drug-containing parts.

Initially, researchers resorted to polymeric filaments already available on the market, loading the active ingredients from solutions by soaking or by re-extrusion (Goyanes et al. 2014, 2015a, b, c; Saviano et al., 2019; Skowyra et al., 2015). However, the main drawbacks of the former process were the limited drug loading (< 2%), swelling of the filament during immersion, and shrinkage after drying. Re-extrusion instead enabled incorporation of relatively higher amounts of drug. Moreover, resorting to re-extrusion enabled the preparation of solid dispersions with an improvement in the dissolution rate of poorly soluble drugs (Jamróz et al., 2018b; Sandler et al., 2014; Solanki et al., 2018). Subsequently, the research focus shifted on evaluating the possibility of preparing filaments by HME starting from pharmaceutical-grade polymers (Alhijjaj et al., 2015; Genina et al., 2016; Holländer et al., 2016; Melocchi et al., 2016). In the frits attempts, simple equipment was tested, for instance, machinery that allow the recycling of plastics (*e.g.*, Filabot). Afterwards, more sophisticated single- and twin-screw extruders (*e.g.*, HAAKE MiniLab and Process 11 parallel twin-screw extruder by Thermo Scientific) were evaluated.

The feeding material (*i.e.* the thermoplastic polymer-based formulation undergoing HME) is of primary importance; as a matter of fact, the need for pharmaceutical-grade ingredients greatly limits the type of polymers that can be used. Even when thermoplastic polymers approved for pharmaceutical use can be identified as suitable candidates, a further requirement comes from the

512 need for the material to flow through the printer nozzle at temperatures that will not cause the
513 degradation of any of the components, *i.e.*, the polymer, the API and other excipients (Aho et al.,
514 2019; https://www.fabrx.co.uk/technologies/?utm_term=0_13f427b78b-78b91812b1-41694769)
515 [84,130]. This often requires the addition of plasticizers, capable of decreasing the viscosity of the
516 raw materials and making them printable at suitably low temperatures (Kempin et al., 2018;
517 Kollamaram et al., 2018; Pereira et al., 2019; Pietrzak et al., 2018). Indeed, the plasticizer reduces
518 the process temperature of the polymer in use and also acts as a softener for the solid filament. This,
519 however, may impair the feeding of the filament into the nozzle of the FDM printer. Therefore, a
520 trade-off between the reduction in melt viscosity at printing temperature and the maintenance of
521 stiffness of the solid filament at feeding - typically room-temperature - is always needed. Besides
522 the need to check that the composition of the filament is homogeneous (particularly when
523 containing a drug either dissolved or suspended), the material itself must fulfill several contrasting
524 requirements to ensure printability as well as quality and safety of the final product (Aho et al.,
525 2019). For example, after deposition from the printer nozzle, the material must solidify fast enough
526 to sustain the weight of upcoming layers but slow enough to allow interdiffusion between adjacent
527 layers, thus ensuring cohesion and structural integrity of the printed product. These opposite
528 requirements are associated with the polymer's thermal behavior and diffusivity, respectively, with
529 the latter ultimately correlated to its melt-viscosity. In this respect, Table 2 lists the most important
530 thermo-mechanical requirements for each phase of the FDM process and the actions to be taken to
531 fulfill them, along with the material/filament properties involved. Specific methods proposed in the
532 literature for their characterization are also reported.

533 **Table 2:** FDM process requirements, relevant material/filament properties and characterization methods.

FDM PHASE	REQUIREMENT	PROPERTY	CHARACTERIZATION METHODS
Filament supply	The filament must be spooled in order to be supplied to the printing facility	Mechanical: - Limited stiffness (limited Young Modulus) - High strength (high stress and strain at yielding/fracture)	- Tensile tests - Bending tests
Feeding and nozzle extrusion	The filament must be pushed into the heating chamber		
	- Without breaking within the feeding gears	Mechanical: - High strength (high stress and strain at fracture)	- Tensile tests - Bending tests - *Ad hoc* tests (*e.g.* Repka-Zhang test)
	- Without slippage within the feeding gears	Mechanical: - Adequate resistance to yielding to compression (high yield stress) / hardness	- Compression tests - Bending tests - Hardness tests
	- Without breaking after the feeding gears and in the nozzle	Mechanical / rheological: - Adequate buckling resistance (*e.g.* Venkataraman criterion)	- Tensile tests - Rotational/capillary rheometry
	- Without excessive deformation between the feeding gears and the nozzle	Mechanical: - Limited dependence of young modulus on temperature	- Dynamic mechanical analysis
		Thermal: - Limited thermal conductivity/diffusivity	- Thermal analysis (Laser flash method)
	The material must flow		
	- Through the nozzle	Rheological: - Adequate viscosity	- Melt flow index - Rotational/capillary rheometry
	- At a controlled rate	Dimensional: - Circular filament cross section - Constant filament diameter	- X and y axes laser measurements, *e.g.* Ovalization
	- Without degradation	Thermal/chemical: - Degradation temperature higher than process temperature	- Thermogravimetry
	- Without instability	Rheological	- Capillary rheometry
Layer by layer deposition / solidification	Deposited layers		
	- Must have the desired size	Rheological: - Adequate extensional viscosity	- Extensional rheometry
	- Must weld to each other	Physical/rheological: - Adequate macromolecule interdiffusion	- Rotational rheometry (as indirect method)
	- Must keep their shape (control over expansion or contraction post extrusion)	Mechanical: - Limited dependence of young modulus on temperature	- Dynamic mechanical analysis
		Thermal: - Adequate thermal conductivity/ diffusivity	- Thermal analysis (Laser flash method)

Thermal characterization was generally carried out through standard techniques, such as thermogravimetry to inspect material degradation behavior, differential scanning calorimetry to determine the thermal behavior and transition temperatures of the material, and to investigate any modification in the glassy/crystalline phase of the API, if present (Alhijjaj et al., 2016; Korte and Quodbach, 2018; Melocchi et al., 2018; Öblom et al., 2019; Sadia et al., 2016). Chemical analyses and solid-state characterization of formulation components were also performed by other analytical techniques (*e.g.*, x-rays, infrared spectroscopy and high performance liquid chromatography) to rule out any modification associated with hot-processing. Rheological characterization was performed by standard methods, such as melt-flow index determination, to get a first indication of material printability; and rotational or capillary rheometry when more accurate data were needed, also in view of the modeling of the FDM process (Aho et al., 2015, 2017; Baldi et al., 2014, 2017; Casati et al., 2018; Matijašić et al., 2019; Sadia et al., 2016). A strict control over the filament diameter and shape is needed, as dimensional fluctuations cause changes in the flow of material through the nozzle and subsequent potential nonconformities in printed part dimensions and drug content. As for the evaluation of mechanical performance, no well-established protocol is available yet. According to recent literature, filaments were characterized in terms of mechanical and surface properties, for example stiffness, brittleness, roughness, using commercially available polylactic acid filament as a reference. In parallel, the suitability of custom-made filaments for loading into commercial 3D printers was only qualitatively evaluated by identifying possible issues that could arise during the process: breakup, wrapping around the loading gears and loading process robustness. Manual adjustment of the equipment configuration (*e.g.*, the compression force applied by the gears) together with changes in the filament formulation (*e.g.*, variation in the amount of plasticizer, addition of reinforcement and blending of different polymers) were shown as alternatives to achieve effective loading (Alhijjaj et al., 2016; Melocchi et al., 2016; Solanki et al., 2018). More specifically, the main methods described for characterizing the mechanical properties of filaments span from standard tensile or flexural testing to dedicated procedures, such as the

Repka-Zhang tests, the combination of dynamic mechanical analysis and tensile tests, as well as various hardness measurements (Aho et al., 2019; Fuenmayor et al., 2018; Nasereddin et al., 2018; Palekar et al., 2019; Yang et al., 2018; Zhang et al., 2017a, 2019).

The information provided by these tests, however, is not enough to predict printability and cannot be used to completely set up or fully control the printing process. Conversely, investigating the characteristic behavior (stress-strain) of the material should be carried out by standard techniques to determine its intrinsic mechanical properties, such as the elastic modulus. At a minimum, these properties can be taken into account to determine the printability of a material by comparison with the reference standard. In more refined setups, these properties could be exploited to design the printing process, taking advantage of purposely built mathematical models. Finally, regarding the definition of reference values for each of the properties highlighted here, the main challenge is represented by the strong and complex correlations between material properties, printer features (*e.g.*, nozzle dimensions and shape, feeding system) and process parameters (*e.g.*, feeding rate, nozzle temperature, relative speed between nozzle and tray). Only in a few cases was it possible to identify material attributes that are independent from the printing parameters, such as those proposed by Venkataraman and colleagues to predict filament buckling in the printer nozzle (Venkataraman et al., 2006).

Besides the difficulties and questions raised by the need for a rigorous characterization of the filament, its use in most FDM equipment poses a fundamental issue related to the presence of a double heating cycle to the material, first in the filament production by HME and then in its deposition by the printer. In fact, even when working with pharmaceutical-grade excipients, the stability of the intermediate and final products should be verified. Moreover, the second heating step raises issues associated with the homogeneity of the molten formulation, especially when a high load of immiscible phase in the melt is involved, impacting the uniform composition of the final drug product. In addition, the configuration of the printer hardware that regulated the feeding rate of the filaments exhibits a limited ability to generate pressure and to force the material through

586 the nozzle, narrowing the number of polymers that can be processed. In this respect, printing relying
587 on piston, auger and droplet-based deposition technology have very recently been tested in order to
588 avoid the need for manufacturing an intermediate product, as was discussed previously.
589
590 **2.4 Controls**
591 For fabrication of personalized medicines by FDM 3D printing, non-destructive, real-time
592 measurements of the critical quality attributes is a promising strategy for reducing the costs
593 associated with testing while ensuring product quality (Trenfield et al., 2018a,b; Radhakrishnan et
594 al., 2020; Preis and Öblom, 2017; Sandler et al., 2014; Edinger et al., 2018a;
595 https://www.usp.org/sites/default/files/usp/document/our-work/research-innovation/research-
596 innovation-3d-printing-drug-products.PDF; Markl et al., 2018). In this respect, the quality by design
597 (QbD) approach is an essential reference (Chandekar et al., 2019; Aucamp and Milne, 2019;
598 Grangeia et al., 2020; Mishra et al., 2018; Yu et al., 2014; Warsi et al., 2018). Its goal is to
599 continuously deliver products with consistent performance by creating a control strategy to
600 guarantee that all sources of process variability are identified, well understood and managed. Risk
601 mitigation may be attained by fostering identification of the critical process parameters (CPPs),
602 which potentially can impact the final product quality (*i.e.*, critical quality attributes, CQAs) as well
603 as its safety, and how these parameters interact with each other. However, such in depth-
604 understanding is yet to be fully attained. CPPs might include printing orientation, layer height,
605 nozzle size, raw material feeding rate, printing speed, nozzle and build plate temperatures, fan speed
606 and relevant variability during the process. Moreover, the characteristics of the starting material
607 should be controlled within specific limits, as discussed before.
608 Such an approach aimed at the optimization of FDM is being pursued in other fields, as it was
609 recognized as critical to improving the overall quality of the printed objects, mostly in terms of
610 aspect, mechanical resistance and sealing between layers (Bähr and Westkämper, 2018; Carlier et
611 al., 2019; Gordeev et al., 2018; Martinez-Marquez et al., 2018; Mohamed et al., 2015; Sood et al.,

612 2009). For example, a study evaluated the possibility of using a custom-made sensor (*i.e.*, a rotation
613 encoder driven by the movement of the filament) to detect the advancement of the filament in the
614 extruder of any FDM printer (Soriano Heras et al., 2018). By checking the encoder rotation
615 repeatedly, control software could determine if the filament is going forward at the desired rate. If
616 no progress is detected, the equipment will stop, allowing the operator to intervene in a timely
617 manner without having to discard the part. This approach, by providing feedback control on the
618 amount of input filament, would also allow for the adjustment of extrusion speed if the measured
619 value does not match the desired one.
620 A few preliminary studies also can be found in the scientific literature relevant to the fabrication of
621 dosage forms/DDSs (Alhijjaj et al., 2019; Gioumouxouzis et al., 2017; Markl et al., 2018; Palekar et
622 al., 2019; Smith et al., 2018a, b). However, in these first attempts only a limited number of
623 operating conditions were taken into account, while numerous processing variables - most of them
624 with intrinsic dependence on each other - still need further investigation. These variables include
625 release performance, aspect, density, porosity, friability, fragility and presence of contaminants,
626 such as heavy metals, microbiological and byproducts. In addition, future studies should analyze the
627 reproducibility of the printing process, not only for a single print but for all the products belonging
628 to a single batch.
629 In order to guarantee batch-to-batch uniformity and accelerate the final batch release, the integration
630 of analytical techniques generally used in quality control laboratories into the printers would be
631 highly beneficial (Aucamp and Milne, 2019; Edinger et al., 2018a; Goyanes et al., 2018; Khorasani
632 et al., 2016; Lamichhane et al., 2019; Markl et al., 2017; Robles-Martinez et al., 2019; Scoutaris et
633 al., 2018; Smith et al., 2018a; Trenfield et al., 2018c, 2020).This approach, already tested in
634 continuous manufacturing processes, can be enabled by process analytical technologies (PAT) such
635 as optical measurements and spectroscopic tools (*e.g.*, different infrared spectroscopy techniques
636 such as FTIR and NIR, X-ray, Raman) (Trenfield et al., 2018a; Rahman et al., 2018). Indeed, the
637 latter has already been demonstrated to be suitable for real-time monitoring of various critical

638 quality attributes, such as mass uniformity, moisture content, polymorphism, purity, air entrapment,
639 size, drug content, hardness and disintegration time. Temperature and image sensors, ultrasound,
640 hyperspectral imaging and lasers also could be implemented in on-line measurement of melting
641 temperature, individual layer thickness and product geometry. For example, image analysis would
642 enable operators to obtain multiple views of a product during fabrication so it could be compared
643 with a virtual model to rule out any possible deviations. Thermal imaging could provide insight into
644 polymeric material interfaces, providing a tool to predict thermomechanical properties of the final
645 product and give early warning of potential degradation. Terahertz pulsed imaging would yield data
646 on the microstructure of the printed products. Mathematical models could also be built from the
647 collected data in order to predict the quality attributes of the systems under fabrication (*e.g.* assay,
648 dissolution and impurities), which then have to be confirmed by analytical testing. The proposed
649 approach would in principle de-risk fabrication *via* 3D printing, especially when dealing with an
650 extensively studied formulation. In this respect, by reducing the number of analytical tests required,
651 it could decrease time and costs associated with the release of a specific batch (Aho et al., 2019).
652 Indeed, the attainment of a personalized drug product might be considered an inverse problem,
653 since its characteristics (*e.g.*, combination of active molecules, release profiles, mechanical
654 properties) are predetermined in view of the needs of specific patients, and the task is to establish
655 which parameters (*e.g.*, infill, number of shells, starting materials, product geometry) would assure
656 their achievement in the printed products (Novák et al., 2018). The concept of finding the solution
657 to an inverse problem, taking advantage of well-known correlations between operating parameters
658 and outputs is a common strategy in many fields of product development. Obviously, before being
659 able to enforce such mathematical models based on reliable correlations (of a deterministic or
660 statistical nature), they need to be developed, optimized and validated. The availability of a
661 significant amount of data collected during 3D printing prototyping campaigns and small-series
662 production runs could help in building models with machine learning algorithms. The models could
663 then be refined as more data are collected in larger-scale production campaigns. A few research

studies were very recently undertaken to focus on this topic, for instance with the goal of gaining insight into how and to which extent process parameters would affect the critical quality attributes of the finished products. The desired characteristics could be attained by following specific modifications of already identified critical 3D printing parameters, including those relevant to the design step (Korte and Quodbach, 2018; Markl et al., 2017, 2018; Smith et al., 2018a,b; Solanki et al., 2018).

