Journal Pre-proofs

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PII: S0378-5173(24)00136-4
DOI: https://doi.org/10.1016/j.ijpharm.2024.123902
Reference: IJP 123902

To appear in: *International Journal of Pharmaceutics*

Received Date: 21 December 2023
Revised Date: 19 January 2024
Accepted Date: 8 February 2024

Please cite this article as: R.L. Milliken, T. Quinten, S.K. Andersen, D.A. Lamprou, Application of 3D printing in early phase development of pharmaceutical solid dosage forms, *International Journal of Pharmaceutics* (2024), doi: https://doi.org/10.1016/j.ijpharm.2024.123902

Application of 3D Printing in Early Phase Development of Pharmaceutical Solid Dosage Forms

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Abstract

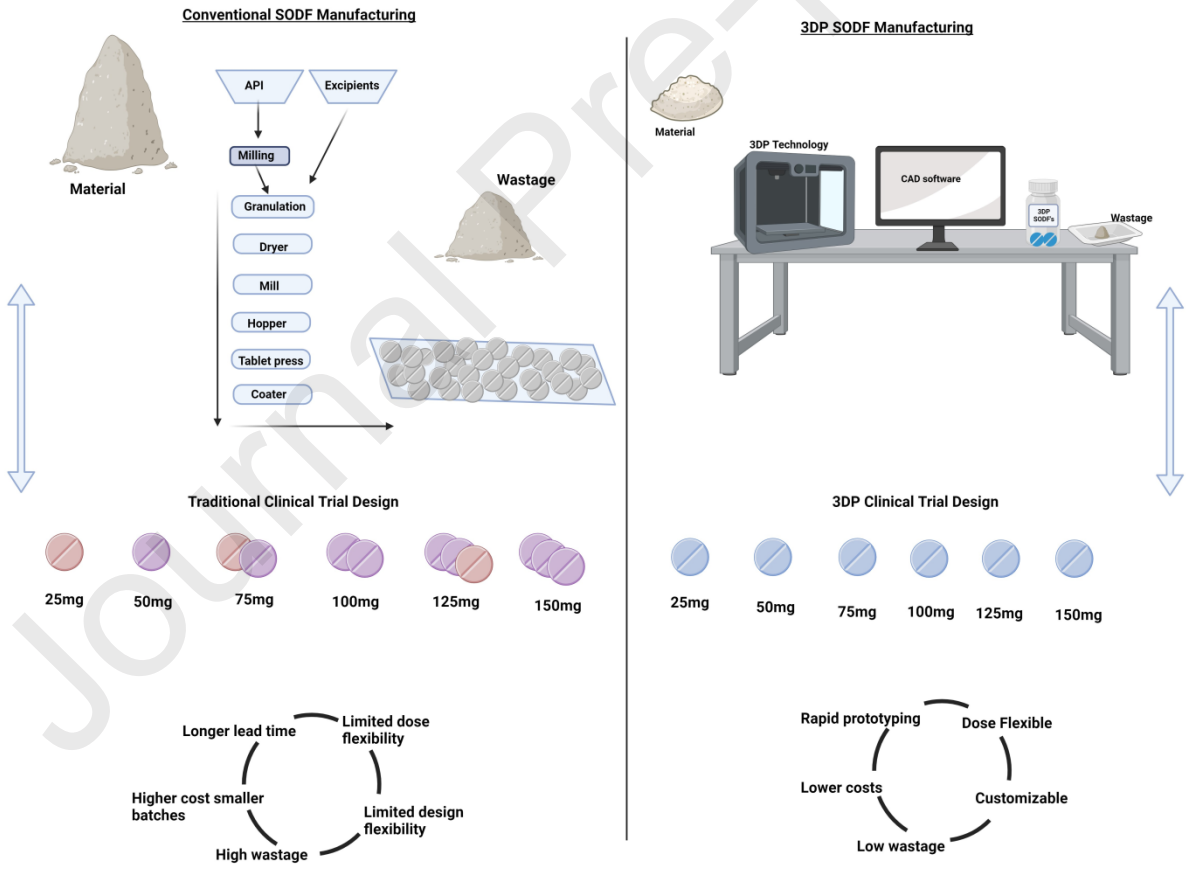
Three-dimensional printing (3DP) is an emerging technology, offering the possibility for the development of dose-customized, effective, and safe solid oral dosage forms (SODFs). Although 3DP has great potential, it does come with certain limitations, and the traditional drug manufacturing platforms remain the industry standard. The consensus appears to be that 3DP technology is expected to benefit personalized medicine the most, but that it is unlikely to replace conventional manufacturing for mass production. The 3DP method, on the other hand, could prove well-suited for producing small batches as an adaptive manufacturing technique for enabling adaptive clinical trial design for early clinical studies. The purpose of this review is to discuss recent advancements in 3DP technologies for SODFs and to focus on the applications for SODFs in the early clinical development stages, including a discussion of current regulatory challenges and quality controls.

