

Review



Expert opinion on extrusion-based pharmaceutical 3D printing from the European Society of Hospital Pharmaceutical Technology (GERPAC)

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ARTICLE INFO

Keywords:

3D printing
Pharmaceutical technology
Hospital pharmacy
Legislation
Quality assurance
Quality control
GMP

ABSTRACT

Three-dimensional (3D) printing technologies have been applied to manufacture a variety of medicinal products. This emerging technology holds significant potential in pharmaceutical applications, offering innovative solutions for both patients and pharmacies. In this paper, we describe the application of 3D printing in the hospital pharmacy setting. To describe the current and future role of 3D printing in hospital pharmacies, we start by discussing the relevant legislation of the three key European regulatory bodies: the European Medicines Agency (EMA, EU), the Swiss Agency for Therapeutic Products (Swissmedic, Switzerland), and the Medicines and Healthcare Products Regulatory Agency (MHRA, UK). Furthermore, we discuss critical elements of the printing process, such as quality assurance aspects of 3D printed tablets, focusing on quality management systems, process validation, and in-process controls. Additionally, we introduce three extrusion-based 3D printing techniques applicable in a clinical setting: fused deposition modelling (FDM), semi-solid extrusion (SSE), and direct powder extrusion (DPE). The different printing materials used for each technique are described, and examples of related GMP-compliant printers are given. We also address quality control measures and propose specifications for the final printed products. The information on the regulatory frameworks, quality assurance, printing techniques, and quality control is combined to develop a practical example of how extrusion-based 3D printing could be implemented in hospital pharmacy practice.

Abbreviations: ASTM, American Society for Testing and Materials; CAD, Computer-Aided Design; CMA, Critical Material Attributes; CPP, Critical Process Parameters; CQA, Critical Quality Attributes; DPE, Direct Powder Extrusion; EMA, European Medicines Agency; FDM, Fused Deposition Modelling; GAMP, Good Automated Manufacturing Practices; GPP, Good Pharmacy Practice; GMP, Good Manufacturing Practices; HME, Hotmelt Extrusion; ISO, International Organization for Standardization; MHRA, The Medicines and Healthcare products Regulatory Agency; NIR, Near-Infrared; PAT, Process Analytical Technology; SSE, Semi-Solid Extrusion; 3D, Three-Dimensional.

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<https://doi.org/10.1016/j.ijpharm.2025.126321>

Received 1 July 2025; Received in revised form 26 October 2025; Accepted 26 October 2025

Available online 30 October 2025

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1. Introduction

Three-dimensional (3D) printing technology can prepare personalised medicines through computer-aided design (CAD). 3D printing has been used to manufacture medicinal products, such as immediate-release and controlled-release tablets, dispersible films, microneedles, implants, and transdermal patches. This emerging technology has great potential in pharmaceutical applications, providing innovative solutions for both patients and pharmacies (Trenfield et al., 2018; Wang et al., 2023).

All over Europe, research groups are exploring this new technique and its possible applications. In hospital pharmacy settings, several projects have already demonstrated the feasibility of 3D printed tablets. For example, at the University Medical Center Hamburg-Eppendorf chewable child-appropriate dexamethasone tablets were developed to prevent chemotherapy-induced nausea and vomiting (Dadkhah et al., 2025). At Vall d'Hebron University Hospital in Barcelona chewable hydrocortisone formulations for a clinical study in children with adrenal insufficiency were developed (Rodríguez-Pombo et al., 2024). At the Leiden University Medical Centre a 3D printed sildenafil tablet formulation was developed and shown to be bioequivalent to the commercially available product (Lyousoufi et al., 2023).

This technology offers precise construction of solid and semi-solid dosage forms. 3D printing provides a versatile solution for producing 3D printed dosage forms such as tablets, capsules, buccal films, and suppositories. It can also print non-enteral dosage forms such as implants and microneedle transdermal drug delivery systems. The technique is adaptable, enabling the provision of different drug formulations and addressing patient-specific needs. It can enhance medicine design by facilitating patient-centric personalized dosing and accommodating treatments for specific disease states and patient populations, for example, the paediatric and geriatric populations. This can be especially beneficial when conventional options are not available (Tracy et al., 2023; Wang et al., 2023).

It is well known that solid oral dosage forms, such as capsules and tablets, are favoured over other routes of administration. The ability to 3D print solid oral dosage forms gives the flexibility to customise dose, shape, size, release profile, appearance, and texture. (Krueger et al., 2022). Rather than replacing existing production methods for solid oral dosage forms, 3D printing is a technology that can be used to enable precision medicine for specific patient populations that require adaptations in dosage forms and strengths (Milliken et al., 2024).

In contrast to traditional preparation methods for extemporaneous products, 3D printing offers an automated, precise, and consistent production process. The precision of 3D printing has the capacity to ensure accuracy in medicine dosing and consistent product quality. This reduces the risk of dosing errors and variability, enhancing overall treatment safety. Automation reduces the workload for pharmacy staff and nurses, minimizes waste through precise and on-demand manufacturing, and therefore supports sustainable pharmaceutical practices (Peng et al., 2024; Wang et al., 2023).

However, guidelines implementing this technique in hospital pharmacy practice are insufficient. To address this deficiency, the European Society of Hospital Pharmaceutical Technology (GERPAC) has launched a series of articles featuring a panel of European experts. The aim of this series is to provide insights into the technological, regulatory, and quality aspects of 3D printed solid oral dosage forms that will help both pharmacists as well as regulators to properly assess the use of this technique. The difference in quality approaches for pharmacies that will develop their own formulations as well as pharmacies that use existing inks will be addressed. In this first article, 3D printing of solid oral dosage forms will be introduced, legislation, quality assurance, and quality control discussed, several printing techniques compared, and some operational examples presented. A second article will present a more detailed quality framework, including equipment validation, formulation design and validation, and a description of the gaps and

challenges of the current regulation for pharmaceutical 3D printing in the hospital pharmacy. Furthermore, the second article will include practical examples to show how quality issues can be addressed.