Notably, development of software able to create and store suitable digital models of specific items, set operating parameters and capture, manage and save resulting data and all other information associated with production records in a dedicated cloud-based system, would be equally important (Gioumouxouzis et al., 2019; Khatri et al., 2018). At the same time, such software has to be protected from undesired external access, as it would contain sensitive metadata. Moreover, it might be proprietary and developed to work with specific printers, thus increasing the security requirements, but also limiting sharing and accessibility. This software would also create a paperless quality control system, which is essential. For example, one could study the feasibility of QR codes to be verified by smart devices equipped with barcode scanners to enable the tracing of different batches, avoiding mix-ups. Recently, this strategy has also been applied to the fabrication of monolithic systems on top of which traceability codes were printed by inkjet printing (Edinger et al., 2018b; Trenfield et al., 2019b).

Software should be checked at pre-established time intervals, to prevent any possible cyber risk (Gioumouxouzis et al., 2019; Khairuzzaman, 2018; Souto et al., 2019). Moreover, issues involving liability, intellectual property and data protection (*e.g.*, digital model, profiles containing the operating parameters, patient data) would need to be addressed to protect manufacturers, operators and end-users.

Appropriate procedures need to be developed, especially regarding batch acceptance/rejection. These would benefit from mathematical models built starting from PAT data. Employees should be

689 trained not only on the hardware (*e.g.*, on how to operate, clean and maintain the printer and solve
690 possible issues or deviations), but also on the software.
691

692 **2.5 Environment**

693 The environment where the FDM process is performed also is a key factor impacting the quality of
694 the finished product, especially if unit operations other than 3D printing are carried out
695 simultaneously, as this increases the risk of cross-contamination and hazards for all manufacturing
696 operators involved (Araújo et al., 2019). Such facilities would benefit from a controlled modular
697 structure, as this would reduce the abovementioned risks and simplify the replication of the
698 manufacturing lines in different locations. In this respect, the number of modules to be installed
699 might depend on the expected production volume. As previously discussed, these facilities might be
700 viewed as small-scale manufacturing plants, as they would be conceived with an industrial mindset;
701 for instance, they would be highly automated. Indeed, manual operation would not be suitable for
702 the safe manufacturing of numerous batches of personalized drug products in view of possible
703 issues related to traceability and mix-up. This awareness would open new and interesting
704 opportunities in the application of robotics in pharmaceutical manufacturing, which has just begun
705 to be explored (Fiorini and Botturi, 2008; Kapoor et al., 2020; Rutherford and Stinger, 2001). The
706 new facilities also would be characterized by consistent design, well-established infrastructures,
707 frequently updated procedures, well-maintained hardware/software and suitable and verified control
708 tools, as well as trained personnel. Overall, these would be difficult and expensive to include in a
709 traditional compounding pharmacy, also due to the considerable amount of electricity required to
710 maintain the infrastructure.
711

3. Risks to the operator

Although researchers currently are making significant efforts to quickly and thoroughly investigate the potential of FDM in fabricating drug products, safety-related studies so far have not been pursued with comparable intensity (Gioumouxouzis et al., 2019; Jamróz et al., 2018a). These issues are crucial in understanding the challenges entailed by a new manufacturing process, for which managing risks and guaranteeing adequate safety conditions for operators' health and for the environment is essential.

Fabricating medicines often entails extended exposure to chemicals and hazardous conditions (Bhusnure et al., 2018; Binks, 2003; Gathuru et al., 2015; https://www.who.int/medicines/areas/quality_safety/quality_assurance/ApplicationHACCPMethodologyPharmaceuticalsTRS908Annex7.pdf?ua=1). These conditions must be strictly controlled and highly regulated to guarantee that personnel will always work under specific levels of tolerated risk for each potentially hazardous variable (*i.e.*, threshold limits). In traditional manufacturing that uses well-established machinery and processes, possible sources of risk are already well-known and easily predictable so that relevant countermeasures can be adopted. Novel technologies, on the other hand, require the development of specifically tailored risk-related studies. In this respect, safety evaluation of the mechanical hazards associated with FDM production cycles, such as hot parts and motors, and the risks associated with exposure to fumes, are needed. While the former would be relatively easy to handle, the latter is still at an initial phase outside of the pharmaceutical area (Byrley et al., 2018; Floyd et al., 2017; Gümperlein et al., 2018; Jeon et al., 2020; Yi et al., 2016; Zhang et al., 2017b).

Indeed, this topic has begun to be addressed in view of the increasing popularity of FDM machines for at-home and office use. Researchers recently have evaluated the contaminants developed during 3D printing processes, due to the high temperatures involved, and the effects of printer and filament properties on levels of contaminants (*e.g.*, approximately 300,000 particles/cm^3 and 65,000 particles/cm^3 for acrylonitrile butadiene styrene and polylactic acid filaments, respectively).

Overall, FDM equipment has been shown to release volatile organic chemicals (VOCs) and ultrafine airborne particles (*i.e.*, < 100 nm in diameter), indicating the potential for inhalation and consequent health risks, especially with long-term exposure. These contaminants are emitted during the thermal processing of many thermoplastic materials and also can be generated when FDM is used to fabricate drug products starting from filaments based on pharmaceutical-grade polymers. While ultrafine particles may have serious health effects, such as increased oxidative stress, inflammation, cardiovascular effects and cytotoxicity, VOCs may contribute to the development of asthma, allergies, obstructive pulmonary disease and lung cancer (House et al., 2017). Particularly, people using 3D printers reportedly may be at risk for respiratory problems, including work-related asthma. Studies on animal models also have shown that such small particles may migrate to the brain through the olfactory system.

Systematic studies have evaluated risks associated with FDM, relying on a wide range of experimental methods, mainly those using commercially available filaments and equipment (Stefaniak et al., 2017; Steinle, 2016; Wojtyła et al., 2017, 2020). Although nozzle temperature has largely been recognized as one of the most important variables for generating contaminants, other factors may play major roles. These include:

i) the type and state of the printer, *e.g.*, presence of an external enclosure, number of nozzles, state of maintenance;

ii) the operating parameters, *e.g.*, print speed, printer nozzle size, layer height, build plate temperature;

iii) the characteristics of the employed filament, *e.g.*, presence of adjuvants or undesired contaminants that could occur in degradation;

iv) the characteristics of the item to be printed, *e.g.*, weight and complexity, which impact fabrication time;

v) environmental factors, *e.g.*, room size, ventilation, presence of filters.

In order to develop a safer-by-design approach, FDM standard emissions testing protocols should be developed, for instance, drawing inspiration from those already available for laser printers.

Scientific works have also advised transforming precautions into operator safety procedures. Recommendations include *i)* using a full enclosure, *ii)* operating the printer in a well-ventilated room and directly ventilating the printer, *iii)* maintaining a certain distance from the equipment to minimize inhalation of emitted particles, *iv)* turning off the printer, in the case of nozzle clogging, and allowing it to ventilate before removing the cover, and *v)* relying on the industrial hygiene hierarchy of controls to mitigate exposures (*i.e.*, from most to least preferable: engineering controls, administrative controls, protective equipment). Also procedures relevant to FDM equipment cleaning should be developed, as heating and purging residues of a previously processed material through load of a new one and would not be compliant. Cleaning operations would be of utmost importance when a new batch of product with different composition has to be printed. In this respect, verification of the printer *status* should also be performed, taking advantage of analytical testing methods to ascertain the absence of contaminants.

When considering structures dedicated to FDM, especially for drug products, installing special filters should be considered (Byrley et al., 2019; Floyd et al., 2017). While HEPA filters seem to be ineffective, filters relying on photocatalysis could represent a possible solution. These do not lead to the adsorption of pollutants, but instead degrade them via the activation of oxidative reactions. Moreover, photocatalysis can remove pollutants in very low concentrations, enabling odorless and safe printing.

4. Regulatory engagement

3D printing is considered as an emerging technology due to its potential to improve product safety, identity, strength, quality, or purity in certain applications (Khairuzzaman, 2018; Souto et al., 2019; Lee and Zidan, 2018; Zidan, 2019; Zidan et al., 2019a, b). Through the Emerging Technology

788 Program (ETP) developed by Office of Pharmaceutical Quality, Center for Drug Evaluation and
789 Research (CDER), sponsors can engage with the Agency to discuss, identify, and resolve potential
790 technical and regulatory issues regarding the development and implementation of a novel
791 technology prior to filing a regulatory submission
792 (https://cdn.ymaws.com/www.casss.org/resource/resmgr/dcdg_events/1218_DCDG_BrorsonKurt.p
793 df; https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-
794 program; https://www.fda.gov/files/drugs/published/Advancement-of-Emerging-Technology-
795 Applications-for-Pharmaceutical-Innovation-and-Modernization-Guidance-for-Industry.pdf;
796 https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/advanced-manufacturing).
797 To support the ETP, FDA engages in proactive research on the impact of emerging technologies on
798 product quality. Knowledge gained from the internal and sponsored research inform the feedback
799 provided the ETP, ensuring that FDA regulatory policies reflect state-of-the-art manufacturing
800 science. FDA representatives also actively participate in ongoing public-private partnerships to
801 collaborate with a broad range of interdisciplinary stakeholders. FDA collaborates with America
802 Makes organization and participates in research, definition of standards, and road-mapping
803 activities to foster high quality innovation in 3D printed medical products
804 (https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/advanced-
805 manufacturing).
806 The controls, characterization, and testing necessary to ensure product quality for 3D printed drug
807 products may depend on a variety of factors, such as properties of the active ingredient and other
808 formulation components, geometry of the product, 3D printing technology and parameters, drug
809 loading and type of product, *e.g.,* single, multiple, personalized or drug-device combination. Given
810 the variety of 3D printing technologies, materials, geometries and designs, there is no one size fits
811 all control strategy that may be applicable in all cases. In this respect, manufacturers are responsible
812 for determining and justifying with supporting information an appropriate control strategy for their
813 products. It is then anticipated that 3D printed drug products will generally follow the same

814 regulatory requirements in terms of safety, efficacy and quality, and submission expectations as any
815 drug product manufactured using other techniques. In some cases of fixed dose combinations and
816 drug-device combination products, 3D printing manufacturing may raise different questions of
817 safety and/or effectiveness specifications. If the type of technical information to be provided in the
818 submission for a 3D printed drug product is unclear, manufacturers may engage with ETP through
819 the pre-submission process to obtain more detailed feedback.
820

821 ## 5. Conclusions

822 Moving to FDM 2.0 in 2020 is a challenge the pharmaceutical community can win. In this respect,
823 this manuscript aims to be a state-of-the-art portrait of FDM, providing readers with a wide and
824 critical overview of the knowledge acquired and areas that still need to be addressed. Indeed, such a
825 provocative approach could be useful in laying the foundation for implementing FDM in the
826 manufacturing of efficacious, safe and high-quality drug products that are suitable for human use.
827 Once the FDM 2.0 phase starts, a next step is to consider good distribution practices, in order to
828 define the role of the printing infrastructure - either direct distribution or just manufacturing and
829 reference for traditional distribution.
830 Much work clearly needs to be done before personalized 3D printed products become widely
831 available to patients, not just from the viewpoint of manufacturing. Understanding which regulatory
832 paths apply to the different phases of the overall process (*e.g.,* approval of starting materials,
833 printers, software, control tools, environment) might be more difficult (Gioumouxouzis et al., 2019;
834 Khairuzzaman, 2018; Stones and Jewell, 2017).
835 Moreover, a debate still exists as to whether 3D printed medicines should be fabricated only for
836 products with expired patents. For example, extemporaneous formulations following the
837 prescription of a licensed professional are exempted and should not be considered patent violations,
838 according to intellectual property law in several countries. On the other hand, if 3D printed

medicines will be industrially produced, the means of undertaking clinical trials or bioequivalence studies to ensure safety are still unclear. However, since these drug products would be fabricated for specific subjects with unique characteristics, and therefore would differ from each other, a quality approach based on the statistical analysis of the data for a predetermined number of volunteers would be particularly challenging and expensive, especially if such studies would be performed on each individual. Gathering patient feedback and monitoring the critical parameters for a specific disease (*e.g.*, blood pressure, insulin level) would therefore represent a potential alternative to evaluating effectiveness of personalized products.

In conclusion, to make FDM-printed personalized drug products available to patients, manufacturers and all the people involved must carefully consider all the aspects described in this review. The effective collaboration of different experts from academia, regulatory agencies, and industry may provide a great start for launching a first personalized product as a proof of concept.

Conflict of interest

No potential conflict of interest was reported by the authors.