Keywords: 3D Printing, Solid oral dosage forms, Preclinical, Pharmaceutical, Rapid prototyping

Abbreviations: 3DP, 3D Printing; SODF's, Solid Oral Dosage Forms; AM, Additive Manufacturing; LbL, Layer-by-Layer; CAD, Computer-aided Design; FDA, Food and Drug Administration; FDM, Fused Deposition Modelling; SSE, Semi-solid Extrusion; SLS, Selective Laser Sintering; SLA, Stereolithography; API, Active Pharmaceutical Ingredient; HME, Hot Melt Extrusion; PAM, Pressure-assisted Microsyringe; HPMC, Hydroxypropyl Methlcellulose; DPE, Direct Powder Extrusion; DMLS, Binder jetting; BJ, Direct Metal Laser Sintering; EBM, Electron Beam Melting; VP, Vat Photopolymerization; UV, Ultraviolet; DLP, Digital Light Processing; CLIP, Continuous Liquid Interface Production; DLP, Digital Light Processing; DOD, Drop-On-Demand; CIJ, Continuous Inkjet

Printing; HPC, Hydroxypropyl cellulose; HPMCAS, Hypromellose acetate succinate; PVA, Polyvinyl alcohol; KIR, Kollicoat IR; KVA, Kollidon VA; PEO, Polyethylene; PEG, Polyethylene; PVP, Polyvinylpyrrolido; PVA, Polyvinyl Acetate; PEGDMA, Polyethylene oxide Dimethacrylate; R&D, Research and Development; FIH, First-in-human; DDSs, Drug Delivery Systems; BP, British Pharmacopeia; Ph.Eur, European Pharmacopeia; IR, Immediate Release; USP, United States Pharmacopeia; BCS, Biopharmaceutics Classification System; ABS, Acid-base solubilization; ASD, Amorphous Solid Dispersions; PEO, Polyethylene oxides; PCL, Polycaprolactone; LEV-PN, Levetiracetam-pyridochloride; ADHD, Attention Deficit Hyperactivity Disorder; PD, Parkinson's disease; ATH, atomoxetine; LD, Levodopa; RH, Relative humidity; PDM, Pramipexole; BZ, Benderazide; EVA, Ethylene-vinyl acetate; GI, Gastrointestinal; QC, Quality control; HIV, Human Immunodeficiency Virus; IBU, Ibuprofen; PCT, Paracetamol; ODTs, Orodispersible tablets; ML, Machine Learning; AI, Artificial intelligence; QbD, Quality by Design; PAT, Process Analytical Technology; CQAs, Critical Quality Attributes; DoE, Design of Experiments; NIRS, Near-infrared Spectroscopy; RS, Raman Spectroscopy; QC, Quality Control; ET, Emerging technology; ICH, International Conference on Harmonisation; LGS, Lennox-Gastaut Syndrome.

Graphical Abstract



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1. Introduction

Three-dimensional printing (3DP) synonymous with additive manufacturing (AM), is a rapid manufacturing technology that utilises computer-aided design (CAD) in the fabrication of physical objects in a layer-by-layer (LbL) manner (Ngo et al., 2018). The advent of 3DP has the potential to cause a paradigm shift in pharmaceuticals and clinical pharmacy practice; evidence of a transition from the traditional mass production of medicines has been identified, along with a distinct move towards more tailored drug products, personalised to the patient (Vaz and Kumar, 2021). Pharmaceutical applications of 3DP have increased over the past years, offering up contemporary opportunities. This includes the manufacturing of medical devices and 'printlets' a term that refers to 3D printed solid oral dosage forms (SODFs) (e.g., tablets and capsules) (Jamróz et al., 2018). 3DP might provide a flexible drug-manufacturing platform, allowing for dose flexibility, drug release profiles, polypill combinations, and the efficiency of printing multiple prototypes (Jamróz et al., 2018). While some of these concepts can be developed using conventional manufacturing methods (eg.,tabletting), it is worth noting that the development process can be complex and time-consuming (Seoane-Viaño et al., 2021b) **(Table 1)**. Advancements in 3DP within the field of pharmaceutics have already made their mark. Spritam (levetiracetam), an anti-epileptic drug, was the first 3D printed orodispersible tablet to be approved by the US Food and Drug Administration (FDA) in August 2015, produced by Aprecia Pharmaceuticals. This 3D-printed anti-epileptic drug was revolutionary, providing an alternative way to mass manufacture Spritam tablets. Spritam is an orally disintegrating tablet (ODT) that includes a fast disintegration rate (11 sec) even with extremely high doses, which is normally challenging to obtain using traditional direct compression devices (Yang and Kim, 2023). Since setting this landmark, pharmaceutical 3DP research has displayed rapid development, such as the use of 3D printing technology to create customized orodispersible films for drug delivery, which dissolve rapidly in the mouth and offer a patient-friendly alternative for those with difficulty swallowing pills (Jamróz et al., 2017). In more recent developments, Triastek, Inc. a China-based pharma company recently received FDA clearance for its Investigational New Drug (IND) application for a 3D-printed medicine T21 (Alqahtani et al., 2023). However, despite these notable developments over the last few years, it is important to acknowledge that Spritam remains the only commercially available 3D-printed pharmaceutical printlet (Bácskay et al., 2022). Challenges persist in this emerging field. The FDA and other regulatory bodies have yet to fully approve and establish guidelines for 3D-printed tablet mass production and there are a few reasons why this is the case. Moreover, most of the printers are designed for the plastic industry and not pharmaceuticals; therefore, more research in the field in collaboration between printing developers and the pharma industry, will be needed. Additionally, it is currently more expensive than traditional tablet manufacturing methods, which can limit the scalability (Park et al., 2019).