2. Legislation

Currently, there is no specific guideline on the preparation of 3D printed medicines. Several research groups have highlighted that the lack of a regulatory framework forms a challenge to implementing the 3D printing technique in practice (Beitler et al., 2022; Parramon-Teixido et al., 2025). In most cases, 3D printing is used for and considered an extemporaneous preparation. This is usually referred to as a magistral medicine in Europe and is a Section 10 medicine in the United Kingdom. Section 10 refers to the Section of the Medicines Act describing a manufacturing license exemption when conducted under the supervision of a pharmacist in suitable premises. Therefore, we believe the general assessment of 3D printing does not differ from other processes, like the extemporaneous preparation of capsules or oral solutions. The apparatus and technology are new, and uncommon excipients are used in current pharmacy preparations; therefore, special attention and guidelines are necessary. The three key European regulatory bodies have different approaches to aligning the new technique with the current guidelines.

2.1. Europe

The European Medicines Agency (EMA) has been playing an active role in the regulatory framework for 3D printed medicines. While the EMA has not yet established specific guidelines exclusively for 3D printed pharmaceuticals, the general principles of Good Manufacturing Practice (GMP) and the existing regulatory framework for medicinal products apply. The EMA emphasises the need for quality control, safety, and efficacy of 3D printed medicines, with traditionally manufactured medicines (Englezos et al., 2023; Kumar Gupta et al., 2022).

Furthermore, the EMA has also set up the Quality Innovation group (QIG) as a multi-disciplinary group which aims to advance medicine regulation by encouraging research and innovation. In April 2025, the QIG organised a Listen and Learn Focus Group (LLFG) on personalised medicines, bringing together representatives from academia and industry in manufacturing. Different case studies of 3D printing have been proposed by stakeholders focusing on scientific challenges and solutions. The QIG considers 3D printing as a promising and emerging pharmaceutical manufacturing technology. During the LLFG, it was discussed that 3D printing is used in some pharmacies as a magistral preparation. To scale this technology, decentralised production is needed. To implement decentralised production, an automated, standardized production process using qualified printers, GMP-compliant pharmaceutical inks, and validated processes is required. While acknowledging current challenges, the QIG emphasizes that risk-based approaches will be essential for successful implementation. Some manufacturing and supply models envisioned by stakeholders do not fully align with the existing EU regulatory framework, but potential pathways may be identified within current legislation. The QIG is committed to developing guidance focused on quality and manufacturing standards, including the regulatory status of pharmaceutical inks. Stakeholders are encouraged to engage with national authorities and share performance data to support harmonisation and regulatory acceptance of 3D print technologies (Quality Innovation Group (QIG) (2025)).

2.2. Switzerland

The Swiss Agency for Therapeutic Products (Swissmedic) is responsible for the regulation of 3D printed medicines. Swissmedic closely follows the regulatory framework established by the European Union, thereby ensuring that 3D printed drugs are subject to the same rigorous

standards for quality, safety, and efficacy as conventional pharmaceuticals. While specific guidelines for 3D printed medicines are still under development, the general principles of GMP and existing pharmaceutical regulations are applicable (Englezos et al., 2023; Kumar Gupta et al., 2022).

2.3. United Kingdom

The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for regulating 3D printed medicines. The MHRA has published documents supporting the implementation of point-of-care (POC) manufacturing, highlighting the regulatory hurdles and quality control requirements. The importance of process analytical technology (PAT) and non-destructive analytical tools in ensuring the quality of 3D printed medicines needs further investigation (Jørgensen et al., 2023).

On 23 July 2025, new UK regulations came into force to enable the manufacture and delivery of two new categories of medicines: POC medicines and modular manufacture (MM) medicines (Medicines & Healthcare products Regulatory Agency, 2025). POC medicines are medicines manufactured at or very close to the POC, such as a hospital ward or even a patient's home. An example is the treatment of a diabetic foot ulcer using blood products derived from the patient and manufactured at their bedside. MM medicines are manufactured in relocatable units, allowing for more flexible and localized production, such as during mass vaccination campaigns (Gray, 2025). POC and MM offer the potential for faster delivery of treatments, especially products with short shelf lives or highly specialized needs. POC products will typically have a shelf life of under an hour, which justifies manufacturing at or near the site of use or administration. 3D printed tablets are being developed to enable dose flexibility, patient-centred design, multidrug combinations, and unique dosage forms. They enable personalising of medicines and are initially expected to target the very young and the elderly. They provide an alternative to extemporaneously dispensed oral solutions. A benefit of 3D printed tablets over oral solutions is that products with poorly aqueous-soluble active substances can be formulated without the need for co-solvents such as ethanol and propylene glycol. 3D printed tablets will generally have a longer shelf life than their oral solution equivalents. However, some 3D tablets may have short shelf lives and be eligible for manufacturing under the POC regulations. It is anticipated that 3D tablets with longer shelf lives will not be eligible. As some 3D tablets are formulated as individual patient doses, there may be a case for MM medicines.

Most 3D printed tablets will be manufactured outside MIA or MIA (IMP) regulations, and under current UK Specials Licences (Unlicensed medicines) or dispensed by a pharmacist under the Section 10 exception of the Medicines Act. However, when these tablets are manufactured, they must comply with the relevant tablet monographs in the European Pharmacopoeia. Tablets with long shelf lives may be expected to comply with all or most of the specifications; however, those with short shelf lives or immediate-use requirements may require less finished product testing and rely on previous validation and good dispensing practices to ensure the quality of the finished product.

Both the QIG report and the new UK regulations are initial steps towards developing regulations that will facilitate the implementation of printing. However, these regulations focus on the printing at the POC and subsequent delivery to the patient. It is anticipated that not all POC pharmacies will produce their own inks. Effective regulations for intermediate products to ensure the delivery of convenient and safe inks to the POC are currently lacking. An option could be to authorize the release and distribution of inks with a Certificate of Analysis, appropriate process quality assurance, and product validation (see Section 3. Quality Assurance of 3D printed tablets). This will facilitate the fast and flexible use of 3D printing, which is necessary to fulfil its promise for personalized medicine. This will improve ink quality as production is rationalised and batch sizes increase.