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***Conflict of Interest**

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Figure 1

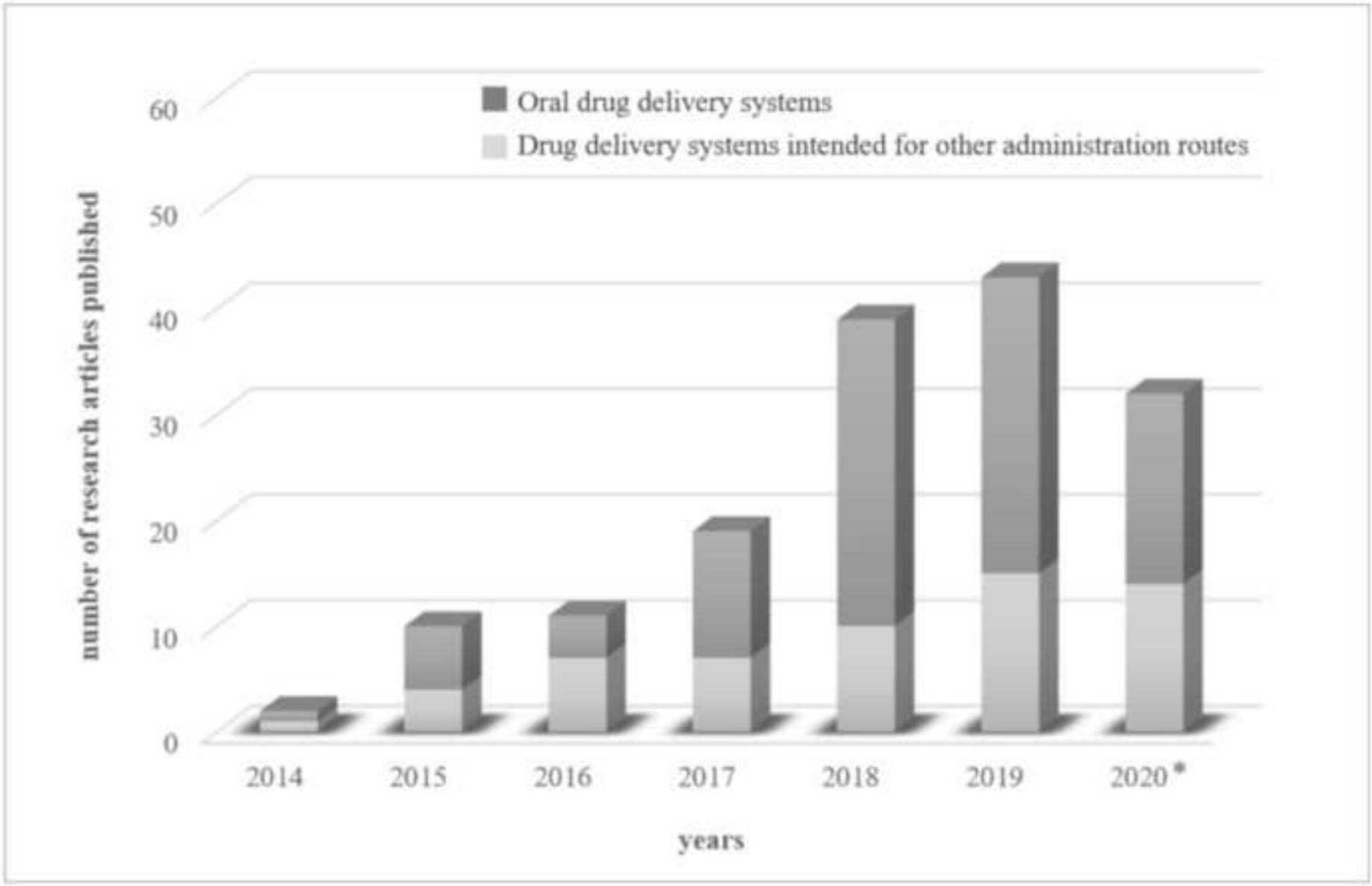

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Figure 2

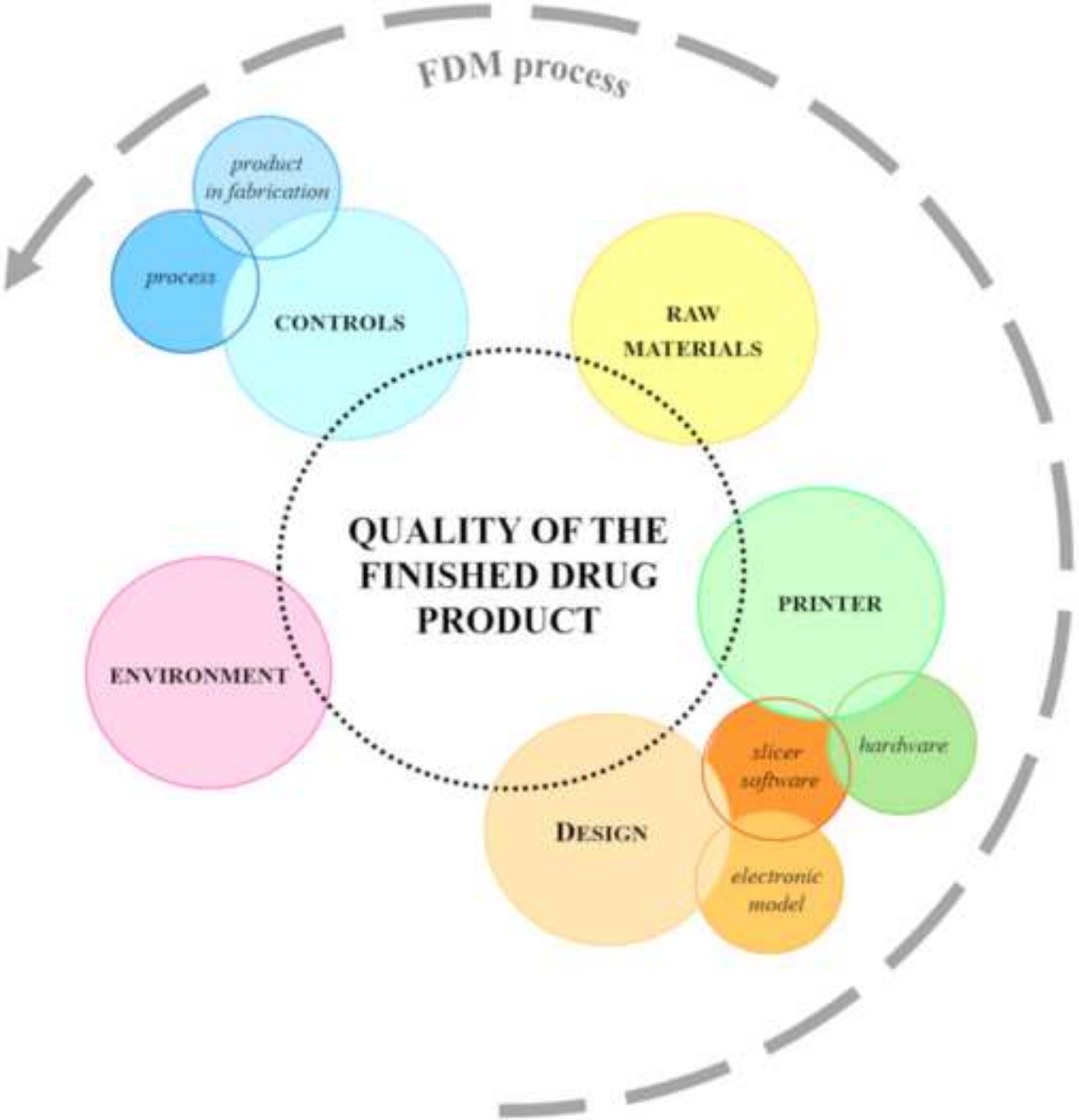
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Figure 3

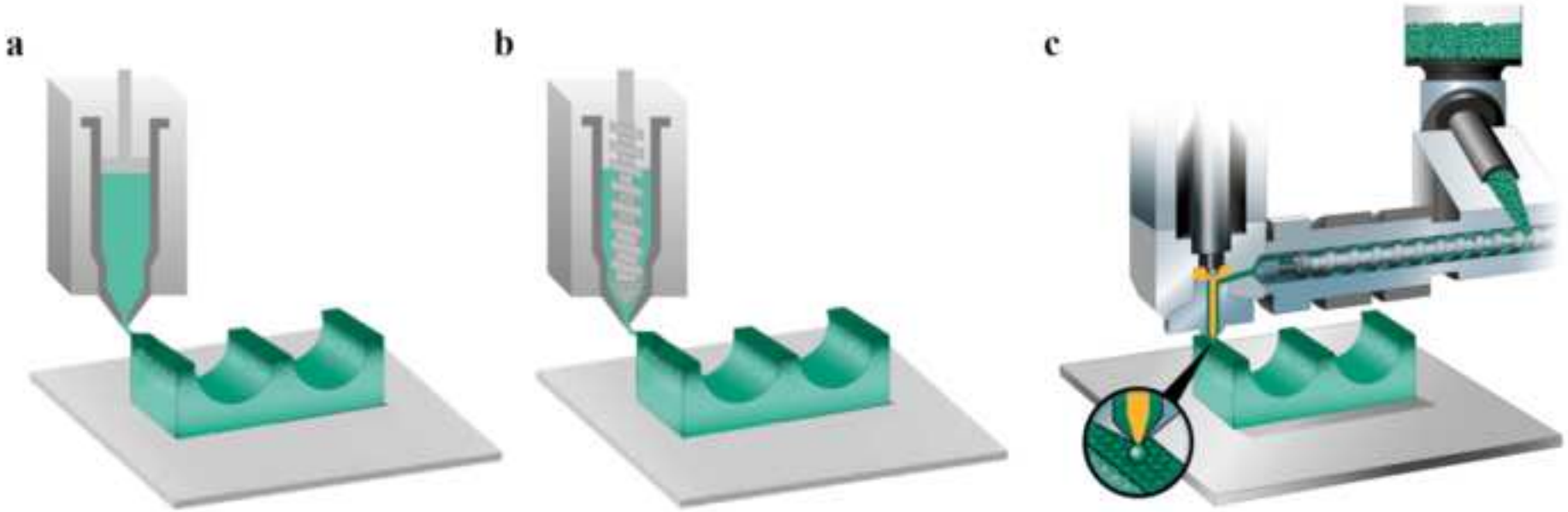


Figure captions

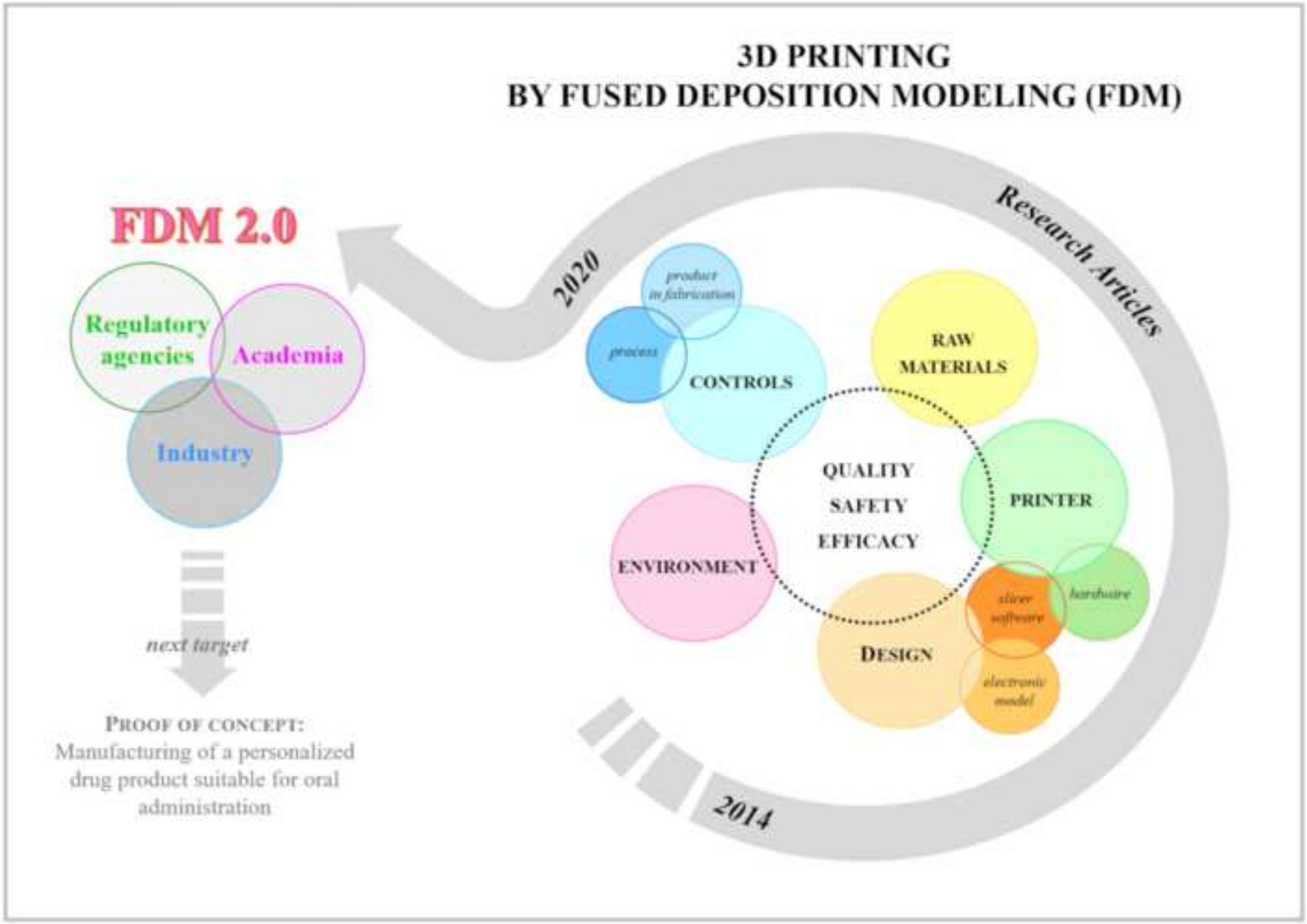
Figure 1: Total number of research articles (review articles excluded) on FDM, sorted by year of publication (sources: PubMed, Web of Science and Embase; search terms used: '3D printing' OR 'additive manufacturing' OR 'fused deposition modeling' AND 'dosage form' OR 'delivery system' OR 'drug.' Only papers referring to drug-loaded formulations were included).