For pharmaceuticals, it is well understood that SODFs such as capsules and tablets, in addition to orally disintegrating tablets, are the most convenient and preferred route of administration (Krueger et al., 2022). It has been forecast that the oral drug delivery market will increase to $148.2 billion by 2027 from $98.3 billion in 2020 (ltd, n.d.) However, the provision of suitable tailored dosages, especially for the paediatric and geriatric populations, remains a challenge. Tablets therefore frequently require manipulation by physicians and relatives, such as having to divide tablets by hand, using knives or using a specific tablet splitter (Januskaite et al., 2020). 3DP has many advantages for producing SODFs that conventional manufacturing does not have. In particular 3DP allows parameters such as dose, shape, size, release profiles along with visual and textural aesthetics to be readily customised (Krueger et al., 2022). In today's pharmaceutical industry, bringing a new drug to market can take more than a decade and at an estimated cost of $2.6 billion, with a low chance of a successful outcome ("Modern Drug Commercialization" 2023) . Therefore, success within the early drug development stages is critical to the saving of both time and money. Due to its flexibility and adaptability, 3DP could

Table 1. Advantages and disadvantages between 3D printing technologies and traditional manufacturing methods.

Manufacturing Methods	***Advantages***	***Disadvantages***
3D printing technologies	• On-demand manufacturing • Dosage flexibility • Design flexibility • Dose & Design flexibility • Low wastage • No scale-up (scaling out instead) • Can improve taste or appearance of tablet • Real-Time-Release • Easy to move/relocating footprint	• High cost • Limited scalability • Limited drug compatibility • Lacking regulatory approval • Low capacity • Complex formulation • Preparation step potentially needed • Limited by the properties of the ingredients (e.g., particle size & flowability)
Compression	• Easy scale up • Allows high degree of precision in tablet weight & strength	• Limited by the properties of the ingredients (e.g., particle size & flowability)
Moulding	• Unique shapes • Wide range of ingredients • Create chewable or dissolvable tablets	• Less precise than compression method
Layering	• Creation multi-layered tablets • Desired release profiles can be achieved • Creation of chewable or dissolvable tablets	• Less precise than compression method for tablet weight & strength
Coating	• Desired release profiles can be achieved • Protection of the active ingredient from degradation • Can improve taste or appearance of tablet	• Time consuming • Labour-intensive • Increase cost of tablet
Sublimation	• Create effervescent tablets	• More complex than other methods • Ingredients limited

	• Mask the taste of active ingredient	
Direct compression	• Easy process • Less time consuming • Eliminates steps such as granulation • Reduces production costs	• Limited by properties of the ingredients (e.g., particle size & flowability)
Wet granulation	• Improve flowability and compression of powders • Improve dissolution rate • Increase content uniformity	• Requires more equipment • Time consuming
Dry granulation	• Improve flowability and compression of powders • Improve dissolution rate • Increase content uniformity	• Requires more equipment • Time consuming

be implemented to streamline, automate and accelerate the manufacturing of dosage forms in the drug development stages (Zheng et al., 2020). While many papers postulate that 3DP might replace conventional tablet manufacturing, it is a well-known fact that 3DP technology cannot compete with the mass production required. For instance, current 3D printers can only process a few hundred tablets per hour, while in comparison a high-speed tablet press are capable of manufacturing up to 240,000 tablets per hour (Elkasabgy et al., 2020). This glaring contrast in production rates highlights the inherent limitations of 3DP technology when it comes to meeting the demands of large-scale pharmaceutical manufacturing. However, it's important to note that 3DP needs to compete on its ability to create a wide range of customised items rather than focusing solely on production capacity. Additionally, studies are still lacking to demonstrate that similar drug release profiles can be achieved with 3D printed tablets compared to traditional tablets (i.e., ODTs). This highlights a critical gap in the current literature regarding the performance of 3D printed dosage forms in comparison to their conventionally manufactured counterparts. Where pharmaceutical companies could take advantage of the 3DP method would be in applications in which mass production is not required (Dong et al., 2022), for example, in the flexible production of small batches to support adaptive clinical trial design to facilitate clinical studies, while saving time and costs (Tracy et al., 2023). Investigating the use of 3D printing (3DP) in early pharmaceutical development is important. This becomes particularly relevant when material availability is limited, as is often the case in the early stages of drug development. During this phase, it is not only preferable but essential to screen as many concepts and strengths as possible to gain a comprehensive understanding of a candidate molecule's behaviour. The formulation's advantages are also dynamic, continually changing as researchers from other fields of science try to understand how the molecule functions. Due to its adaptability and flexibility, 3DP stands out as a powerful tool in this situation. It helps pharmaceutical researchers to adaptably create small batches of therapeutic dosage forms, considering the continuously shifting scientific knowledge base. This flexibility not only supports adaptive clinical trial designs but also allows pharmaceutical companies to stay agile and responsive to emerging knowledge. By leveraging 3DP in early development, companies can efficiently

explore a range of formulations, making the most of limited materials and aligning with the dynamic nature of pharmaceutical research. The strategic implementation of roadmaps emerges as a pivotal solution to overcome the challenges associated with the intellectualization and industrialization of 3D printing (3DP). Serving as a vital compass, roadmaps navigate the intricate landscape of 3DP, guiding the way toward advancements and seamless industrial integration. In the field of SODFs, this strategic approach takes on heightened significance. In addition to providing guidance for the advancement of 3DP technologies, the roadmap also directs their implementation in the accurate and effective creation of SODFs. Fundamentally, the integration of 3DP and SODFs with roadmaps presents a promising path forward, marking the beginning of a new era in pharmaceutical manufacturing that will be defined by improved intellectualization, streamlined industrial procedures, and the production of superior, patient-focused pharmaceuticals (Tian et al., 2022).This review will provide a brief overview of 3DP, with a timely perspective on the latest developments of 3DP technologies for SODFs and focus on the applications that can be used to produce SODFs for the early clinical development stages within the pharmaceutical sector. The primary objective is to critically analyse the existing literature to identify any gaps or restrictions on the use of 3DP in pharmaceutical contexts. This analysis delves into various aspects, including the practical implementation of 3DP, common misconceptions, and areas where further research may be required.