3. Quality assurance of 3D printed tablets

Given that the regulatory landscape on 3D printing is still evolving, the quality strategy must be carefully considered to ensure the quality of the product. The quality strategy should include the printer, digital design, raw and intermediate materials, manufacturing, and controls. (Auel et al., 2025). As 3D printing is mostly used for extemporaneous preparations in the hospital setting, this section will follow the quality assurance principles for extemporaneous preparations. However, 3D printing may also be used for other purposes, such as in clinical trials, where clear regulatory requirements are already established (European Parliament (Council of the European Union), 2014).

The time scale and limited shelf life of extemporaneously prepared medicines usually preclude finished product analytical testing. As batches are small, destructive quality testing is ideally avoided or kept to a minimum. Therefore, the quality of the medicine is reliant on overall quality management, including process validation and in-process controls (IPC).

Process validation and equipment qualification assure that the finished product is reproducibly prepared to the required quality specifications. A documented risk assessment of the facilities, equipment, utilities, and processes should be undertaken to determine the extent of the qualification and validation required (European Commission, 2003; World Health Organization, 2011). Pharmacists should follow Good Pharmacy Practice for the preparation of extemporaneous medicine. Consider testing three consecutive, independent batches to ensure the batch complies with the in-process and finished product specifications. Use at least two separate and independent batches of starting materials. Equipment incorporating novel or complex technology should undergo a comprehensive qualification process, which includes user requirement specification, design qualification, factory and site acceptance testing, installation qualification, operational qualification, and performance qualification. Validation and qualification are important where finished product testing is limited. Statistical process control will be of value (Le Brun et al., 2024).

The printing process can be summarized in four steps (Fig. 1). The object is first digitally created using CAD or other imaging techniques. The CAD is then converted into a file (for example, .stl or .obj file), which contains the information regarding the design and geometry of the object. This file is converted into a printer-specific coding file (.gcode), containing instructions for the layer-by-layer production of the three-dimensional object. The final step is design optimization, which uses several printed samples and an analysis of printing parameters to refine and revise the printing file (Jamróz et al., 2018; Le Brun et al., 2024). Although not strictly part of the printing, it is possible to print directly onto suitable packaging. This could be a valuable addition to the POC.

A healthcare establishment's 3D printing hardware, firmware, and software must be fit for use to print human medication. The software should comply with Good Automated Manufacturing Practices (GAMP). Compliance ensures data integrity, product quality, and patient safety (International Society for Pharmaceutical Engineering, 2022).

Pharmaceutical process validation identifies potential sources of variability and risk that could impact product quality. The parameters used to identify these sources are critical quality attributes (CQA), critical process parameters (CPP), and critical material attributes (CMA). CPP and CMA can impact the CQA. The CQA for most 3D printed tablets are the same as for regular tablets. While the CPP and CMA are dependent on the printing technique (see further in Section 4) (Rathore and Mhatre, 2008; Step, 2017). An example of how CQA were determined for 3D printed tablets is the preparation of 3D printed furosemide and sildenafil via a novel heated, piston-driven semi-solid extrusion 3D printer. The designers considered what quality tests were appropriate to measure the CQA and which were not (See Table 1, (Lafeber et al., 2021)). Although the table is for a specific printing technique (SSE), it applies to other printing techniques, as the quality tests are performed on the final dosage form.

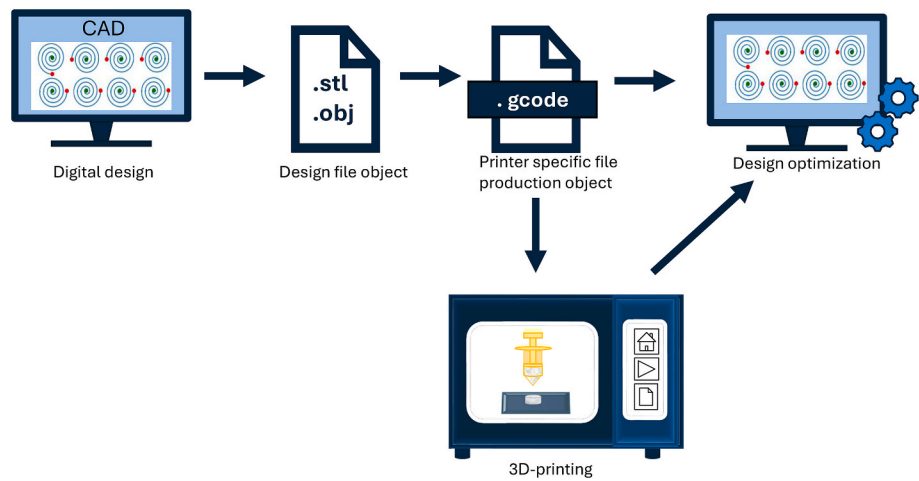


Fig. 1. Summary of the 3D printing process.

Table 1
Example of quality requirements as stated by the Ph. Eur. general monograph concerning their suitability to SSE 3D printed tablets (from Lafeber, et al., 2021 – with permission).

Critical quality attribute (CQA)	Corresponding Quality test by EP	Purpose of the Quality Test	Suitability for 3D printed tablets
Disintegration	2.9.1. Disintegration	Testing the prescribed time needed to disintegrate	Suitable when no dissolution test is performed
Dissolution	2.9.3 Dissolution	Reflect the measured dissolution rate to the intended dissolution rate	Suitable
Weight uniformity	2.9.5 Uniformity of mass	Identify individual deviation of average tablet mass	Suitable when no EP 2.9.40 test is performed
Content uniformity	2.9.6 Uniformity of content	Testing the individual tablet content limits	Suitable when no EP 2.9.40 test is performed
Friability	2.9.7 Friability of uncoated tablets	Ensure sufficient mechanical strength	Not suitable, test is intended for compressed tablets
Hardness	2.9.8 Resistance to crushing	Ensure sufficient mechanical strength	Not suitable, test is more likely to fail due to layering of the tablets
Assay	2.9.40 Uniformity of dosage units	Testing the consistency of the measured tablet content as reflected in the declared content	Suitable
Microbiological quality	5.4.1 Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use.	Ensure microbiological quality	Suitable

The printing process validation is performed differently depending on the type of pharmaceutical ink used. If ready-to-use GMP-compliant pharmaceutical inks were available, additional formulation and product validation would not be needed. In this situation, the focus can be on the

validation of the printer and the related process parameters (for example, temperature, print speed, and nozzle size). In-house formulated pharmaceutical inks require validation of both the ink preparation and the final product. Interactions between the excipients and active pharmaceutical ingredient (API), the printability of the matrix, the melt and solidification behaviour, and the stability should all be assessed before the ink can be used in routine clinical practice.