Figure 2: Outline of key parameters involved in the quality of FDM drug products

Figure 3: Outline of FDM 3D printers using granules/pellets as starting materials relying on (a) piston, (b) auger and (c) droplet-based deposition system (adapted from Welsh et al., 2019 and Ceskova and Lenfeld, 2018).

*Graphical Abstract (for review)

…portrait of the state of the art



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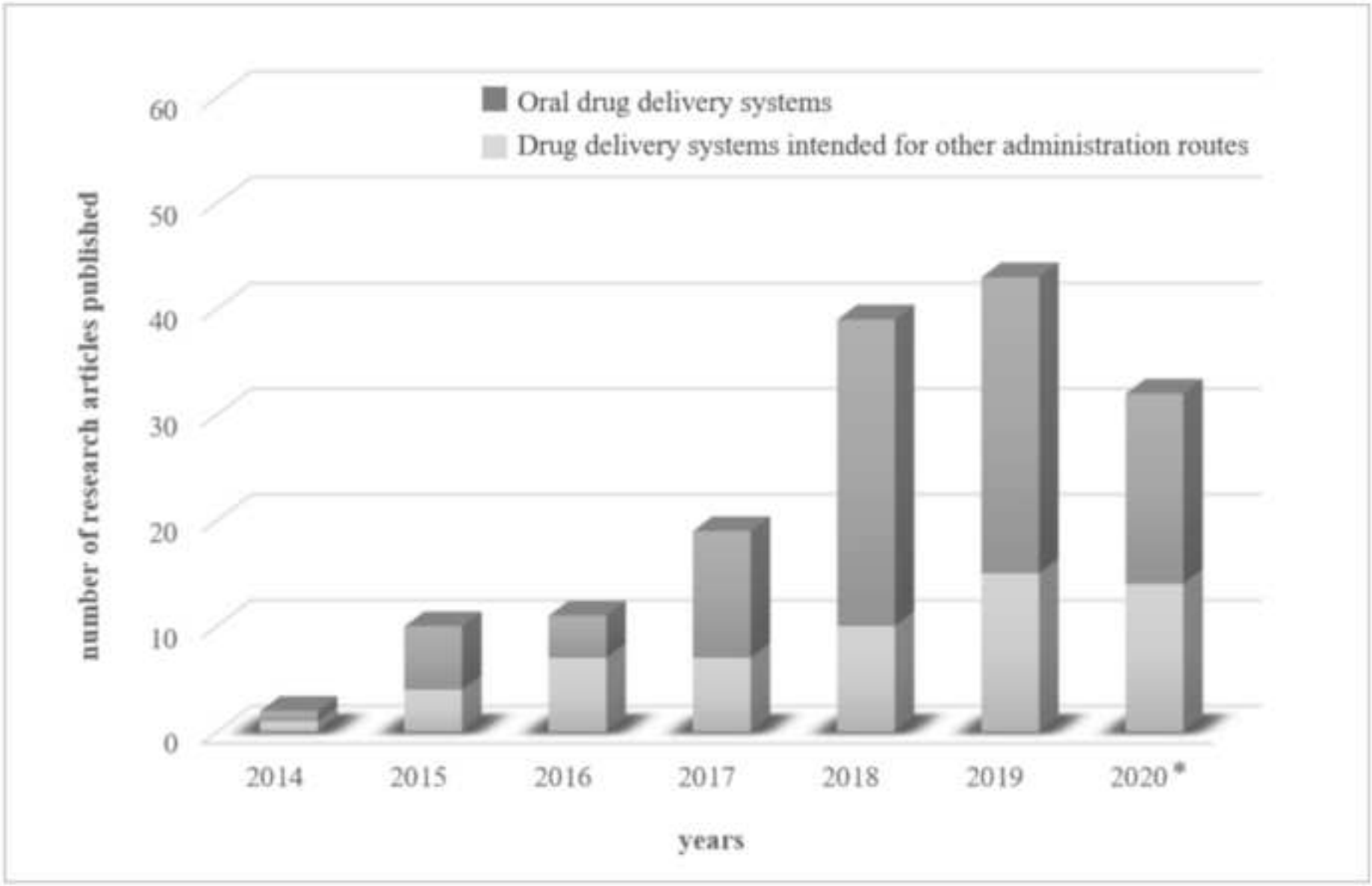

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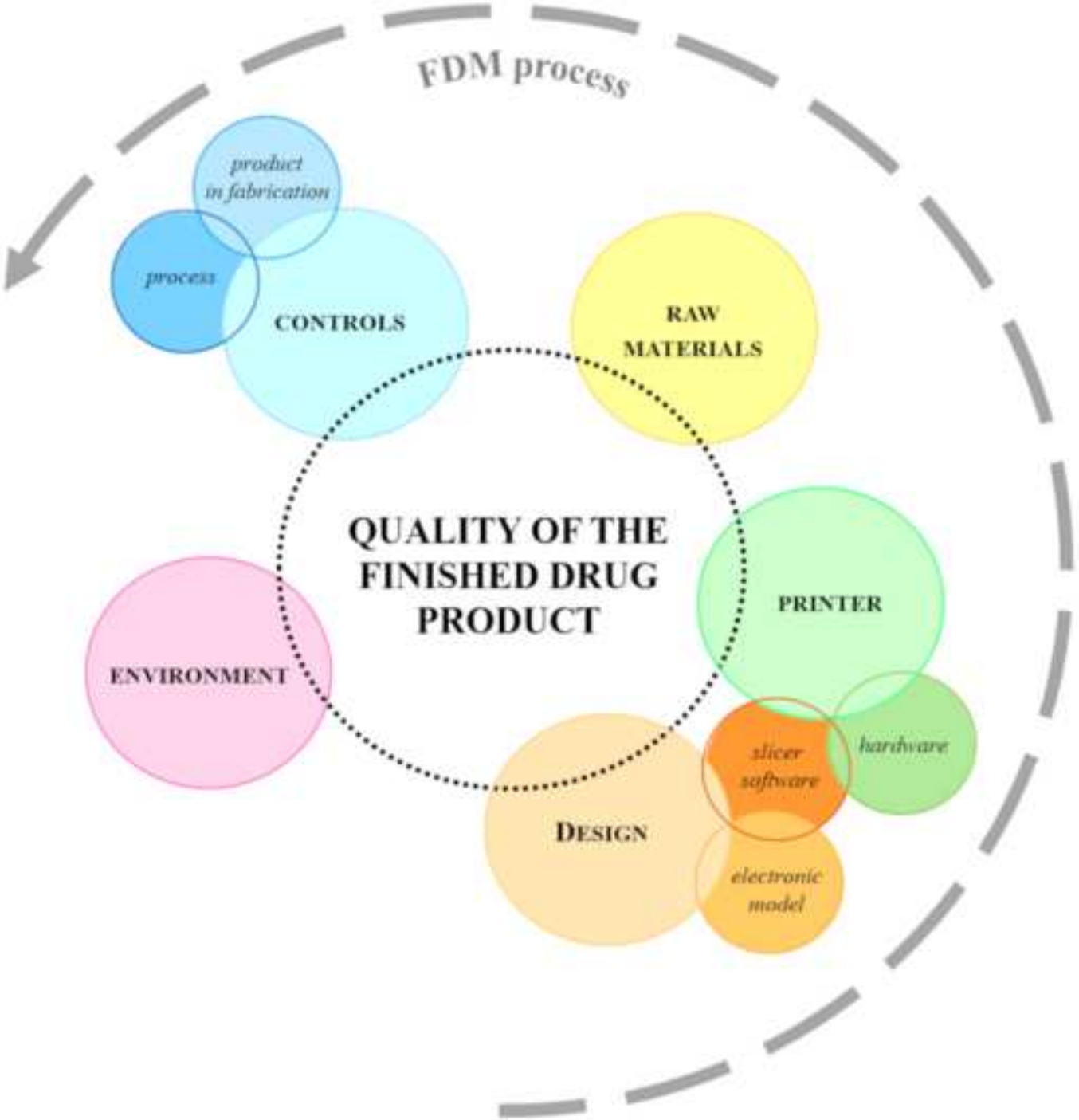
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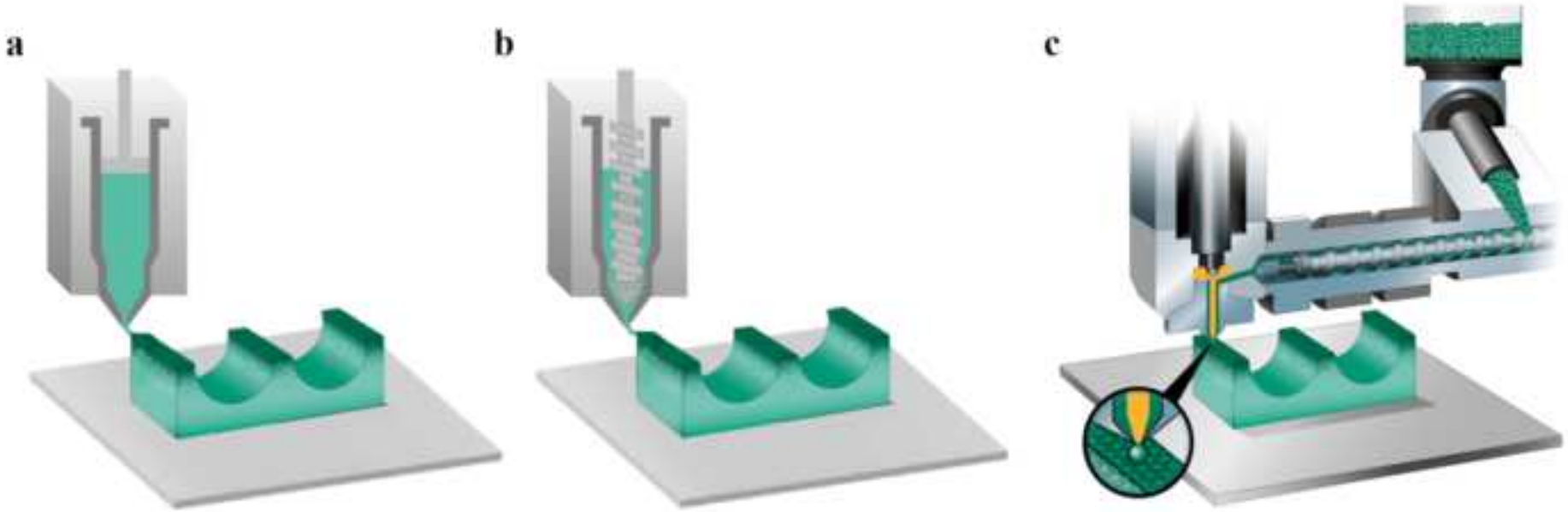
Figure 3



Quality considerations on the pharmaceutical applications of fused deposition modeling 3D printing

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Abstract

3D printing, and particularly fused deposition modeling (FDM), has rapidly brought the possibility of personalizing drug therapies to the forefront of pharmaceutical research and media attention. Applications for this technology, described in published articles, are expected to grow significantly in 2020. Where are we on this path, and what needs to be done to develop a FDM 2.0 process and make personalized medicines available to patients? Based on literature analysis, this manuscript aims to answer these questions and highlight the critical technical aspects of FDM as an emerging technology for manufacturing safe, high-quality personalized oral drug products. In this collaborative paper, experts from different fields contribute strategies for ensuring the quality of starting materials and discuss the design phase, printer hardware and software, the process, the environment and the resulting products, from the perspectives of both patients and operators.

Keywords: 3D printing, fused deposition modeling, drug product fabrication, quality, safety.

List of contents

1. Introduction

1.1 Overview of 3D printing through 2020

3D printing began officially in 1984, with the approval of the first stereolithography patent (Hull, 1986). However, this technology did not achieve widespread adoption for more than 10 years, as its use was limited by numerous other patents (https://www.wipo.int/edocs/pubdocs/en/wipo_pub_944_2015.pdf). Only after the patents' expiration did desktop 3D printers become easily available on the market, resulting in the birth of the consumer 3D printing community. Thereafter, the 3D printing industry, encompassing not only companies employing printers but also those building them, grew very quickly. It is likely to reach a market size of more than $17 B in 2020 and is expected to increase to $34.8 B by 2024 (https://www2.deloitte.com/content/dam/Deloitte/de/Documents/operations/Deloitte_Challenges_of_Additive_Manufacturing.pdf; https://downloads.3dhubs.com/3D_printing_trends_report_2020.pdf; https://www.grandviewresearch.com/industry-analysis/3d-printing-industry-analysis; https://www.marketsandmarkets.com/Market-Reports/3d-printing-market-1276.html; https://www.marketresearch.com/Expeditious-Research-v4071/3D-Printing-Outlook-9903905/). This expected continuous growth spurred venture capital funding of 3D printing-related startups, which exceeded $300 M in 2019.

In its evolution, 3D printing has shifted from being considered just a prototyping tool, to being employed as the additive manufacturing (AM) method of choice for low-volume batches of high-value products. For such products, the upfront investment in tooling required by subtractive methods would not be cost-effective (Ford and Despeisse, 2016; https://nvlpubs.nist.gov/nistpubs/SpecialPublications/NIST.SP.1176.pdf). Moreover, novel interesting applications have been identified. These include printing of metals and electronics to reduce assembly time and human labor in the manufacturing of sensors; generative design in the fields of art, architecture, communication and product design (*i.e.*, a fast method to explore design

possibilities providing physical prototypes to simplify visualization); and 4D printing (*i.e.*, the fabrication of objects capable of changing their shape in response to an external non-mechanical stimulus) (Lukin et al., 2019; Maroni et al., 2019; Mehrpouya et al., 2019; Melocchi et al., 2019a; Savolainen et al., 2020; Trenfield et al., 2019a).