2. Methods

Data sources were obtained from main databases such as PubMed, Web of Science, Scopus, Embase, and clinicaltrials.gov databases. Employing the combinations of the terms, “recent advances in solid oral dosage forms”, “oral formulations” “tablet”, “capsule” “3D printing”, “pharmaceutical sector” and “early clinical development stages”. The investigated time interval was from June 2020 to March 2023. **Table 2** represents the detailed data selection procedure followed in this literature review. **Fig 1** illustrates the database keyword search results.

Table 2. Table summarizing the data selection procedure for literature review.

Data source selection	
Included sources	• Original articles • Case reports
Excluded sources	• Unpublished articles • Websites
Perspectives of data selection	
Dosage form *Release profiles* *Tailored dosage* ***3D printing technology***	• Solid oral dosage form • Immediate or Modified- release • Paediatric & geriatric • Extrusion based, direct powder extrusion, powder-based, Vat photopolymerization, Drop-on-demand, pressure-assisted microsyringe
Formulation development evaluation	• Formulation strategies • Polymer type & role • 3D printed tablet properties

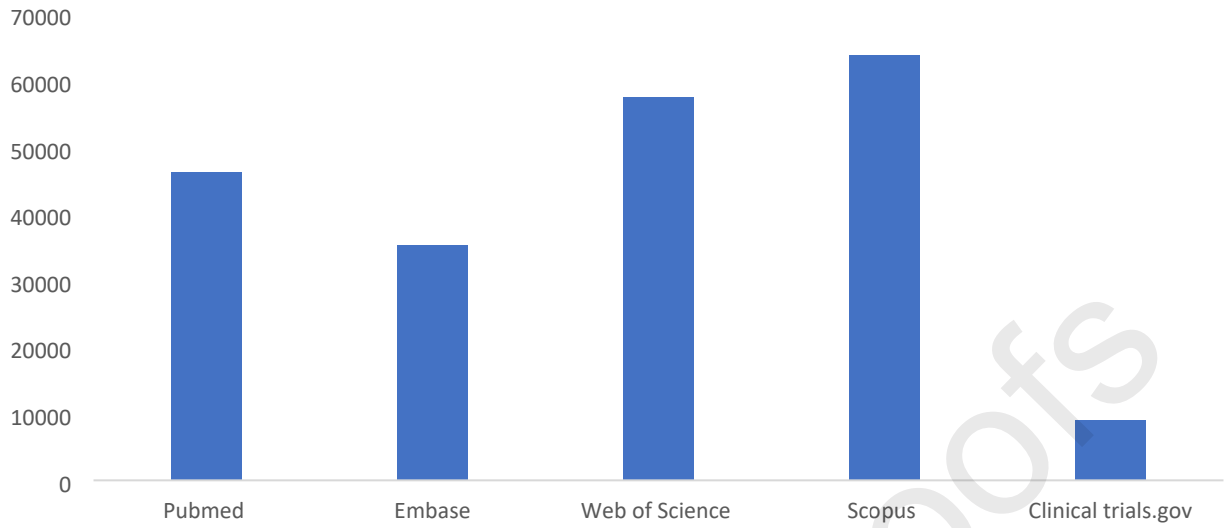

Fig. 1. Database comparison of keyword search results from the main databases. PubMed; 46,219, Embase; 35,319, Web of science; 57,535, Scopus; 63,826, Clinical trials.gov; 9,020 search results.

3. 3D printing technologies employed within pharmaceutical manufacturing

3DP is an umbrella term, encompassing a variety of different printing technologies; these include binder jetting, fused deposition modelling (FDM), semi-solid extrusion (SSE), selective laser sintering (SLS) and Stereolithography (SLA). As has been previously described in the introduction, 3DP fabricates solid structures by depositing successive layers of materials onto a substrate, using CAD software (Ngo et al., 2018). The selection of feed materials depends on the 3DP technology selected, with pharmaceutical manufacturing for drug product development utilising extrusion-based printing, inkjet printing or powder-based binding method. Additionally, the choice of 3DP technique depends on the API properties (melting point, degradation temperature, etc.), further influencing the suitability of materials and printing processes. These various methods vary in their function and productivity, with the key difference between them is the way in which a layer deposits onto another layer. Polymers possess unique characteristics that complement with the layer-by-layer additive manufacturing process of 3DP. Their ability to be precisely melted, solidified, or bonded under controlled conditions makes them highly adaptable to creating complex and customized drug delivery structures. Furthermore, polymers can effectively serve as carriers for APIs, ensuring uniform dispersion and controlled release (Govender et al., 2021). However, it's important to note that the significance of polymers in 3DP can vary based on the specific application and objectives. They are frequently utilised, however depending on the project's objectives and required qualities, alternative materials, such ceramics, metals, or biodegradable polymers, may be preferred. The study of novel methods to the development of drug delivery systems within the 3DP framework is made possible by the dynamic interaction between material selection, formulation design, and 3DP parameters, which continues to be an important field of research. The main characteristics of a 3DP formulation, such as the release rate for example, may be precisely modified by the printing parameters, in, say, manipulations of the number of printed layers (Samiei, 2020). However, it is essential to note that the formulation itself also plays a crucial role in this complex interplay between formulation and process. As 3DP technologies and their applications have been thoroughly reviewed for use in pharmaceutical applications (Cui et al., 2021; Kim et al., 2022; Pitzanti et al., 2021), this review will only provide a brief description of each technology. **Table 3** provides the advantages and limitations of each commonly used 3DP technique to produce SODFs.