Pharmaceutical ink starting materials for 3D printing must comply with the same standards as other pharmaceutical APIs or excipients. Some excipients (e.g., colouring matters, flavouring agents) have internationally accepted food purity criteria, according to FAO/WHO standards, and are acceptable for medicinal products in most countries based on national regulations (Committee for medicinal products for human use (CHMP), 2007).

4. 3D printing techniques most applicable in hospital pharmacy

Seven different categories of 3D printing are recognized by the International Organization for Standardization (ISO) and the American Society for Testing and Materials (ASTM) (ISO/ASTM 52900:2021). The classification of the categories is based on the additive shaping principle and the physical build of the 3D object. These categories are material extrusion, powder bed fusion, sheet lamination, material jetting, binder jetting, vat photopolymerization, and directed energy deposition. Material extrusion is the most used method for pharmaceutical preparation.

This article focuses on the principle of material extrusion and the associated printing techniques. An overview of the techniques is shown in Table 2 and illustrated in Fig. 2.

4.1. Material extrusion

Extrusion-based printing is the layer-by-layer fabrication of printable material through a nozzle onto a print platform. There are three printing techniques associated with extrusion-based printing: fused deposition modelling, semi-solid extrusion, and direct powder extrusion printing. Different printable materials are used for each technique (Annaji et al., 2020).

4.1.1. Fused deposition modelling

In fused deposition modelling (FDM), printers extrude thermoplastic polymer filaments through the printer head at a precise temperature and in specific directions. The semi-molten material is deposited on the build plate to form the layers. The drug-loaded thermoplastic filaments used in FDM can be produced by active substance incorporation into the polymer by hot melt extrusion (HME) or impregnation. By impregnation, placebo filaments are produced via HME and soaked in a bath

Table 2

Overview of the printing material, GMP-compliant printers, advantages and disadvantages of the extrusion-based 3D printing techniques (from Practical Pharmaceutics ed. 2 (Le Brun et al., 2024) with modifications).

Technique	Printing material	Critical Material Attributes (CMA)	GMP-compliant printers	Advantages	Disadvantages
Fused deposition modelling (FDM)	Drug-loaded thermoplastic filament	- Rheological properties - Mechanical properties (tensile strength)	- M3DIMAKER (FabRx, UK) - Flexdose™ (Digital Health Systems, Germany) - 3DForMe (Formulators, Italy) - 3D Cultures (USA) - Med U Modular (MB therapeutics, France) - doprOne (Goatam, Germany)	- Complex geometries and structures - Controlled drug release - No post-processing - Low cost	- Difficulty drug loading filament above 30 % - Thermal degradation risk - Pre-processing
Semi-solid extrusion (SSE)	Semi-solid drug mixture (gel or paste)	- Rheological properties –Moisture content - Texture - Particle size of the powders (solid dispersion)	- DoseRx1 (Doser, Netherlands) - M3DIMAKER (FabRx, UK) - Pharma Printer 1 (CurifyLabs, Finland)^a - CraftMake™ (Craft Health, Singapore) - Med U Modular (MB therapeutics, France): - Med U Prod (MB therapeutics, France): - M3DIMAKER (FabRx, UK)	- Multiple printing syringes can be used at once - Suitable for thermolabile drugs - Relatively easy and fast production of inks - No pre-processing - Ability to print soft chewable tablets (gummies) - Low cost - Single step process - More suitable for thermolabile drugs than FDM - High drug load possible - No pre and post-processing - Low cost	- Ratio raw materials critical semi-solid mixture - Post-processing drying residual solvents
Direct powder extrusion (DPE)	Drug-pellet mixture	- Powder flowability - Particle size distribution - Moisture content			- New technique - Low printing resolution - Weight variation risk - Powder exposure

^a : the technique used by this printer is ‘dispensing’ instead of ‘additive manufacturing’ thereby may not be considered as a ‘true’ 3D printer. However due to the similarities of the use of the ink and the final purpose, it is mentioned in this table.