Given the improvement of 3D printing and the widespread awareness that it can help connect marginalized and difficult-to-reach populations with essential products, several industries (including automotive, defense and healthcare) have begun to experience 3D printing-related production, business and supply-chain transformations (Chan et al., 2018; Despeisse et al., 2017; Ghobadian et al., 2020). In this respect, the percentage of companies using AM for specific production purposes increased from 24% to 65% in 2019 (https://assets.ey.com/content/dam/ey-sites/ey-com/en_gl/topics/advisory/ey-3d-printing-game-changer.pdf; https://cdn2.hubspot.net/hubfs/5154612/downloads/Sculpteo_The%20State%20of%203D%20Printing_2019.pdf). At the same time, the news media started to pay great attention to 3D printing and to incorporate it into the concepts of the fourth industrial revolution and a new manufacturing renaissance (Baines et al., 2019; Berman, 2012; Garret 2014; Prince, 2014).

Despite the initial enthusiasm about 3D printing technology, its actual application potential in different industries is only now beginning to be tested in depth (Achillas et al., 2015; Anton et al., 2014; Bogers et al., 2016; Culot et al., 2019; Garmulewicz et al., 2018; Huang et al., 2013; Kleer et al., 2019; Mir and Nakamura, 2017; Petrick and Simpson, 2013; Rehnberg and Ponte, 2016; Tran 2017; Yao and Lin, 2015). In particular, due to a few technological bottlenecks such as production speed, as well as cost and labor associated with pre- and post-printing operations, 3D printing currently is filling a niche as a complement to other existing manufacturing processes. In this context, the unique capabilities of 3D printing in terms of on-demand and delocalized production, product customization and realization of complex designs might find their full application.

1.2. 3D printing for precision medicine

In parallel with the increasing attention to 3D printing in many different areas, scientists have been investigating its suitability for the manufacturing of drug products enabling precision medicine, for the treatment of subpopulations with specific needs even of a single patient (*i.e.* personalized drug products) (Alhnan et al., 2016; Economidou et al., 2018; Jamróz et al., 2018a; Kjar and Huang, 2019; Musazzi et al., 2020; Trenfield et al., 2018a, b; Zhang et al., 2018). Indeed, the concept of precision medicine, an emerging approach regarding treatment and prevention of illness that accounts for each individual's genes, environment and lifestyle, is completely transforming the healthcare field (Collins et al., 2016; https://ghr.nlm.nih.gov/primer/precisionmedicine/definition; https://www.fda.gov/drugs/precision-dosing-defining-need-and-approaches-deliver-individualized-drug-dosing-real-world-setting; https://www.fda.gov/Drugs/NewsEvents/ucm132703.htm; Lamichhane et al., 2019; Mirza and Iqbal, 2018; Rahman et al., 2018). For instance, the importance of genomics has been highlighted in clinical decision making and for identifying optimal pharmacological treatments (Alomari et al., 2015; Kaae et al., 2018; Menditto et al., 2020; Radhakrishnan et al., 2020). However, an unmet need exists in the caring cycle for drug products tailored to the variables identified as crucial for a specific subject. In this respect, 3D printing is described as one of the most cost-effective alternatives for moving from mass production (*i.e.*, a one-size-fits-all approach) to fabrication of small batches that are not all the same (Aquino et al., 2018; Awad et al., 2018; Chandekar et al., 2019; Fastø et al., 2019; Goole and Amighi, 2016; Goyanes et al., 2017; Kjar and Huang, 2019; Liang et al., 2019). Indeed, 3D printing would enable: *i)* personalization of the amount of active ingredient in a drug product, *ii)* achievement of high drug loads, *iii)* co-administration of drugs in the same dosage form, *iv)* avoidance of the use of specific excipients in cases of intolerance, *v)* modulation of the release kinetics of drugs, and *vi)* definition of the flavor and other aspects of drug products in order to improve patient compliance, for instance favoring swallowability, especially from a psychological point of view. Adjustments and modifications needed would be made possible by real-time changes in the digital models of

products and process parameters (*e.g.*, number of shells, infill percentage, layer overlap), as discussed extensively in the recent literature (Trenfield et al., 2018a, b, 2019; Joo et al., 2020; Norman et al., 2017; Zema et al., 2017). A new and exciting possibility with AM is the manufacturing of medicines on demand and at the point of care, thus removing the need for long-term storage and stability studies. In addition, 3D printing can easily be adapted to fulfill the need for continuous manufacturing, taking advantage of the limited space required to set up a production facility (Cunha-Filho et al., 2017; Desai et al., 2017; Mascia et al., 2013; Melocchi et al., 2015a; Puri et al., 2017; Zhang et al., 2017a). In this respect, it may be possible to implement an innovative AM-based approach to larger-scale production.

The availability of customized drug products not only would decrease healthcare system expenses associated with side effects and hospitalization, but it also may be of utmost importance for patients with special needs (Norman et al., 2017; Hsiao et al., 2018). These patients include, in particular, those affected by rare diseases, children, the elderly, the poor or the high metabolizers, individuals with illnesses affecting elimination organs and people taking multiple medicines. Indeed, concomitant use of numerous prescription drugs, or polypharmacy, has largely increased in recent years. Combination products, in addition to enhancing patient adherence, also have the potential to extend patency on the drugs involved and improve cost-effectiveness by creating a single product pipeline. This would reduce the costs associated with packaging, prescribing and dispensing. Moreover, the use of 3D printing can also facilitate the formulation of molecules that may interact by separating them into different compartments within the same product.

Finally, 3D printing may become an effective tool in the near future for developing telemedicine (Araújo et al., 2019; Johnson and Brownlee, 2018; Wang and Kricka, 2018; Wen, 2017). This is defined as the remote delivery of healthcare services (*i.e.*, consultation, diagnosis, intervention, monitoring and education) by taking advantage of communication technologies whenever physicians and patients are not physically close. Telemedicine could advantageously be integrated with other technological advancements, such as smart health monitors, mobile applications and

cloud-based computing, which would allow physicians to evaluate patient health in real-time and to collect any data about modifications of the status quo. Telemedicine could also provide a tool to enable the adjustment of the pharmacological treatment when needed. In this respect, an FDM printer, supplied with the necessary raw materials and remotely controlled, may become a crucial element in making home therapy possible.

Despite the great potential for 3D printing to change current treatment strategies, only one 3D-printed drug product is on the market, which was registered after years of research aimed at making the technology suitable for mass manufacturing. In fact, Spritam, was approved by the U.S. Food and Drug Administration (FDA) in 2015 only. It was manufactured by the binder jetting technology proposed in the late 1980s in the labs of the Massachusetts Institute of Technology and then fully developed by Aprecia Pharmaceuticals (Alhnan et al., 2016; https://www.spritam.com/#/hcp/zipdose-technology/what-is-zipdose-technology). Consequently, Spritam fast-dissolving tablets, with an increasing load of levetiracetam, were approved through a traditional regulatory pathway (Goole and Amighi, 2016; Boudriau et al., 2016; Preis and Öblom, 2017). Some of the challenges of producing 3D-printed personalized drug products include difficulties in generating real-world evidence during the new drug development process to support precision dosing and the application of individualized dosing regimens in clinical practice.

In addition, a specific regulatory framework for assessing the quality and safety of personalized medicine is lacking. Indeed, the conventional approach of quality assurance would hardly apply in this respect (Khairuzzaman, 2018). For example, quality controls (*e.g.*, content uniformity, weight uniformity, dissolution rate) established in traditional manufacturing based on sampling units from each batch and evaluating them for critical parameters, while retaining at least twice the quantity necessary to perform all the required tests, would be difficult to apply to personalized products. In this case, the result would be numerous batches, each consisting of a few units and each differing from the others. Therefore, new strategies to ensure quality of the starting materials, robustness of the printing process, and specification of finished product should be developed by the

pharmaceutical industry and assessed by regulators for suitability. In this context, newly-on-the-market startups involved in the manufacturing of 3D printed products could play a pivotal role because they benefit from greater flexibility, cutting-edge approaches and an application-specific focus.

In recent years, the research community has focused their interest on investigating the feasibility of 3D printing in manufacturing a range of customizable dosage forms and drug delivery systems (DDSs). They considered not only binder jetting, but also extrusion printing, encompassing gel deposition and fused deposition modeling (FDM), selective laser sintering and stereolithography techniques. Among those technologies, the last probably was the most challenging, as evidenced by the limited number of applications proposed in the scientific literature. This could be associated with the need for using photosensitive polymers to build up the item structure layer by layer. These polymers need to be cured upon irradiation with UV light, which would hardly fulfill the safety and quality requirements of drug products.

Based on the analyses of the scientific literature published so far, FDM was found to be the most studied 3D printing technique (Lamichhane et al., 2019; Gioumouxouzis et al., 2019). Indeed, the number of research articles increased from fewer than five in 2014 to almost forty in 2019, with a growth trend confirmed for 2020 and an evident focus on the oral route of administration (Figure 1). This phenomenon could be explained by the similarity of FDM to other hot processing techniques already known in the pharmaceutical industry, for example hot melt extrusion (HME), and the possibility of using thermoplastic polymers commonly employed in the formulation of drug products (Norman et al., 2017; Thakkar et al., 2020; Zema et al., 2012, 2017). Moreover, the cost-accessibility of desktop FDM equipment and the possibility of modifying it were key factors favoring its adoption. Analyzing the available scientific literature, in the following sections we made an effort in this critical overview to highlight all aspects that should be addressed before implementing FDM in the fabrication of personalized drug products for human use, which could correspond with the beginning of a new FDM era we named FDM 2.0. Notably, we purposely

focused solely on the oral route, which allows us to circumvent at least those issues associated with sterility.

2. Technology implementation challenges of FDM

The FDM process involves deposition of softened/molten material layers that are fused together in a controlled pattern to create a 3D object, following its digital model. The material is generally fed into the FDM equipment in the form of a filament, with defined size and thermo-mechanical characteristics, fabricated by HME starting from a thermoplastic polymer (Araújo et al., 2019; Aho et al., 2019; Azad et al., 2020; Long et al., 2017; Palo et al., 2017; Konta et al., 2017; Zema et al., 2017). The filament is then heated in the 3D printer and extruded onto the build plate through the nozzle. Objects produced by FDM are generally characterized by good mechanical resistance, except for highly porous structures that may be friable. On the other hand, surface smoothness often needs to be enhanced eventually through post-processing operations, as the layer deposition pattern often can be evident and might affect user compliance. Resolution of details also can be an issue, particularly when these are geometric features critical to the printed item's performance (*e.g,*. thickness of a release-modifying coating layer, overlapping parts of capsule closure).

According to the analyzed literature, FDM was initially investigated for its intrinsic suitability for low-volume production of traditional orally-administered dosage forms such as tablets, capsules and matrices). This was translated to the fabrication of personalized medicines (Algahtani et al., 2018; Awad et al., 2018; Cunha-Filho et al., 2017; Tan et al., 2018). In this respect, the main advantages of FDM resemble those already identified for other hot-processing techniques, such as the lack of solvents, which both reduces overall time and cost of the manufacturing process and is beneficial to product stability (Zema et al., 2017). Moreover, the operating temperatures limit microbial contamination and promote drug-polymer interaction with the formation of solid dispersions, possibly leading to better bioavailability of the active pharmaceutical ingredient (API).

On the other hand, temperatures could impact the drug and excipient chemical stability and the physical stability of the finished item (*e.g.*, presence of byproducts, shrinkage and warpage phenomena). In a narrow and more advanced set of applications, FDM also was tested as a rapid prototyping tool with respect to other processes that are more suitable for mass manufacturing, for example injection molding (IM) (Melocchi et al., 2015b; Maroni et al., 2017; Shin et al., 2019). Currently, FDM is undergoing a reevaluation for the fabrication of DDSs with increasing design complexity (*e.g.*, coated, hollow, pierced, multilayered and with gradient composition) and performance (*e.g.*, combined-release kinetics, shape memory response), using the same equipment, possibly in a single production step (Genina et al., 2017; Joo et al., 2020; Matijašić et al., 2019a; Melocchi et al., 2020a,b). Indeed, this would hardly be achievable by employing other production methods. In addition, some of the new proposed systems target either novel or uncommon therapeutic needs (*e.g.*, microneedles for transdermal drug delivery, biodegradable prolonged-release projectiles for administration of contraceptives to wildlife) as well as administration routes (*e.g.*, topical, vaginal, rectal, intraauricular, intragastric and intravesical) (Fu et al., 2018; Liang et al., 2018; Lim et al., 2018; Long et al., 2018; Luzuriaga et al., 2018; Melocchi et al., 2019b; Tagami et al., 2019).

Extemporaneous 3D printing by FDM within pharmacies was initially described in the scientific literature as a way to make personalized drug products available (Araújo et al., 2019; Jamróz et al., 2018a; Lind et al., 2016; Prasad and Smyth, 2016; Rautamo et al., 2020)]. In this environment, FDM would increase not only the variety of products that could be prepared (*e.g.*, controlled-release DDSs), but also their reproducibility, thanks to the intrinsic automation of the 3D printing process. This approach was proposed as it could in principle take advantage of *i)* the presence of educated staff, *ii)* the already-regulated possibility of preparing extemporaneous medicines tailored to single patients, and *iii)* the well-established system for dispensing drug products. However, it could result in poor quality control for these more complex finished products, in view of the limited resources/instrumentations available within compounding and hospital pharmacies.

On the other hand, the chance to decentralize printing infrastructures (*i.e.*, the availability of printers to fabricate medications at home and in small clinics; these printers would be operated either by the patients themselves or remotely/in person by healthcare professionals other than pharmacists) might not be feasible, as it would raise issues not only of quality but also of responsibility (Trenfield et al., 2018a). Currently, such issues can be better addressed in an industrial-like environment, which generally is characterized by a quality-oriented mindset. By way of example, this results in, the enforcement of standard operating procedures, the presence of trained and continuously updated personnel, the possibility of performing an increased number and a wider range of quality control tests. However, even considering this approach to the production of personalized pharmaceuticals, concerns about differing social and/or regulatory impact and relevant questions remain that need to be answered, such as the following (Mirza and Iqbal, 2018; Kaae et al., 2018; Awad et al., 2018; Preis and Öblom, 2017):

i) Should all patients have access to personalized products, or should they be available only to people with identified special needs?

ii) If the 3D printing of drug products were to be implemented within a pharmacy, would this be an optional or a mandatory service?

iii) In the case of at-home printing, what would happen if patients were to unintentionally print in a wrong way, or if they decided to print too many drug products for selling/abuse purposes?

iv) How could counterfeiting issues be prevented?

v) Who would be responsible for the finished product quality and its evaluation?

vi) In the case of combination products, how would manufacturers address side effects possibly related to a combination of multiple active ingredients that either were not previously in the same product or have been combined, but in different doses?