Table 3. Advantages and limitations of commonly used 3DP techniques used for SODFs.

3DP technique	Material form	Advantages	Limitations
Fused Deposition Modelling	Filaments	• Cost effective • Ease of use • Range of material • Rapid prototyping • Customizability • Versatility for different shapes and sizes • Low waste	• Surface finish • Precision • Material compatibility • Low drug loading • Scalability • Filament physical properties • Preprocessing step needed • API melting point
Semi Solid Extrusion	Gel or paste	• Surface finish • Precision • Fast & efficient • Range of material • Customizability • Low waste • Low printing temperature • High drug loading	• High cost • Material compatibility • Complex post processing • Low resolutions • Use of solvents • Post-fabrication drying
Direct Powder Extrusion	Powder or pellets	• Requires minimal number of materials	• Low drug loading
SLS Selective Laser Sintering	Powders	• High resolution • Absence post-processing steps • Complex geometries • Solvent-free process	• Material compatibility • High temperatures • Risk of drug degradation
Binder jetting	Powders	• Printing at room temperature • Wide range of material • Fast disintegrating dosage forms can be produced	• Use of solvents • Wastage • Produces fragile dosage forms • Post-processing • Material compatibility
SLA Stereolithography	Resins	• High resolution • Ability to print micro-sized	• Material compatibility • Post-curing steps

3.1 Extrusion-based Printing

Extrusion-based printing has garnered growing interest due, in part, to its very promising potential, with pharmaceutical researchers being attracted to its low cost, flexibility of design and the varied types of polymers that can be used in the printing. There are several types of extrusion-based printing techniques, with the two of the most commonly used been FDM and SSE (Algahtani et al., 2018).

3.1.1. Fused Deposition Modelling (FDM)

FDM printers are one of the most widely used forms of 3DP, with a significant amount of research devoted to the improvement and optimisation of the process. FDM's popularity stems in some degree to its low cost, ease of use, and versatility, allowing it to be used by a diverse range of users, from hobbyists to industrial manufacturers (Azlin et al., 2022). FDM is 3DP technique, involving the depositing of a molten polymer layer-by-layer (LbL) onto a platform, in order to create a 3D object (Okafor-Muo et al., 2020). Drug-loaded polymeric filaments with selected excipients can be developed and usually prepared using the hot-melt extrusion (HME) method. HME is a straightforward and dependable method (Krueger et al., 2022), used by the pharmaceutical industry and paired with FDM in order to produce SODFs **(Fig 2)**. The general concept behind HME is the use of heat and pressure, in the melting and mixing of a combination of drugs, excipients and other additives. The melted mixture is then cooled, solidifying to form a drug-loaded filament that is then used as the feed for an FDM 3D printer (Brambilla et al., 2021). The importance of HME resides in its capacity to achieve uniform dispersion of APIs inside an excipient matrix, enabling precise control over drug release rates and dosage form properties. The method's versatility allows for the incorporation of various APIs, excipients, and even additives like taste-masking agents or colorants, enabling the creation of customized drug products tailored to specific patient needs. HME is a cornerstone technology in the field of pharmaceutical 3D printing thanks to its reputation for dependability and efficacy. It provides pharmaceutical researchers and manufacturers with a powerful tool to develop medication formulation and delivery systems.

FDM offers substantial advantages over traditional manufacturing techniques, including the development of printlets with the shapes and geometries (e.g., cube, pyramid, sphere, torous) that are difficult or impossible to produce using conventional powder compaction techniques (Bandari et al., 2021). This advantage was clearly demonstrated in the work by Tabriz and colleagues (Ghanizadeh Tabriz et al., 2023), who produced LEGO®-like tablets containing compartments with varying drug release profiles of melatonin and caffeine to help treat sleeping disorders. However, one of the major research issues surrounding the FDM process has been its ability to produce components with visually appealing geometry (Mohamed et al., 2016), which requires the optimal selection of FDM process parameters. Achieving such qualities requires the meticulous selection and optimization of FDM process parameters. These parameters, including but not limited to layer height, print speed, temperature, and infill density, must be thoughtfully chosen and fine-tuned to attain the desired level of component quality. It is this requirement which makes it of critical importance that researchers seek to improve any issues which may be raised, especially those in relation to component quality, surface roughness and content uniformity with FDM technology (Cappellini et al., 2022). Ensuring content uniformity is particularly vital, as it pertains to the consistency of the API distribution within multiple tablets produced using the same parameters. Researchers must address these multifaceted challenges to enhance the reliability and performance of FDM 3D-printed pharmaceuticals. In addition, FDM 3DP may raise sustainability concerns, due to high energy consumption and a questionable level of fume emissions. There is, however, the potential to be a sustainable technology, especially in the preclinical stages, where prototypes can be printed quickly and cheaply with FDM, allowing the testing, amending and iterating printlets more efficiently, thereby reducing wastage (Weaver et al., 2022).