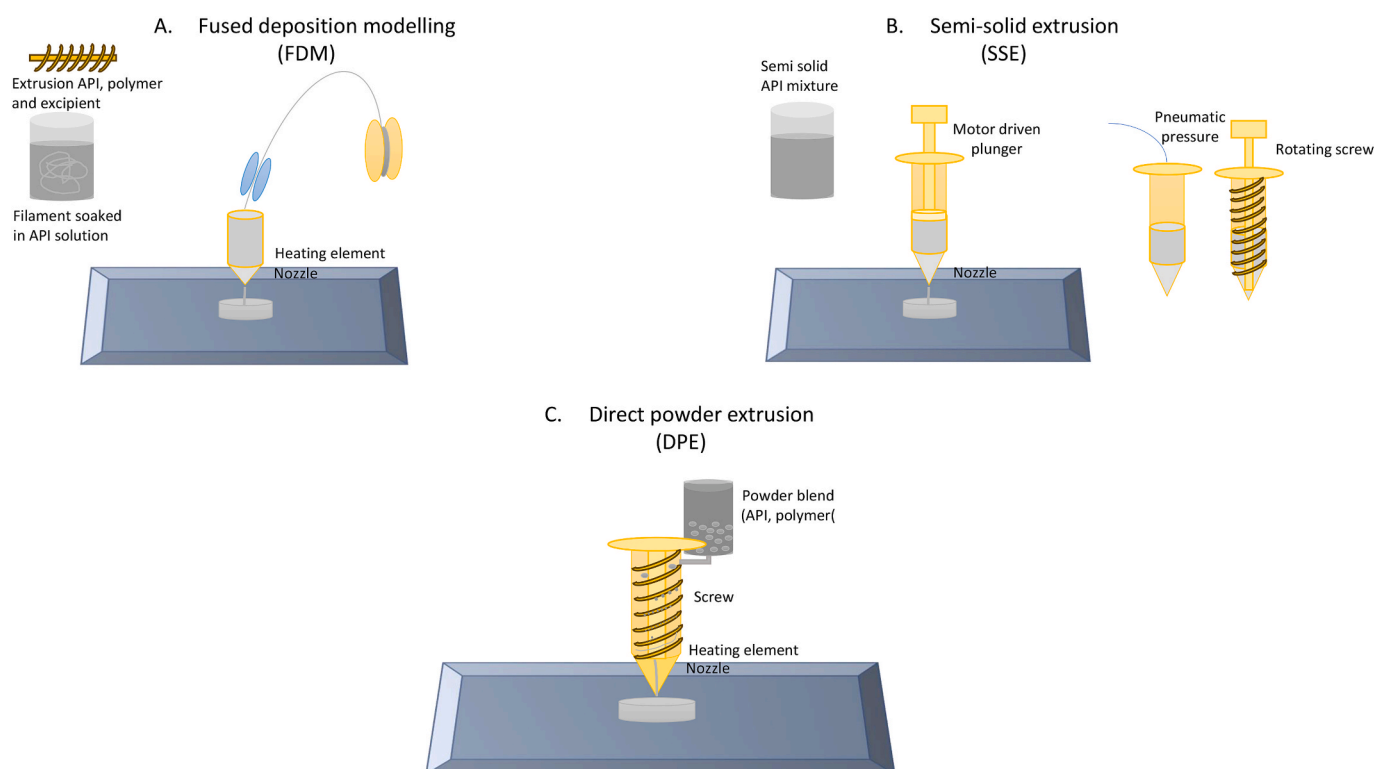


Fig. 2. Illustration of the three extrusion based printing techniques. A. Fused deposition modelling, B. Semi-solid extrusion, C. Direct Powder extrusion.

containing the API. In contrast, with the HME method, the API is directly mixed with the excipients. These two techniques result in different drug loading capacities and release profiles after printing. Thanawuth et al.

demonstrated that a higher percentage (up to 20 %) of indomethacin could be loaded into PVA filaments using HME, compared to a maximum of 5 % via the impregnation method (Thanawuth et al., 2021).

Moreover, drug release is faster with impregnated filaments during dissolution testing, due to different interactions of the API and the behaviour with the polymer matrix. For these reasons, most of the research on FDM ink development relies on HME. Drug loading rates typically range from 1 % to 25 %, and the release kinetics depend on the polymer matrix used, the loading percentage, and the printed morphology (infill and geometry) (Jennotte et al., 2023; Parulski et al., 2023).

The FDM process can be divided into three parts: (i) the extrusion of molten material, (ii) the deposition of material layers, and (iii) the solidification of the layers (generally the cooling of the printed layers). In each zone, various stresses are applied to the filament. Filament brittleness is one of the primary causes of printing defects. To be fed towards the hot end without bending or compressing, and to demonstrate sufficient strength to extrude the molten filament, the filaments must exhibit a good balance between flexibility and stiffness while maintaining appropriate tensile strength (Acierno and Patti, 2023; Alhijjaj et al., 2019; Araújo et al., 2019). In addition to mechanical properties, the rheological properties of the filament are important as they affect the Melt Flow Index and the polymer behaviour after extrusion (layer coalescence and the ability to solidify) (Acierno and Patti, 2023). The rheological and mechanical properties of the filament can be considered as a CMA for the printing process (Acierno and Patti, 2023; Le Brun et al., 2024).

In the case of FDM, the heating poses a risk to the stability of thermosensitive drugs. Studies have shown that high temperatures used in FDM can lead to the degradation of APIs. For example, the degradation of escitalopram oxalate during FDM 3D printing was observed, although the use of protective polymeric matrices can mitigate this risk to some extent (Hoffmann et al., 2023). Similarly, the study on ramipril demonstrated that reducing the FDM printing temperature can help maintain drug stability, but exceeding the melting point can lead to degradation (Kollamaram et al., 2018).

4.1.2. Semi-solid extrusion

In semi-solid extrusion (SSE), a semi-solid mixture is extruded via a syringe-based tool-head nozzle by pneumatic or mechanical pistons. Different dosage forms, such as soft chewable tablets, can be printed with SSE. During the print process, the semi-solid mixture is printed layer by layer on the build plate. The semi-solid mixture consists of a polymer, the active substance, solvents, and excipients. The carrier is usually melted and mixed with the other excipients and API to form the ink. Based on its physical characteristics, the API will either dissolve in the matrix or remain as a solid dispersion. Depending on the printer, the molten mixture will be transferred to a syringe or cartridge. A mortar and pestle, beakers, and simple mixing can be utilised for small-scale preparation (Annaji et al., 2020; Firth et al., 2018; Le Brun et al., 2024; Sun et al., 2024).

There are two types of ink used in SSE 3D printing: solvent-based and solvent-free. Usually, the ink consists of API, gel-forming polymer(s), filler(s), and solvent(s). Colouring agents, flavours, and sweeteners can be added to improve patient compliance. In solvent-free ink, an API is dissolved or suspended in the molten/softened polymer and this ink is suitable for moisture/solvent-sensitive APIs. The CMA for SSE are linked to the rheological properties of the ink, and in the case of a solid dispersion, the particle size of the powders (Annaji et al., 2020; Le Brun et al., 2024).