To find solutions, increasing awareness of these issues among domain experts and establishing multidisciplinary collaborations will be necessary.

Quality, regardless of where the personalized product ultimately is manufactured, is of paramount importance, both from patients' and operators' perspectives. In this respect, control of all the variables involved in the fabrication of drug products by FDM will play a pivotal role (Figure 2). Indeed, the quality of the final product will depend on the design phase of the dosage form, slicing parameters, starting materials and software settings, as well as mechanical performance achievable by the printers and on the environmental conditions at the production site. Based on these considerations, all abovementioned aspects will be discussed in depth in the following sections.

2.1. Geometric design of the product

Product design and all iterations needed to fabricate customized medicines should be carried out through an appropriate computer aided design (CAD) suite enabling the 3D representation of objects in a file format, which can then be transformed into instructions for the printer (*i.e.*, .stl file) (Zhang et al., 2018; Heikkinen et al., 2018; Junk and Kuen, 2016). Currently, a large variety of commercial and non-commercial CAD systems with a range of licensing features and computing requirements are available. The selection of the CAD software generally is a trade-off between ease of use (*i.e.* easy and intuitive operability) and scope of function (*i.e.*, range of available geometric features and the possibility of modifying them afterwards). Most high-performance CAD systems also allow simulations, enabling the reduction of prototyping needs and physical testing costs by identifying and correcting possible issues during the core design phase. Some of these software suites are tailored for use in specific fields, such as automotive and aerospace (Cicconi et al., 2018; Hirz et al., 2017). However, users need to complete comprehensive training and accumulate years of experience before being able to fully benefit from and master all of the functionalities (Chester, 2007; Ye et al., 2004). Actual printing then requires a .stl file, generally written in a binary format, which specifies the x, y and z coordinates of the vertices of the triangular elements adapted to approximate the surface of the object in the so-called tessellation process (Adhikary and

328 Gurumoorthy, 2018; Leong et al., 1996a,b; Liu et al., 2009; Livesu et al., 2017; Ma et al., 2001;
329 Manmadhachary et al., 2016; Rypl and Bittnar, 2006). Notably, the more detailed and complex the
330 digital model, and the higher the accuracy sought for fabrication, the more triangular elements the
331 program will use to create its representation. The main advantages associated with the .stl file are its
332 simplicity and independence from the 3D software and the AM process employed. For many
333 shapes, this file format can provide an effective and accurate model.
334 This approach, however, is very limited in the functionality it supports. For example, duplicating
335 vertices and edges results in a high degree of redundancy. In the case of electronic models with
336 smooth curves, thousands of triangles may be required to represent the shapes with sufficient
337 accuracy/precision. Moreover, complex geometries, as for example pierced or encompassing hollow
338 parts, often have led to defective .stl files that are time-consuming to fix. Similarly, the tessellation
339 process can be challenging, leading to the formation of gaps and holes in the cross-sections of the
340 model, which impair the deposition of continuous layers. Many repair tools have been developed to
341 improve the generation of .stl files and reduce errors, although their use always entails a trial-and-
342 error approach.
343 Finally, the file encoding the entire surface geometry of the object is processed by slicer software to
344 convert the model into a series of thin layers and produce the associated G-code, *i.e.*, a series of
345 instructions written in a numerical control programming language that should, in principle, be
346 tailored to a specific printer (Leong et al., 1996a,b). Indeed, the FDM equipment follows the G-code
347 to fabricate successive layers of material and additively build the item through a series of cross-
348 sections from the CAD model. Currently, a variety of available slicing tools, both open-source and
349 proprietary, are available. Evaluating their advantages and disadvantages when used with specific
350 equipment and materials is ongoing in the desktop 3D printing community. Such an approach also
351 would be worth implementing in the pharmaceutical field, considering the possible impact of the
352 thermomechanical characteristics of the formulation on the selection of slicing parameters.
353

2.2 FDM equipment

FDM printers, like any other machine used in pharmaceutical manufacturing, should comply with current good manufacturing practices (cGMP) (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211). Indeed, as per CFR 21 Part 211 Section 211.63 "equipment used in the manufacturing, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance." Moreover, these machines should be built so that the surfaces that contact components, in-process materials, or finished products should not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements. Currently, commercially available 3D printers, which generally are those used in research applications, hardly meet the cGMP regulations, and thus may render the 3D printed drug products unsafe for human consumption. Consequently, a limited number of publications have focused on the *in vivo* performance of 3D printed medicines, mainly on those orally administered (Arafat et al., 2018; Charoenying et al., 2020; Genina et al., 2017; Goyanes et al., 2018; Scoutaris et al., 2018; Shin et al., 2019). To overcome such limitations, preliminary attempts to attain equipment compliance recently have been described (Araújo et al., 2019; https://www.fabrx.co.uk/technologies/?utm_term=0_13f427b78b-78b91812b1-41694769; Melocchi et al., 2018). Many involved with 3D printing of medicines are still developing their knowledge base on this topic. Most manufacturers that currently design and build 3D printers have relatively limited experience in pharmaceutical manufacturing and need to deepen their knowledge of specific strategies in this area (Lamichhane et al., 2019)]. Collaboration among engineers with different backgrounds, overseen by regulators, could be helpful in this regard.

The quality of a final product depends not only on the printing settings but also on the ability of the printer to execute them consistently so that both software and hardware play pivotal roles (Livesu et al., 2017; Feuerbach et al., 2018; Roberson et al., 2013; Šljivic et al., 2019). As was mentioned

previously, slicers are responsible for the conversion of the electronic model of the object into elaborated G-code, which serves as instructions for the printer. The latest software suites have setup configurations dedicated to specific printers and can manage many parameters independently, enabling the tuning of many details of the printing process in a way that determines the printing time and the quality of the finished product. Validation of the software *per* the Part 11 and 21 CFR 211.68 would also be key components of meeting the CGMPs requirements (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.68; https://www.fda.gov/media/75414/download). Although developing new slicer software could make it possible to precisely set an even larger variety of parameters, the real limiting step is in the ability of the hardware to precisely execute the settings. In fact, the construction materials, the geometry of different parts and their assembly (including engineering design and tolerance stacks), are responsible for the precision of the response of the FDM machines to software commands. In this respect, there are important differences between printers specifically developed for industrial production and desktop printers for customer use. The former initially were developed in the field of plastics manufacturing as a powerful alternative to IM presses, enabling the fabrication of complicated geometries while maintaining repeatable quality. For these reasons, they were designed from scratch to guarantee a certain level of performance, mainly working with high-quality materials and proprietary closed-source software. These characteristics are impediments to the operator's ability to make adjustment and also make the equipment very expensive and strictly related to specific applications, both in terms of materials employed and its scope of use.

As a result of these limitations, desktop FDM printers have drawn a lot of interest. They were derived from the industrial printers by simplifying both the hardware; for instance, in their structure, materials and the internal electronics, with the main objective of making them much more economical. Simplification of the hardware, however, caused a loss of mechanical performance, decreasing the tolerances and lowering the resolution of the objects printed. Initially, such a reduction in the FDM outcome was not considered a big limitation by the consumer community

406 compared to the possibility of making the technology more affordable, and thus available to a wider
407 variety of users. Indeed, the cost reduction played a key role in the widespread adoption of FDM
408 technology, encouraging consumers to also be developers of new materials and products, including
409 pharmaceuticals. Notably, the growing interest in personalized medicine, coupled with the low cost
410 of desktop equipment, created fertile ground for the realization of FDM's potential. However, after
411 a promising initial exploration phase, the limitations became more evident. In this respect, the main
412 issues were associated with the degree of resolution and with the reproducibility of the printing
413 process itself.
414 The requirements for final products are currently pushing standard desktop printers to their limits,
415 demonstrating the drawbacks of the cheaper equipment in meeting the needs of pharmaceutical
416 manufacturing. In fact, when dealing with DDSs, tolerances of tenths/hundreds of microns become
417 crucial to product performance over time (Melocchi et al., 2020a). Some important restrictions need
418 to be addressed in view of the low-budget printer hardware's poor mechanical precision; for
419 instance, by identifying their true achievement potential for a piece of equipment, *i.e.*, the ratio of a
420 nominal software setting to the real output value. Table 1 is a matrix of the core parts of commercial
421 desktop FDM equipment, analyzing their features, issues and possible improvements/insights.
422

423 **Table 1:** Function, features, issues and possible improvements/insights relevant to core parts of the FDM equipment currently in use.

	FUNCTION	FEATURES	ISSUES	IMPROVEMENTS/INSIGHTS
CHASSIS	- Holds the equipment - Determines the shape of the printing chamber - Locates the electric motors and control electronics - Acts as a guide for all the moving parts	- Consists of extruded bars of round section made of basic steel (balance between cost, resistance, straightness and weight) *Equipment examples:* makerbot replicator ii, prusa i3, duplicator i3, ultimaker - Comprises coupling parts with high tolerances *Equipment examples:* Makerbot replicator II (*e.g.* The building plate position is set manually by screws and springs)	- Vibrations, deflections and oscillations during the nozzle/printing head movements - Unstable printing conditions due to absence of isolation from the external environment	- Using more rigid and expensive material (*e.g*. Grounded tempered steel) - Implementing an isolated, heated and closed chamber to stabilize the conditions of the printing area *Equipment examples*: Kloner twin, Davinci series

MOVING PARTS	- Stepper motors connected to a single endless screw for the movement in the z axis
	- Stepper motors connected to pulley-belt transmission for the movement on x and y axes
	Equipment examples: Ninjabot, Zmorph, UP plus, Makerbot replicator
	OR
	- Stepper motors connected to belts and brackets for the movement on x, y and z axes
	Equipment examples: Kloner twin, Delta wasp
		- Rigidity and straightness
		- Presence of intermediate parts
		  - Mechanical connections to convert force in the actual x- and y-axis translation (belt-mediated transmission)
		- A single mechanical connection coupling moving parts to only one end of the endless screw
		Equipment examples: Printrbot simple metal, Lulzbot taz
			- High tolerances in coupling between transmission components and loose connections
			- Deviations between the pulling value given by the code and the actual movement of the parts
			- Oscillations
			- Non-linear loss of force in the translation of the endless screw movement
			- Uncontrolled cooling of the material due to ventilation phenomena
			  - Unreleased tensile forces inside the printed object, leading to shrinking, cracking, deflection, fragility, layer detaching and mismatch with designed dimensions
				- Improving assembly including tighter tolerances
				- Reducing number of intermediate parts
				- Using double joints on the two ends of the endless screw
				- Using backlash for the mechanical connection between the screw and the arm
				- Limiting as much as possible the reciprocal motion of the parts
				- Implementing an isolated, heated and closed chamber to stabilize the conditions of the printing area

ELECTRONICS	- Regulate movements and temperature	- Low-performance and low-budget electronics	- Instability in temperature control - Oscillation in positioning of the moving elements	- Increasing processor computing power

PRINTING HEAD	- Extrusion of the material	- Composed of:
		  - Heating block, containing thermal resistor for increasing the temperature and thermocouple for temperature control;
		  - Nozzle, *i.e.* A metallic channel composed of
		  - A steel or aluminum cold end, where the filament is gripped by a gear placed on a motor and is pulled down in the hot end
		  - An aluminum or brass hot end directly in touch with the heating block, allowing the thermal exchange needed to soften/melt the material and the relevant extrusion through a calibrated orifice
		- Parts made of different materials and adapted from existing components coming from other fields (*e.g.* brass nozzles are those used in gas plants)
			- Gears with limited ability to generate pressure and to force the material through the nozzle
			- Variable and uncontrollable thermal exchange
			  - Stability issues (*e.g.* Depolymerization, carbonization, degradation)
			  - Inadequate melting of the material in the hot end with relevant clogging of the nozzle
			  - Softening of the material in the cold end leading to filament erosion or sticking to the gear, thus compromising the control of the amount of extruded material
				- Using custom-designed parts
				- Using compatible materials (in terms of thermal exchange) for interconnected parts
				- Improving the feeding mechanism to allow the generation of greater pressures

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As we discuss more extensively in the next section, attempts to overcome limitations encountered in the FDM process generally were made by tuning material behavior to adapt to the printer setup instead of empowering the machinery. However, some attempts to use already well-known technologies like piston-based extruders and auger conveyors have been proposed to move FDM printers beyond filament-based processes (Figure 3a, b) (Fanous et al., 2020; Goyanes et al., 2019; Musazzi et al., 2018; Ong et al., 2020) . This would enable the machines not only to overcome specific issues related to raw materials, but also to avoid one of the two hot-processing steps required by current FDM printers, removing at least the need for filament production. In particular, the power and robustness of the abovementioned setups might be rapidly adapted to 3D printing hardware, allowing operators to feed the machine with many grades of raw material, in the form either of granules/pellets or powders (Guo et al., 2019). Although skipping the use of filaments represents a significant improvement, in most reviewed cases this was still achieved with custom adjustments to commercial printers. On the other hand, when dealing with pharmaceutical processes, many further improvements are required: for instance, the ability of the device to effectively mix, plasticate and achieve steady flow of the homogeneous melt through the nozzle. In this respect, few researchers have investigated the use of more expensive industrial FDM equipment, comparing the characteristics of the final products with those obtained by other mass manufacturing processes, such as IM (Welsh et al., 2019). The Freeformer equipment employed is derived from the IM technology traditionally used in the plastics industry to process polymeric granules/pellets (https://www.arburg.com/products-and-services/additive-manufacturing/; Ceskova and Lenfeld, 2018). It was initially implemented with separate material preparation units and other specific tools for the fabrication of medical devices in agreement with ISO 13485 standards. The Freeformer, based on a droplet deposition modeling technique, can operate at temperatures and pressures greater than 300 °C and 400 bar, respectively, being particularly suitable for viscous melts (Figure 3c). It is equipped with servo motors and a never-ending screw for material preparation, precise linear axes for the micrometer positioning of the part carrier, and a closed air/ventilation

system for ensuring uniform temperature control in the heated build chamber. One of its main differentiation elements from desktop FDM printers is the presence of a piezo controlled nozzle to finely control the flow of material as a continuous strand of droplets. As each layer would be composed of a number of these droplets, a higher level of control of shape and morphology as well as density - impacting overall performance of the printed drug product - would be assured. With freedom in adjusting slicing and process parameters an undeniable advantage of new FDM printers, the Freeformer software was designed as an open system in which the user can fine-tune the conditions to different formulations. Moreover, the extruder assembly can be disassembled for cleaning, and all the parts in contact with the in-process material can be changed. In this respect, it should be stressed that the central problem is still that actual FDM equipment available on the market is generally very far from being standardized for fabricating medicines. Indeed, it lacks many industrial-grade requirements, due to the absence of: *i)* a printing environment well isolated from either the external environment or contaminants, such as lubricants and oils coming from the moving parts; *ii)* the entire assembly made of compliant materials and designed to be safely disassembled for cleaning and maintenance, including parts dedicated to the processing of specific materials; *iii)* the evaluation of any possible contaminants released during a single process and along the entire life of the machine; and *iv)* standards of process-process and printer-printer reproducibility.