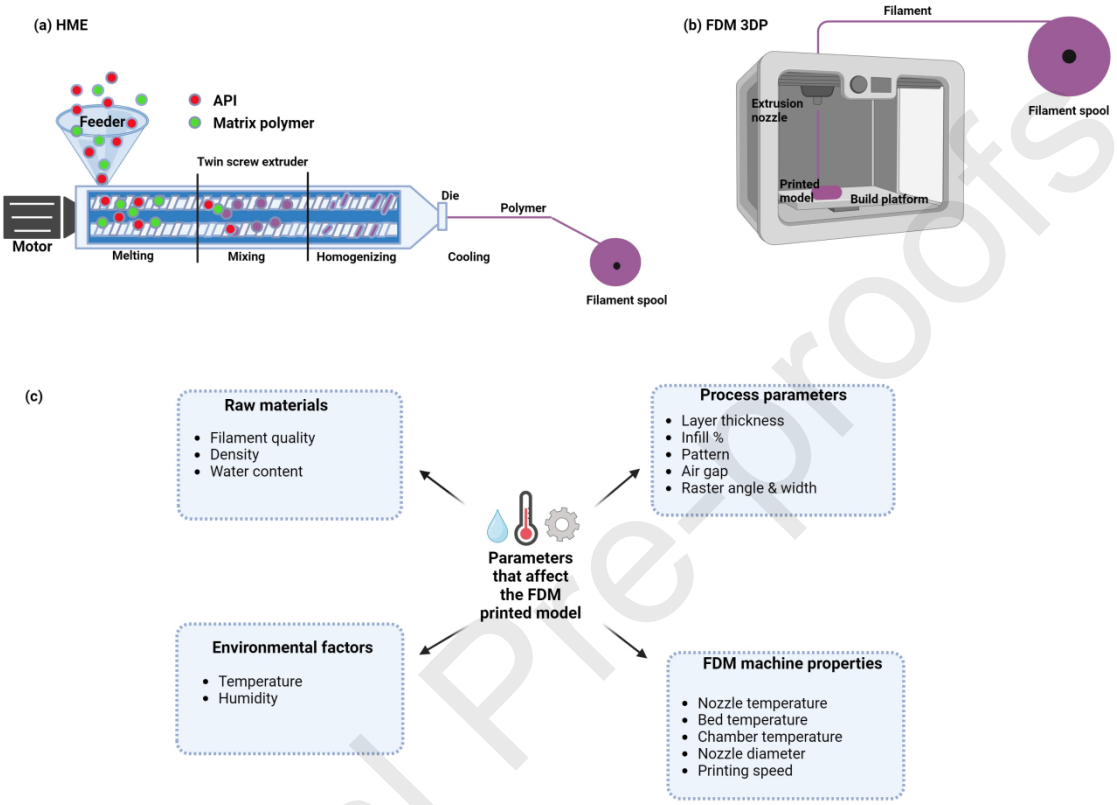

Fig 2. Schematic illustration of: (a) HME twin-screw process pairing with (b) FDM printer to produce 3D printlet (c) Overview of process parameters that affect 3D printed objects with the FDM printer.

3.1.2. Semi-solid Extrusion (SSE)

SSE, also known as pressure-assisted microsyringe extrusion technology (PAM), is like FDM, but instead of filaments or powder, the system prints from a syringe filled with a gel or a paste. The semi-solid material is fed into a 3D printer's hot end, where it is melted and deposited LbL, in order to build the final object (Seoane-Viaño et al., 2021a). In comparison to traditional extrusion-based 3DP methods, this technique allows for the creation of more complex geometries. Another difference is the low printing temperature, making SSE a suitable candidate for thermosensitive drug delivery (Dumpa et al., 2021). The inherent qualities of SSE's materials are what allow it to operate at lower temperatures. Compared to solid filaments or powders used in conventional FDM or extrusion-based 3D printing, semi-solid gels and pastes have lower melting points by nature. Furthermore, SSE systems are also carefully built to reduce heat exposure during the printing process. This careful control ensures that the material remains within a temperature range that is optimal for extrusion without subjecting it to high temperatures that could cause degradation or alterations in its properties. In recent years, research has shifted toward the use of semisolid materials that are well suited for the preparation of chewable tablets, such as soft candy, which may greatly improve compliance in paediatric patients (Zuccari et al., 2022).

These findings were confirmed in a similar study where Tagami and team (Tagami et al., 2021) focused on creating gummy formulations for children using the SSE technique. The team created formulations of gelatine, hydroxypropyl methylcellulose (HPMC), syrup, water, and the antiepileptic drug lamotrigine. However, unlike FDM, SSE prints at low resolutions, proving to be one of its main limitations (Awad et al., 2022). This results in 3D objects produced that may have coarser surface finishes, thicker layers, and fewer intricate details than being produced by other methods. However, advances in technology and materials are constantly being made, and the resolution limitations of SSE 3DP it might be successfully addressed in the near future (Funk et al., 2022).