Since SSE 3D printing technique is flexible, fast, and ready to be manufactured at room temperature, it holds considerable potential for POC applications. However, the challenges remain in identifying CPPs and understanding the behaviour of the ink. To get a thorough understanding of the ink, it is necessary to analyse the rheological and textural characteristics of the formulation, with this understanding, reproducibility, mechanical stability, and the desired release profile can be obtained. (Aina et al., 2025; Liang et al., 2023) The rheological properties of the ink are important to obtain successful extrusion and maintain the

structural integrity of the printed product. The flowability and consistency of the polymer mixture ensure smooth extrusion and retention of the shape and integrity of the printed material. The properties and concentration of the polymer and the choice of excipients influence the mechanical properties and extrudability of the ink. (Aina et al., 2025; Zhang et al., 2023) Additionally, the solvent-based inks require post-processing steps, such as drying or cross-linking, to consolidate the structure and influence the mechanical integrity and drug release of the printed materials. However, these steps can be time-consuming, introduce safety concerns, affect content uniformity, and change the release profile of an API. The choice of post-treatment method has a significant impact on the mechanical properties, stability, functionality, and of SSE-printed materials. Due to these challenges, the formulation and process development of SSE 3D printed dosage forms often relies on trial-and-error, with rheological characterization as one of the most challenging CPP. To scale this technique, GMP-compliant pharmaceutical inks are needed. (Aina et al., 2025).

4.1.3. Direct powder extrusion

In direct powder extrusion (DPE) printing, the printing material consists of a powder or dry pellet mixture instead of a filament (FDM) or a semi-solid formulation (SSE). The powder/pellets are fed by a single screw towards a heating element, and they are melted and extruded through the nozzle head to be deposited layer by layer onto the build plate. Since DPE is a single-step method, the selection of raw materials and the formulation are critical to ensure optimal printability and quality of the final dosage forms. The formulation typically comprises a polymer matrix, APIs, and various excipients, which collectively influence the mechanical properties, drug release profiles, and processability of the printed products. The CMA of the powder formulations are:

– *Powder Flowability*: Consistent powder flow is crucial for uninterrupted printing. Flowability is typically assessed using techniques such as angle of repose, bulk density, and tapped density measurements. Ensuring good flow prevents blockages in the extruder and ensures even layer deposition during printing. For cohesive powders, glidants to the powder blend or mechanical feeders to the printhead may be incorporated to improve flow. (Rosch et al., 2023).

– *Powder Particle Size Distribution*: The particle size of the raw materials, especially the API, needs to be controlled to ensure uniform distribution within the blend and consistent drug content in the printed dosage forms. Laser diffraction can be used to assess particle size distribution, ensuring that particles are neither too large (which could affect print precision) nor too small (which could cause cohesion issues).

– *Moisture Content*: Controlling the moisture content of the powder is important to avoid issues during extrusion, such as clumping or poor flow. Therefore, storing all powders in airtight containers is crucial to ensure a steady level of moisture content (Aguilar-de-Leyva et al., 2024; Goyanes et al., 2019; Le Brun et al., 2024).

4.2. Critical process parameters (CPP)

Even though the techniques of the three extrusion-based methods are different, the CPPs are quite similar. The most common CPP for the printing techniques are:

- Print, nozzle, and build plate temperature
- Feed rate
- Print speed
- Screw geometry (FDM and DPE, for SSE only applicable if a rotating screw is used)
- Object geometry
- Nozzle diameter
- G-code integrity

All these CPP can affect the CQA. The impact of each CPP on the CQA is different for each printing technique. For instance, the build plate

temperature is much more critical for FDM than it is for SSE. In this paragraph, we will discuss the main CPPs and their impact on the CQA.

4.2.0.1. Temperature

Extrusion temperature is a key process parameter significantly influencing the quality of 3D printed tablets, particularly in terms of API stability, amorphization, and polymer viscosity. The extrusion temperature should be optimized to process a printing material to have adequate physical and rheological characteristics during the extrusion process, and further effective layer deposition on the building platform (Azad et al., 2020; Sierra-Vega et al., 2025). The main CQAs impacted by this CPP are dissolution, weight, and content uniformity, mechanical strength.

For FDM, the temperature of the building platform and the temperature of the extrusion nozzle are also CPPs. The temperature of the building platform is usually lower than the extrusion temperature, but the difference between both temperatures should be small enough to guarantee the adherence of the deposited layers. (El Aita et al., 2018; Sierra-Vega et al., 2025) For SSE, the temperature of the cartridge is a CCP due to its influence on stability and the characteristics of the printing material. Nozzle temperature in SSE is generally less critical. However, it still impacts the consistency of extrusion and the quality of the product. It is important to control the temperature of the cartridge and the nozzle as an IPC to ensure the quality of the printed product. (Lafeber et al., 2024).

4.2.0.2. Printing speed

Printing speed is crucial for determining the resolution and details of printed products. The optimal printing speed depends on the desired resolution and the viscosity of the printing material. The interaction between the printing speeds and the flow properties should be optimized: when the printing speed is less or greater than the material flow rate, printing defects such as over- and under extrusion can occur (Mohammed et al., 2021; Sierra-Vega et al., 2025). The main CQA impacted by this CPP is weight uniformity.

4.2.0.3. Nozzle diameter

Nozzle diameter may also impact the quality of the 3D printed product; the diameter may affect the extrusion rate of the printing material, resolution, density, and tensile strength of deposited filament. Additionally, the selection of the nozzle diameter is related to the viscosity of the printing material. Materials of high viscosity require a broader diameter to avoid nozzle clogging and buildup of back pressure (Sierra-Vega et al., 2025; Triyono et al., 2020).

4.3. Raw materials

Polymers are the main components as they provide 2 to 99 % of the structural matrix for the filament. Their characteristics determine the release profiles and processing characteristics of the product (Aguilar-de-Leyva et al., 2024; Azad et al., 2020). Four major families of pharmaceutical polymers have been studied, as well as other excipients (plasticizers, diluents, lubricants, and solvents), as listed in Table 3. The different excipients and polymers can be used for the different techniques:

1. FDM (or HME-FDM) typically includes: (i) thermoplastic polymer, (ii) disintegrant, and (iii) plasticizer. (Banerjee, 2023)
2. SSE typically includes: (i) water-insoluble polymer as a release modifier and/or disintegrant, (ii) water-soluble polymer as a matrix former and/or disintegrant, (iii) solvent. (Banerjee, 2023)
3. DPE typically includes: (i) polymer, (ii) optional excipients (plasticizer, disintegrant, for printability and powder flow)(Aguilar-de-Leyva et al., 2024)

In Table 3, we provide an overview of the different raw materials and

Table 3

Raw material used for FDM, SSE and DPE.