2.3 Raw materials

A strict control on the characteristics of raw materials may be applied to ensure the quality of the FDM process and the safety of the printed products (Awad et al., 2018; Joo et al., 2020; Jain et al., 2018). With FDM 3D printing, the most common form for raw materials is currently represented by filaments prepared by HME. Depending on the intended use, filaments may be formulated starting from a thermoplastic polymer either adding only processing adjuvants and release modifiers, or also

drugs (Hsiao et al., 2018; Melocchi et al., 2016). While in the latter case monolithic dosage forms (either having immediate or modified release performance) would be printed, in the former case, shells, coatings or separating structures may be fabricated to be combined with drug-containing parts.

Initially, researchers resorted to polymeric filaments already available on the market, loading the active ingredients from solutions by soaking or by re-extrusion (Goyanes et al. 2014, 2015a, b, c; Saviano et al., 2019; Skowyra et al., 2015). However, the main drawbacks of the former process were the limited drug loading (< 2%), swelling of the filament during immersion, and shrinkage after drying. Re-extrusion instead enabled incorporation of relatively higher amounts of drug. Moreover, resorting to re-extrusion enabled the preparation of solid dispersions with an improvement in the dissolution rate of poorly soluble drugs (Jamróz et al., 2018b; Sandler et al., 2014; Solanki et al., 2018). Subsequently, the research focus shifted on evaluating the possibility of preparing filaments by HME starting from pharmaceutical-grade polymers (Alhijjaj et al., 2015; Genina et al., 2016; Holländer et al., 2016; Melocchi et al., 2016). In the frits attempts, simple equipment was tested, for instance, machinery that allow the recycling of plastics (*e.g.,* Filabot). Afterwards, more sophisticated single- and twin-screw extruders (*e.g.,* HAAKE MiniLab and Process 11 parallel twin-screw extruder by Thermo Scientific) were evaluated.

The feeding material (*i.e.* the thermoplastic polymer-based formulation undergoing HME) is of primary importance; as a matter of fact, the need for pharmaceutical-grade ingredients greatly limits the type of polymers that can be used. Even when thermoplastic polymers approved for pharmaceutical use can be identified as suitable candidates, a further requirement comes from the need for the material to flow through the printer nozzle at temperatures that will not cause the degradation of any of the components, *i.e.*, the polymer, the API and other excipients (Aho et al., 2019; https://www.fabrx.co.uk/technologies/?utm_term=0_13f427b78b-78b91812b1-41694769) [84,130]. This often requires the addition of plasticizers, capable of decreasing the viscosity of the raw materials and making them printable at suitably low temperatures (Kempin et al., 2018;

Kollamaram et al., 2018; Pereira et al., 2019; Pietrzak et al., 2018). Indeed, the plasticizer reduces the process temperature of the polymer in use and also acts as a softener for the solid filament. This, however, may impair the feeding of the filament into the nozzle of the FDM printer. Therefore, a trade-off between the reduction in melt viscosity at printing temperature and the maintenance of stiffness of the solid filament at feeding - typically room-temperature - is always needed. Besides the need to check that the composition of the filament is homogeneous (particularly when containing a drug either dissolved or suspended), the material itself must fulfill several contrasting requirements to ensure printability as well as quality and safety of the final product (Aho et al., 2019). For example, after deposition from the printer nozzle, the material must solidify fast enough to sustain the weight of upcoming layers but slow enough to allow interdiffusion between adjacent layers, thus ensuring cohesion and structural integrity of the printed product. These opposite requirements are associated with the polymer's thermal behavior and diffusivity, respectively, with the latter ultimately correlated to its melt-viscosity. In this respect, Table 2 lists the most important requirements for each phase of the FDM process and the actions to be taken to fulfill them, along with the material/filament properties involved. Specific methods proposed in the literature for their characterization are also reported.

519 **Table 2:** FDM process requirements, relevant material/filament properties and characterization methods.

FDM PHASE	REQUIREMENT	PROPERTY	CHARACTERIZATION METHODS
Filament supply	The filament must be spooled in order to be supplied to the printing facility	Mechanical: - Limited stiffness (limited Young Modulus) - High strength (high stress and strain at yielding/fracture)	- Tensile tests - Bending tests
Feeding and nozzle extrusion	The filament must be pushed into the heating chamber		
	- Without breaking within the feeding gears	Mechanical: - High strength (high stress and strain at fracture)	- Tensile tests - Bending tests - *Ad hoc* tests (*e.g.* Repka-Zhang test)
	- Without slippage within the feeding gears	Mechanical: - Adequate resistance to yielding to compression (high yield stress) / hardness	- Compression tests - Bending tests - Hardness tests
	- Without breaking after the feeding gears and in the nozzle	Mechanical / rheological: - Adequate buckling resistance (*e.g.* Venkataraman criterion)	- Tensile tests - Rotational/capillary rheometry
	- Without excessive deformation between the feeding gears and the nozzle	Mechanical: - Limited dependence of young modulus on temperature	- Dynamic mechanical analysis
		Thermal: - Limited thermal conductivity/diffusivity	- Thermal analysis (Laser flash method)
	The material must flow		
	- Through the nozzle	Rheological: - Adequate viscosity	- Melt flow index - Rotational/capillary rheometry
	- At a controlled rate	Dimensional: - Circular filament cross section - Constant filament diameter	- X and y axes laser measurements, *e.g.* Ovalization
	- Without degradation	Thermal/chemical: - Degradation temperature higher than process temperature	- Thermogravimetry
	- Without instability	Rheological	- Capillary rheometry
Layer by layer deposition / solidification	Deposited layers		
	- Must have the desired size	Rheological: - Adequate extensional viscosity	- Extensional rheometry
	- Must weld to each other	Physical/rheological: - Adequate macromolecule interdiffusion	- Rotational rheometry (as indirect method)
	- Must keep their shape	Mechanical: - Limited dependence of young modulus on temperature	- Dynamic mechanical analysis
		Thermal: - Adequate thermal conductivity/ diffusivity	- Thermal analysis (Laser flash method)

Thermal characterization was generally carried out through standard techniques, such as thermogravimetry to inspect material degradation behavior, differential scanning calorimetry to determine the thermal behavior and transition temperatures of the material, and to investigate any modification in the glassy/crystalline phase of the API, if present (Alhijjaj et al., 2016; Korte and Quodbach, 2018; Öblom et al., 2019; Sadia et al., 2016). Moreover, the solid-state characterization of active ingredients also was investigated by spectroscopic techniques (*e.g.,* x-rays and infrared spectroscopy). Rheological characterization was performed by standard methods, such as melt-flow index determination, to get a first indication of material printability; and rotational or capillary rheometry when more accurate data were needed, also in view of the modeling of the FDM process (Aho et al., 2015, 2017; Baldi et al., 2014, 2017; Casati et al., 2018; Matijašić et al., 2019; Sadia et al., 2016). A strict control over the filament diameter and shape is needed, as dimensional fluctuations cause changes in the flow of material through the nozzle and subsequent potential nonconformities in printed part dimensions and drug content. As for the evaluation of mechanical performance, no well-established protocol is available yet. According to recent literature, filaments were characterized in terms of mechanical and surface properties, for example stiffness, brittleness, roughness, using commercially available polylactic acid filament as a reference. In parallel, the suitability of custom-made filaments for loading into commercial 3D printers was only qualitatively evaluated by identifying possible issues that could arise during the process: breakup, wrapping around the loading gears and loading process robustness. Manual adjustment of the equipment configuration (*e.g.,* the compression force applied by the gears) together with changes in the filament formulation (*e.g.,* variation in the amount of plasticizer, addition of reinforcement and blending of different polymers) were shown as alternatives to achieve effective loading (Alhijjaj et al., 2016; Melocchi et al., 2016; Solanki et al., 2018). More specifically, the main methods described for characterizing the mechanical properties of filaments span from standard tensile or flexural testing to dedicated procedures, such as the Repka-Zhang tests, the combination of dynamic mechanical analysis and tensile tests, as well as various hardness measurements (Aho et al., 2019;

546 Fuenmayor et al., 2018; Nasereddin et al., 2018; Palekar et al., 2019; Yang et al., 2018; Zhang et al.,
547 2017a, 2019).
548 The information provided by these tests, however, is not enough to predict printability and cannot
549 be used to completely set up or fully control the printing process. Conversely, investigating the
550 characteristic behavior (stress-strain) of the material should be carried out by standard techniques to
551 determine its intrinsic mechanical properties, such as the elastic modulus. At a minimum, these
552 properties can be taken into account to determine the printability of a material by comparison with
553 the reference standard. In more refined setups, these properties could be exploited to design the
554 printing process, taking advantage of purposely built mathematical models. Finally, regarding the
555 definition of reference values for each of the properties highlighted here, the main challenge is
556 represented by the strong and complex correlations between material properties, printer features
557 (*e.g.*, nozzle dimensions and shape, feeding system) and process parameters (*e.g.*, feeding rate,
558 nozzle temperature, relative speed between nozzle and tray). Only in a few cases was it possible to
559 identify material attributes that are independent from the printing parameters, such as those
560 proposed by Venkataraman and colleagues to predict filament buckling in the printer nozzle
561 (Venkataraman et al., 2006).
562 Besides the difficulties and questions raised by the need for a rigorous characterization of the
563 filament, its use in most FDM equipment poses a fundamental issue related to the presence of a
564 double heating cycle to the material, first in the filament production by HME and then in its
565 deposition by the printer. In fact, even when working with pharmaceutical-grade excipients, the
566 stability of the intermediate and final products should be verified. Moreover, the second heating
567 step raises issues associated with the homogeneity of the molten formulation, especially when a
568 high load of immiscible phase in the melt is involved, impacting the uniform composition of the
569 final drug product. In addition, the configuration of the printer hardware that regulated the feeding
570 rate of the filaments exhibits a limited ability to generate pressure and to force the material through
571 the nozzle, narrowing the number of polymers that can be processed. In this respect, printing relying

572 on piston, auger and Freeformer technology have very recently been tested in order to avoid the
573 need for manufacturing an intermediate product, as was discussed previously.
574
575 **2.4 Controls**
576 For fabrication of personalized medicines by FDM 3D printing, non-destructive, real-time
577 measurements of the critical quality attributes is a promising strategy for reducing the costs
578 associated with testing while ensuring product quality (Trenfield et al., 2018a,b; Radhakrishnan et
579 al., 2020; Preis and Öblom, 2017; Sandler et al., 2014; Edinger et al., 2018a;
580 https://www.usp.org/sites/default/files/usp/document/our-work/research-innovation/research-
581 innovation-3d-printing-drug-products.PDF; Markl et al., 2018). In this respect, the quality by design
582 (QbD) approach is an essential reference (Chandekar et al., 2019; Aucamp and Milne, 2019;
583 Grangeia et al., 2020; Mishra et al., 2018; Yu et al., 2014; Warsi et al., 2018). Its goal is to
584 continuously deliver products with consistent performance by creating a control strategy to
585 guarantee that all sources of process variability are identified, well understood and managed. Risk
586 mitigation may be attained by fostering identification of the critical process parameters (CPPs),
587 which potentially can impact the final product quality (*i.e.*, critical quality attributes, CQAs) as well
588 as its safety, and how these parameters interact with each other. However, such in depth-
589 understanding is yet to be fully attained. CPPs might include printing orientation, layer height,
590 nozzle size, raw material feeding rate, printing speed, nozzle and build plate temperatures, fan speed
591 and relevant variability during the process. Moreover, the characteristics of the starting material
592 should be controlled within specific limits, as discussed before.
593 Such an approach aimed at the optimization of FDM is being pursued in other fields, as it was
594 recognized as critical to improving the overall quality of the printed objects, mostly in terms of
595 aspect, mechanical resistance and sealing between layers (Bähr and Westkämper, 2018; Carlier et
596 al., 2019; Gordeev et al., 2018; Martinez-Marquez et al., 2018; Mohamed et al., 2015; Sood et al.,
597 2009). For example, a study evaluated the possibility of using a custom-made sensor (*i.e.*, a rotation

encoder driven by the movement of the filament) to detect the advancement of the filament in the extruder of any FDM printer (Soriano Heras et al., 2018). By checking the encoder rotation repeatedly, control software could determine if the filament is going forward at the desired rate. If no progress is detected, the equipment will stop, allowing the operator to intervene in a timely manner without having to discard the part. This approach, by providing feedback control on the amount of input filament, would also allow for the adjustment of extrusion speed if the measured value does not match the desired one.

A few preliminary studies also can be found in the scientific literature relevant to the fabrication of dosage forms/DDSs (Alhijjaj et al., 2019; Gioumouxouzis et al., 2017; Markl et al., 2018; Palekar et al., 2019; Smith et al., 2018a, b). However, in these first attempts only a limited number of operating conditions were taken into account, while numerous processing variables - most of them with intrinsic dependence on each other - still need further investigation. These variables include release performance, aspect, density, porosity, friability, fragility and presence of contaminants, such as heavy metals, microbiological and byproducts. In addition, future studies should analyze the reproducibility of the printing process, not only for a single print but for all the products belonging to a single batch.