3.1.3. Direct Powder Extrusion (DPE)

Direct powder extrusion (DPE) falls under the extrusion-based umbrella. Instead of extruding a filament, DPE involves the extrusion of material via the printer's nozzle in the form of powder or pellets obtained from by HME (Goyanes et al., 2019). The main advantage of DPE is that it circumvents drug-loading restrictions that frequently arise with conventional HME and FDM process. DPE achieves this by starting with a well-mixed drug-polymer blend for even drug distribution. This blend is continuously extruded to maintain consistent drug content throughout printing. DPE allows precise control over parameters, ensuring accurate dosing and adaptability for specific formulations. Additionally, it also minimizes drug agglomeration and ensures uniform drug dispersion. As a result, it would create a quicker, more cost-effective single step 3DP manufacturing process (Sánchez-Guirales et al., 2021). A further benefit of DPE is that it only requires minimal amounts of the drug and excipients, making it particularly suitable for creating formulations for preclinical research (Seoane-Viaño et al., 2021b). The use of DPE for pharmaceuticals is relatively recent, by comparison to the FDM and SSE techniques, and therefore requires further research (Lafeber et al., 2022).

3.2 Powder Bed Fusion

Another commonly used 3DP technique is that of the powder-based binding method, which includes the following commonly used printing techniques: selective laser sintering (SLS), direct metal laser sintering (DMLS), binder jetting (BJ) , and electron beam melting (EBM). Each of these techniques uses a different process to bond the particles and create the final object, and are used for different applications and materials (Singh et al., 2023). SLS and BJ are most relevant to pharmaceutical manufacturing. They excel due to their speed, material versatility, GMP compliance, maturity, ability to create complex designs, customization options, API integration, and sustainability benefits. These attributes make SLS and BJ efficient and regulatory-compliant choices for producing pharmaceutical products.

3.2.1 Selective Laser Sintering

SLS embodies one of the latest and advanced technologies in the manufacture of printlets (Friday et al., n.d.). In this form of printing, a liquid binder solution is sprayed as droplets with an inkjet printhead over a thin layer of powder and where the binder solution contacts the powder bed, the powder particles adhere together **(Fig 3)**. A CO_2 laser then selectively sinters the powder layer and the process repeats, until the desired printlets are formed (Abdulhameed et al., 2019). The approximate temperature generated by a CO2 laser used in Selective Laser Sintering (SLS) typically falls within the range of 1000°C to 1600°C. his high temperature is necessary to selectively fuse or sinter the powdered material in the desired areas, allowing for the precise layer-by-layer formation of the 3D object. The exact temperature can vary depending on the specific material being processed and the settings of the SLS printer (Gueche et al., 2021a). The liquid binder solution is a crucial element in the formation of

printlets. Its properties play a significant role in the precision and success of the printing process. To ensure optimal performance, the binder solution must meet certain specifications. Surface tension, for example, should be within a particular range to allow for consistent droplet production and distribution. Furthermore, the viscosity of the binder solution is carefully managed to ensure that droplet size and flow through the inkjet printer are uniform. Wettability and compatibility with the target powder material are critical variables since the solution must easily distribute and wet the powder surface for successful adhesion to occur. Equally crucial is the spreadability of the solution, which ensures even coverage of the powder bed, which is critical for uniformity. SLS demonstrates a number of advantages over other forms of 3DP, it provides high resolution and an absence of post-processing treatments such as drying or UV curing, allowing printlets be dispensed and consumed immediately (Awad et al., 2020). Giri and a team of researchers in 2022, initiated a study into the adaptation of the SLS technique aiming to create tablets that would release a drug over time, as usually 3D printed tablets dissolve quickly due to being porous and loose. However, it is important to note that the extent of porosity and dissolution rate can vary depending on the specific 3D printing technology, materials, and printing parameters used. Some 3D printing techniques and formulations can produce tablets with less porosity and tighter structures, which can result in slower and more controlled drug release. This technique produced 3D printed tablets that were strong and exhibited controlled drug release over a period of 12 hours (Giri and Maniruzzaman, 2022). However, there are several technical and regulatory challenges that prevent SLS from being widely used in pharmaceutical manufacturing, not at least that of material compatibility, which when hampered by the high localised temperatures required to sinter powder materials, may display levels of drug degradation. (Seoane-Viaño et al., 2021b). Despite these challenges, SLS has gained significant attention in the last few years for the production of SODFS (Gueche et al., 2021b), due to its ability to fabricate printlets with complex geometries (Trenfield et al., 2023).

3.2.2 Binder Jetting

Binder Jet 3DP is a promising technology within the pharmaceutical industry, as exemplified by the FDA approved printlet, Spritam as shown in figure 4 produced by Binder Jetting. The process involves the method in which powdered material is spread into a layer and selectively joined into the desired layer shape with a liquid binder (Mostafaei et al., 2021). Unlike other printing processes, BJ does not require thermoplastic polymers as the printing is performed at room temperature. Regardless of its success, there is still much to learn regarding the applications of binder jetting in pharmaceuticals as it presently remains in its infancy. While it has already showcased its capability in producing relatively low volume products like Spritam, there is still room for optimization in the formulation development process. The goal is to establish a reliable source for high-quantity production that can effectively compete with conventional dosage forms (Sen et al., 2021).