Excipients	Examples	Concentration range
POLYMERS	Alcohol-derived polymers, particularly Poly (Vinyl) Alcohol (PVA);Poly(vinyl) pyrrolidone and its derivatives. Cellulose-derived polymers such as ethylcellulose, hydroxypropyl cellulose, or hydroxypropylmethyl cellulose.Acrylic derivatives like poly (butyl methacrylate-co-(2-demethylaminoethyl) methacrylate-co-methyl methacrylate) 1:2:1, marketed under the name Eudragit® E PO.	- FDM: 45 – 99 % (mostly used ethyl-cellulose, Eudragit®, Polycaprolactone, Polylactic Acid, Polyvinyl alcohol, Soluplus® (=polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer) (Azad et al., 2020) - SSE: 2 – 99 % (mostly used crosslinked polyacrylic acid polymers, Hydroxypropyl (Methyl)cellulose, Polyvinylpyrrolidone, Poly (Ethylene Glycol) (Azad et al., 2020) - DPE: 10 – 99 % (mostly used, Hydroxypropyl(Methyl) cellulose, ethyl-cellulose, Eudragit®, Poly(Ethylene Glycol), crosslinked polyacrylic acid polymers, polyvinylpyrrolidone. (Aguilar-de-Leyva et al., 2024)
PLASTICIZERS	Triethyl citrate Mannitol, sorbitol	The type of excipient and the concentration range that is used varies based on the printing technique, the formulation and the drug load. The formulation is often based on experience and trial-and-error.
DILUENTS	Microcrystalline cellulose, Starch Mannitol, sorbitol	
LUBRICANTS	Magnesium stearate	
DISINTEGRANTS	Sodium starch glycolate	
SOLVENTS (only used in SSE.)	Water Ethanol	

their concentration ranges used for FDM, SSE, and DPE. The ranges that are given in Table 3 are indicative and based on some exploratory literature. The ranges are far from complete because the formulation of the pharmaceutical ink is still mainly based on trial-and-error, and new publications emerge frequently.

5. Quality control of 3D printed tablets

“Pharmaceutical Preparation” is defined in the European Pharmacopeia as unlicensed medicines that are prepared to meet the specific needs of a patient (Magistral or Section 10 dispensed medicine). They do not have to be tested to the finished product specification. However, they would be expected to comply if an analysis was undertaken. The product should comply with the specification at release and shelf-life. These specifications would be similar but not identical; for example, related substances may have wider limits at shelf life. The definition of the pharmaceutical form is of utmost importance in determining which European Pharmacopeia assays can be assigned to 3D printing.

The printed dosage forms vary depending on the 3D technology used. The 3D printed product may comply to the pharmacopoeia definition of tablets or orodispersible films. Quality control parameters for release will depend on the final pharmaceutical form and should be adapted accordingly. Table 4 gives a first approach for release specifications of 3D printed tablets, which will be completed for the other solid oral dosage forms in the next paper.

Table 4 proposes a finished product and shelf-life specification for a 3D printed tablet. A risk analysis of the parameters in Table 4 has been added to assess their impact on the overall quality and their relevance across different 3D printing techniques. This specification is based on a theoretical 3D tablet and the European Pharmacopoeia tablet monographs. It could be used for all 3D printed tablets. Many of the quality control parameters are based on the pharmacopoeia. However, the

Table 4

Finished Product and Shelf-Life Specifications of 3D printed tablets used for the validation of the 3D printing process, including a risk analysis (The European Directorate for the Quality of Medicines and Healthcare, 2024).

Test	Release Specification	Method	Risk level	Relevance 3D printing technique
Appearance	Colour and shape Dimensions – Thickness Diameter Mass	Visual Callipers Balance	Low	Relevant to all techniques
Identification	Extract a quantity of the powdered tablets, the residue complies with the following tests: Infrared Absorption Spectrum Melting point	Ph. Eur. Method 2.2.24 Ph. Eur. Method 2.2.14, 2.2.15, 2.2.16	Medium	Relevant to all techniques
Content of Active Ingredient	95.0 to 105.0 % of the stated amount (at release) 90.0 to 110.0 % of the stated amount (at end of shelf life)	Liquid ChromatographyPh. Eur. Method 2.2.29 (destructive) Near-infrared spectroscopyPh. Eur. Method 2.2.40. (non-destructive) Raman spectroscopyPh. Eur. Method 2.2.48. (non-destructive)	High	Relevant to all techniques
Related Substances	Complies	Liquid Chromatography Ph. Eur. Method 2.2.29 ICH Q3	Medium	Relevant to all techniques
Disintegration	Complies e.g. 15 min	Ph. Eur. 2.9.1	Low – medium	Relevant to FDM and DPE, less relevant to SSE. <i>Dissolutions is considered more critical.</i>
Dissolution	Complies	Ph Eur 2.9.3	High	Relevant to all techniques
Uniformity of dosage units	Uniformity of content Or Uniformity of mass	Ph. Eur. 2.9.40 Ph. Eur. 2.9.6 Ph. Eur. 2.9.5 Ph. Eur. 2.9.7	High	Relevant to all techniques
Friability	Complies, e.g. 1 %. (if applicable, for SSE not applicable)	Ph. Eur. 2.9.7	Low	Relevant to FDM, less relevant to DPE, not applicable for SSE.
Resistance to crushing of tablets	Complies only for tablets	Ph. Eur. Method 2.9.8	Medium	Relevant to FDM, less relevant to DPE, not applicable for SSE.
Microbiological assay for oral form	Complies	Ph. Eur. 5.1.4	Medium	Relevant to all techniques

different printing techniques and materials may require additional or alternative analytical methods. For instance, mechanical strength testing such as texture profile analysis may be more appropriate than traditional friability and hardness tests for DPE and SSE. Rheological analysis is relevant for SSE to assess the printability (Johannesson et al., 2023). The approaches for quality control of the technique-specific products and of the inks used in different techniques will be described in the second article of this series.