In order to guarantee batch-to-batch uniformity and accelerate the final batch release, the integration of analytical techniques generally used in quality control laboratories into the printers would be highly beneficial (Aucamp and Milne, 2019; Edinger et al., 2018a; Goyantes et al., 2018; Khorasani et al., 2016; Lamichhane et al., 2019; Markl et al., 2017; Robles-Martinez et al., 2019; Scoutaris et al., 2018; Smith et al., 2018a; Trenfield et al., 2018c, 2020).This approach, already tested in continuous manufacturing processes, can be enabled by process analytical technologies (PAT) such as optical measurements and spectroscopic tools (*e.g.*, different infrared spectroscopy techniques such as FTIR and NIR, X-ray, Raman) (Trenfield et al., 2018a; Rahman et al., 2018). Indeed, the latter has already been demonstrated to be suitable for real-time monitoring of various critical quality attributes, such as mass uniformity, moisture content, polymorphism, purity, air entrapment,

size, drug content, hardness and disintegration time. Temperature and image sensors, ultrasound, hyperspectral imaging and lasers also could be implemented in on-line measurement of melting temperature, individual layer thickness and product geometry. For example, image analysis would enable operators to obtain multiple views of a product during fabrication so it could be compared with a virtual model to rule out any possible deviations. Thermal imaging could provide insight into polymeric material interfaces, providing a tool to predict thermomechanical properties of the final product and give early warning of potential degradation. Terahertz pulsed imaging would yield data on the microstructure of the printed products. Mathematical models also could be built from the collected data in order to predict the quality attributes of the systems under fabrication, such as assay, dissolution and impurities, to enable the release of a batch without conventional analytical testing (Aho et al., 2019).

Indeed, the attainment of a personalized drug product might be considered an inverse problem, since its characteristics (*e.g.*, combination of active molecules, release profiles, mechanical properties) are predetermined in view of the needs of specific patients, and the task is to establish which parameters (*e.g.*, infill, number of shells, starting materials, product geometry) would assure quality of the printed products (Novák et al., 2018). The concept of finding the solution to an inverse problem, taking advantage of well-known correlations between operating parameters and outputs is a common strategy in many fields of product development. Obviously, before being able to enforce such mathematical models based on reliable correlations (of a deterministic or statistical nature), they need to be developed, optimized and validated. The availability of a significant amount of data collected during 3D printing prototyping campaigns and small-series production runs could help in building models with machine learning algorithms. The models could then be refined as more data are collected in larger-scale production campaigns. Highlighting the importance of this approach, a few research studies very recently began to focus on this topic, for instance, with the goal of generating a library of critical quality attributes. This library could be attained by following specific modifications of already identified critical 3D printing parameters,

including those relevant to the design step (Korte and Quodbach, 2018; Markl et al., 2017, 2018; Smith et al., 2018a,b; Solanki et al., 2018).

Notably, development of software able to create and store suitable digital models of specific items, set operating parameters and capture, manage and save resulting data and all other information associated with production records in a dedicated cloud-based system, would be equally important (Gioumouxouzis et al., 2019; Khatri et al., 2018). At the same time, such software has to be protected from undesired external access, as it would contain sensitive metadata. Moreover, it might be proprietary and developed to work with specific printers, thus increasing the security requirements, but also limiting sharing and accessibility. This software would also create a paperless quality control system, which is essential. For example, one could study the feasibility of QR codes to be verified by smart devices equipped with barcode scanners to enable the tracing of different batches, avoiding mix-ups. Recently, this strategy has also been applied to the fabrication of monolithic systems on top of which traceability codes were printed by inkjet printing (Edinger et al., 2018b; Trenfield et al., 2019b).

Software should be checked at pre-established time intervals, to prevent any possible cyber risk (Gioumouxouzis et al., 2019; Khairuzzaman, 2018; Souto et al., 2019). Moreover, issues involving liability, intellectual property and data protection (*e.g.,* digital model, profiles containing the operating parameters, patient data) would need to be addressed to protect manufacturers, operators and end-users.

Appropriate procedures need to be developed, especially regarding batch acceptance/rejection. These would benefit from mathematical models built starting from PAT data. Employees should be trained not only on the hardware (*e.g.,* on how to operate, clean and maintain the printer and solve possible issues or deviations), but also on the software.

2.5 Environment

The environment where the FDM process is performed also is a key factor impacting the quality of the finished product, especially if unit operations other than 3D printing are carried out simultaneously, as this increases the risk of cross-contamination and hazards for all manufacturing operators involved (Araújo et al., 2019). Such facilities would benefit from a controlled modular structure, as this would reduce the abovementioned risks and simplify the replication of the manufacturing lines in different locations. In this respect, the number of modules to be installed might depend on the expected production volume. As previously discussed, these facilities might be viewed as small-scale manufacturing plants, as they would be conceived with an industrial mindset; for instance, they would be highly automated. Indeed, manual operation would not be suitable for the safe manufacturing of numerous batches of personalized drug products in view of possible issues related to traceability and mix-up. This awareness would open new and interesting opportunities in the application of robotics in pharmaceutical manufacturing, which has just begun to be explored (Fiorini and Botturi, 2008; Kapoor et al., 2020; Rutherford and Stinger, 2001). The new facilities also would be characterized by consistent design, well-established infrastructures, frequently updated procedures, well-maintained hardware/software and suitable and verified control tools, as well as trained personnel. Overall, these would be difficult and expensive to include in a traditional compounding pharmacy, also due to the considerable amount of electricity required to maintain the infrastructure.

3. Risks to the operator

Although researchers currently are making significant efforts to quickly and thoroughly investigate the potential of FDM in fabricating drug products, safety-related studies so far have not been pursued with comparable intensity (Gioumouxouzis et al., 2019; Jamróz et al., 2018a). These issues are crucial in understanding the challenges entailed by a new manufacturing process, for which

699 managing risks and guaranteeing adequate safety conditions for operators' health and for the
700 environment is essential.
701 Fabricating medicines often entails extended exposure to chemicals and hazardous conditions
702 (Bhusnure et al., 2018; Binks, 2003; Gathuru et al., 2015;
703 https://www.who.int/medicines/areas/quality_safety/quality_assurance/ApplicationHACCPMethod
704 ologyPharmaceuticalsTRS908Annex7.pdf?ua=1). These conditions must be strictly controlled and
705 highly regulated to guarantee that personnel will always work under specific levels of tolerated risk
706 for each potentially hazardous variable (*i.e.*, threshold limits). In traditional manufacturing that uses
707 well-established machinery and processes, possible sources of risk are already well-known and
708 easily predictable so that relevant countermeasures can be adopted. Novel technologies, on the other
709 hand, require the development of specifically tailored risk-related studies. In this respect, safety
710 evaluation of the mechanical hazards associated with FDM production cycles, such as hot parts and
711 motors, and the risks associated with exposure to fumes, are needed. While the former would be
712 relatively easy to handle, the latter is still at an initial phase outside of the pharmaceutical area
713 (Byrley et al., 2018; Floyd et al., 2017; Gümperlein et al., 2018; Jeon et al., 2020; Yi et al., 2016;
714 Zhang et al., 2017b).
715 Indeed, this topic has begun to be addressed in view of the increasing popularity of FDM machines
716 for at-home and office use. Researchers recently have evaluated the contaminants developed during
717 3D printing processes, due to the high temperatures involved, and the effects of printer and filament
718 properties on levels of contaminants (*e.g.*, approximately 300,000 particles/cm^3 and
719 65,000 particles/cm^3 for acrylonitrile butadiene styrene and polylactic acid filaments, respectively).
720 Overall, FDM equipment has been shown to release volatile organic chemicals (VOCs) and
721 ultrafine airborne particles (*i.e.*, < 100 nm in diameter), indicating the potential for inhalation and
722 consequent health risks, especially with long-term exposure. These contaminants are emitted during
723 the thermal processing of many thermoplastic materials and also can be generated when FDM is
724 used to fabricate drug products starting from filaments based on pharmaceutical-grade polymers.

While ultrafine particles may have serious health effects, such as increased oxidative stress, inflammation, cardiovascular effects and cytotoxicity, VOCs may contribute to the development of asthma, allergies, obstructive pulmonary disease and lung cancer (House et al., 2017). Particularly, people using 3D printers reportedly may be at risk for respiratory problems, including work-related asthma. Studies on animal models also have shown that such small particles may migrate to the brain through the olfactory system.

Systematic studies have evaluated risks associated with FDM, relying on a wide range of experimental methods, mainly those using commercially available filaments and equipment (Stefaniak et al., 2017; Steinle, 2016; Wojtyła et al., 2017, 2020). Although nozzle temperature has largely been recognized as one of the most important variables for generating contaminants, other factors may play major roles. These include:

i) the type and state of the printer, *e.g.,* presence of an external enclosure, number of nozzles, state of maintenance;

ii) the operating parameters, *e.g.,* print speed, printer nozzle size, layer height, build plate temperature;

iii) the characteristics of the employed filament, *e.g.,* presence of adjuvants or undesired contaminants that could occur in degradation;

iv) the characteristics of the item to be printed, *e.g.,* weight and complexity, which impact fabrication time;

v) environmental factors, *e.g.,* room size, ventilation, presence of filters.

In order to develop a safer-by-design approach, FDM standard emissions testing protocols should be developed, for instance, drawing inspiration from those already available for laser printers.

Scientific works have also advised transforming precautions into operator safety procedures. Recommendations include *i)* using a full enclosure, *ii)* operating the printer in a well-ventilated room and directly ventilating the printer, *iii)* maintaining a certain distance from the equipment to

minimize inhalation of emitted particles, *iv)* turning off the printer, in the case of nozzle clogging, and allowing it to ventilate before removing the cover, and *v)* relying on the industrial hygiene hierarchy of controls to mitigate exposures (*i.e.*, from most to least preferable: engineering controls, administrative controls, protective equipment).

When considering structures dedicated to FDM, especially for drug products, installing special filters should be considered (Byrley et al., 2019; Floyd et al., 2017). While HEPA filters seem to be ineffective, filters relying on photocatalysis could represent a possible solution. These do not lead to the adsorption of pollutants, but instead degrade them via the activation of oxidative reactions. Moreover, photocatalysis can remove pollutants in very low concentrations, enabling odorless and safe printing.

4. Regulatory engagement

3D printing is considered as an emerging technology due to its potential to improve product safety, identity, strength, quality, or purity in certain applications (Khairuzzaman, 2018; Souto et al., 2019; Lee and Zidan, 2018; Zidan, 2019; Zidan et al., 2019a, b). Through the Emerging Technology Program (ETP) developed by Office of Pharmaceutical Quality, Center for Drug Evaluation and Research (CDER), sponsors can engage with the Agency to discuss, identify, and resolve potential technical and regulatory issues regarding the development and implementation of a novel technology prior to filing a regulatory submission (https://cdn.ymaws.com/www.casss.org/resource/resmgr/dcdg_events/1218_DCDG_BrorsonKurt.pdf; https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program; https://www.fda.gov/files/drugs/published/Advancement-of-Emerging-Technology-Applications-for-Pharmaceutical-Innovation-and-Modernization-Guidance-for-Industry.pdf; https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/advanced-manufacturing).

To support the ETP, FDA engages in proactive research on the impact of emerging technologies on

product quality. Knowledge gained from the internal and sponsored research inform the feedback provided the ETP, ensuring that FDA regulatory policies reflect state-of-the-art manufacturing science. FDA representatives also actively participate in ongoing public-private partnerships to collaborate with a broad range of interdisciplinary stakeholders. FDA is a member of America Makes and participates in research, standards, and road-mapping activities to foster high quality innovation in 3D printed medical products (https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/advanced-manufacturing).

The controls, characterization, and testing necessary to ensure product quality for 3D printed drug products may depend on a variety of factors, such as properties of the active ingredient and other formulation components, geometry of the product, 3D printing technology and parameters, drug loading and type of product, *e.g.*, single, multiple, personalized or drug-device combination. Given the variety of 3D printing technologies, materials, geometries and designs, there is no one size fits all control strategy that may be applicable in all cases. In this respect, manufacturers are responsible for determining and justifying with supporting information an appropriate control strategy for their products. It is then anticipated that 3D printed drug products will generally follow the same regulatory requirements in terms of safety, efficacy and quality, and submission expectations as any drug product manufactured using other techniques. In some cases of fixed dose combinations and drug-device combination products, 3D printing manufacturing may raise different questions of safety and/or effectiveness specifications. If the type of technical information to be provided in the submission for a 3D printed drug product is unclear, manufacturers may engage with ETP through the pre-submission process to obtain more detailed feedback.

5. Conclusions

Moving to FDM 2.0 in 2020 is a challenge the pharmaceutical community can win. In this respect, this manuscript aims to be a state-of-the-art portrait of FDM, providing readers with a wide and

critical overview of the knowledge acquired and areas that still need to be addressed. Indeed, such a provocative approach could be useful in laying the foundation for implementing FDM in the manufacturing of efficacious, safe and high-quality drug products that are suitable for human use. Once the FDM 2.0 phase starts, a next step is to consider good distribution practices, in order to define the role of the printing infrastructure–direct distribution or just manufacturing and reference for traditional distribution?

Much work clearly needs to be done before personalized 3D printed products become widely available to patients, not just from the viewpoint of manufacturing. Understanding which regulatory paths apply to the different phases of the overall process (*e.g.*, approval of starting materials, printers, software, control tools, environment) might be more difficult (Gioumouxouzis et al., 2019; Khairuzzaman, 2018; Stones and Jewell, 2017).

Moreover, a debate still exists as to whether 3D printed medicines should be fabricated only for products with expired patents. For example, extemporaneous formulations following the prescription of a licensed professional are exempted and should not be considered patent violations, according to intellectual property law in several countries. On the other hand, if 3D printed medicines will be industrially produced, the means of undertaking clinical trials or bioequivalence studies to ensure safety are still unclear. However, since these drug products would be fabricated for specific subjects with unique characteristics, and therefore would differ from each other, a quality approach based on the statistical analysis of the data for a predetermined number of volunteers would be particularly challenging and expensive, especially if such studies would be performed on each individual. Gathering patient feedback and monitoring the critical parameters for a specific disease (*e.g.*, blood pressure, insulin level) would therefore represent a potential alternative to evaluating effectiveness of personalized products.

In conclusion, to make FDM-printed personalized drug products available to patients, manufacturers and all the people involved must carefully consider all the aspects described in this

review. The effective collaboration of different experts from academia, regulatory agencies, and industry may provide a great start for launching a first personalized product as a proof of concept.

Conflict of interest

No potential conflict of interest was reported by the authors.

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