To ensure end product quality, non-destructive and fast analytical methods are required (See Section 3 Quality Assurance). These methods are preferably in-line. For example, near-infrared (NIR) technique could be used as a PAT for the identity and content of the tablet (as IPC and/or as final control). NIR is a non-destructive analytical technique that can be used to determine the content and identity of the API in the tablet (Vakili et al., 2017; Yang et al., 2023). NIR could be applied to the use of self-formulated pharmaceutical inks, for which the analytical control of the pharmaceutical ink is not fully conducted. The application of NIR should be considered only if a model has been developed for the specific API in the printing matrix. The development and validation of NIR models come with challenges, and expertise is required for their implementation. For ready-to-use GMP-compliant pharmaceutical inks, the use of NIR is less relevant because the controls on the pharmaceutical inks should already be conducted before the release of the materials. In this case, we would recommend using gravimetric control.

6. Discussion and future prospectives

This article introduces extrusion-based 3D printing and describes the associated legislation, quality assurance, and quality control. This information is used to show what is needed to implement extrusion-based 3D printing in hospital pharmacy practice. The implementation of 3D printing in a hospital setting holds great potential for the application of personalised medicine; it will give us flexibility in the production of

different doses, and it will help us combine multiple APIs in one tablet. This will significantly enhance patient compliance.

Currently, the most used extrusion-based 3D printing technique in hospitals is SSE. Even though DPE and FDM have great potential, their limitations are that either the production of suitable inks for the application is more difficult and requires more research than the inks used for SSE, or there is not much experience with the technique. For SSE, the pharmaceutical ink can be produced at POC. Pharmaceutical inks for FDM are not commercialised yet and cannot be produced at POC. From our knowledge, there is only one GMP-compliant 3D printer available for DPE. Additionally, it is necessary to have good flowability and a homogenous mixture of the powder to have a robust system. However, we believe that the utilisation of 3D printing in a hospital setting will spread once commercial (partial) GMP-compliant pharmaceutical ink becomes available.

The design and production of the pharmaceutical ink play a crucial role in the implementation of extrusion-based 3D printing in the hospital pharmacy. To implement the practice of extrusion-based 3D printing, three different approaches are possible:

- 1. Full design of the pharmaceutical ink by the hospital pharmacy.** The ink is entirely validated in-house, and the product quality is also tested by the hospital pharmacy.
- 2. Partial design using a GMP-compliant base.** A validated base ink is used, and APIs are incorporated by the hospital pharmacy based on earlier validated homogeneity tests of the APIs in this base. The validation of the homogeneity is done by the commercial party that provides the base.
- 3. Ready-to-use GMP-compliant ink with APIs.** GMP-compliant ink with API is supplied by a commercial party and can be directly used in the printer

The implementation of decentralised production will only be feasible

if (partial) GMP-compliant pharmaceutical inks become available. Without the availability of these inks, every formulation must be extensively tested and individually validated before it can be used in routine practice.

Furthermore, to ensure end product quality, non-destructive and fast analytical methods are necessary. For extensively tested pharmaceutical inks, we recommend having a validated production process with a GMP-compliant printer and controlling the produced tablets with a gravimetric control. For pharmaceutical inks that have not been thoroughly tested, the NIR technique could serve as a PAT for identifying and determining the content of the tablets. This can only be applied with a fully developed and validated NIR model for each API and formulation.

A second article will give a more in-depth description of the quality framework, including validation of hardware, software, process, and product. Moreover, quality control approaches for the intermediate pharmaceutical ink and for the 3D printed solid oral dosage forms printed with the different techniques will be proposed. The existing framework for solid oral dosage forms is based on higher volumes and a one-size-fits-all model. However, 3D printing of solid oral dosage forms will be used for small batch-sized personalised medicine, and the gaps and challenges of the current regulation will be described.

CRedit authorship contribution statement

Aisha A. Ahmed: Writing – original draft, Writing – review & editing, Visualization. **Kirsten J.M. Schimmel:** Writing – review & editing, Supervision, Conceptualization. **Marija Tubic-Grozdanis:** Writing – review & editing, Conceptualization. **Catherine Tuleu:** Writing – review & editing, Conceptualization. **Julian Smith:** Writing – review & editing, Conceptualization. **Ian Soulaïrol:** Writing – review & editing, Conceptualization. **Adrin Dadkhah:** Writing – review & editing, Conceptualization. **Mattias Paulson:** Writing – review & editing, Conceptualization. **Anna Lechanteur:** Writing – review & editing, Conceptualization. **Laurent Carrez:** Writing – review & editing, Conceptualization. **Trine Schnor:** Writing – review & editing, Conceptualization. **Frederic Lagarce:** Writing – review & editing, Supervision, Conceptualization. **Paul P.H. Le Brun:** Writing – review & editing, Supervision, Conceptualization. **Sylvie Crauste-Manciet:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Ian Soulaïrol reports a relationship with MB Therapeutics that includes: board membership. Some of the authors are users of commercial 3D-printers that are mentioned in the paper: - Anna Lechanteur: exclusively uses FDM technology. The laboratory owns several non-pharmagrade FDM printers as well as the Medimaker 2 (FabRX). Anna Lechanteur is also involved in a research project aimed at creating a spinoff company specialized in the production of filaments for FDM printers. - Catherine Tuleu: is on the steering committee of the spinoff company specialized in the production of filaments for FDM printers mentioned by Anna Lechanteur. Is also co supervising a UK based PhD project: Mr Munsur Ahmed, funded doctoral fellowship NIHR305227 Research Title “Would the implementation of 3D printing of medicines be acceptable in children undergoing cancer to help to improve adherence, compared to conventional dose forms?” - Frédéric Lagarce, Sylvie Crauste-Manciet, Trine Schnor: Curifylabs-printer are used in their hospital - Adrin Dadkhah: University Medical Center Hamburg-Eppendorf uses Medimaker V1, FabRx - Aisha Ahmed, Kirsten Schimmel: At the LUMC, we use SSE technique with a printer from Doser Medical. We have a research collaboration with Doser (no commercial collaboration). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper].

Data availability

No data was used for the research described in the article.

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