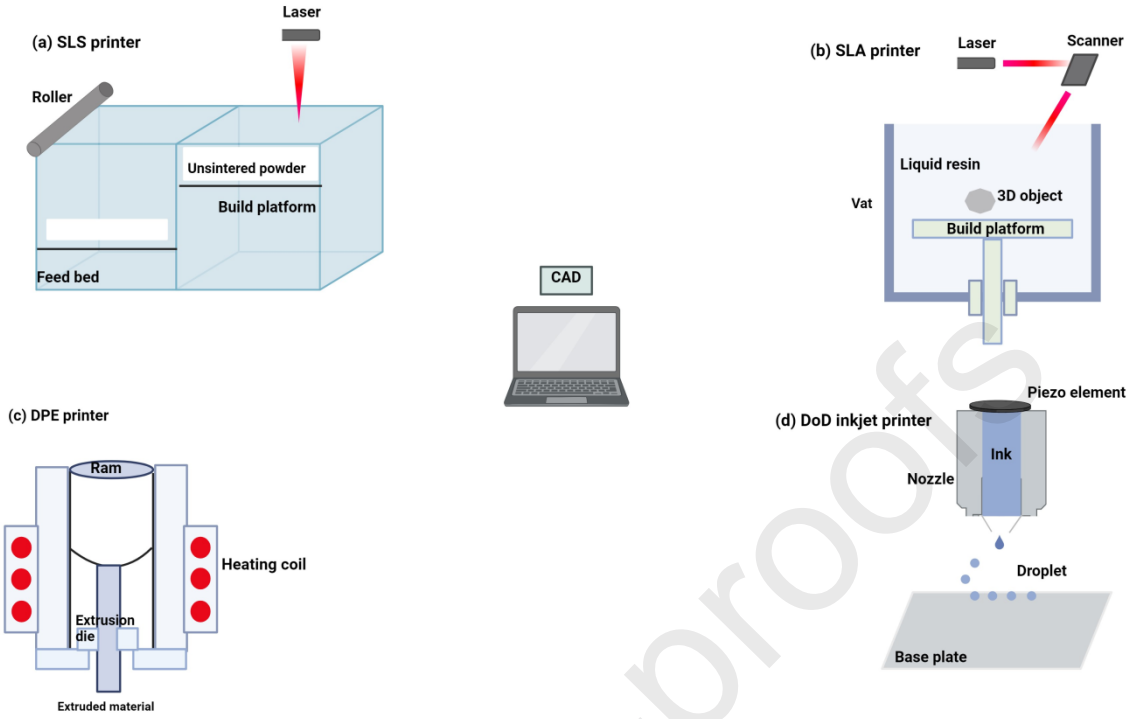

Fig 3. Schematic illustration of: (a) SLS printer, (b) SLA printer, (c) DPE printer and (d) DoD inkjet printing system.

Fig 4. Available commercial product Spritam by Aprecia Pharmaceuticals ("Taking SPRITAM," n.d.).

3.3 Vat Photopolymerization (VP)

VAT photopolymerization is a 3DP process that builds 3D objects LbL, by utilizing the hardening of a photopolymer with ultraviolet (UV) light (Pagac et al., 2021). In photopolymerization, the term "curing" refers to the process of solidifying or hardening the liquid photopolymer material when it's exposed to UV light. This curing process is crucial for building each layer of the object. Photopolymerization can be further classified based on the method used for curing, which includes lasers (SLA) **(Fig 3)**, digital light processing (DLP), and continuous liquid interface production (CLIP) (Al Rashid et al., 2021). SLA is the most frequently used variant of VAT polymerisation for pharmaceutical manufacturing, with the technology being able to produce very rapid and highly accurate finished products of uniform quality, including hearing aids and microneedles (Bozkurt and Karayel, 2021). In 2019 Robles-Martinez and colleagues applied this method for the manufacture of polypills, containing up to six different drugs (Robles-Martinez et al., 2019), with the production of personalised polypills. However, due to material limitations and concerns about the potential toxicity of photopolymer resins, SLA is not typically used to produce finished drug products, with other 3DP technologies such as FDM or SLS, that are more commonly adopted (Pagac et al., 2021). Considering

these negative aspects means that the use of SLA for printlet production is still in its early stages and more research is needed to determine its viability as a commercial manufacturing process.

3.4 Ink-Jet Printing

In contrast to other 3DP technologies that use solid materials, inkjet 3DP allows the use of a variety of materials such as resins, ceramics, and even edible ink. The technology works by precisely depositing droplets of material in a specific pattern by virtue of an inkjet print head, LbL, until the final product is completed **(Fig 3)** (Gupta et al., 2021). This automated, high-throughput technology is primarily classified into two categories, based on the physical process of droplet generation; continuous inkjet printing (CIJ) and drop-on-demand printing (DOD) (Uddin et al., 2022). DOD has garnered growing interest amongst pharmaceutical researchers, fuelled by its low cost, high precision and reduction in drug waste for the formulation of various 3D dosage forms (Gültekin et al., 2022). In 2022, Lu et al. (Lu et al., 2022) reported the use of DoD deposition to dispense drug solutions onto binder jetting-based 3D printed multi-compartment tablets containing three model anti-viral drugs (e.g., hydroxychloroquine sulphate - HCS, ritonavir, and favipiravir). The team examined the printed tablets using solid-state characterization techniques such as DSC and XRD. The *in vitro* drug release study revealed that the tablets' outer and middle layers were suitable for immediate release, while the core could be used for delayed release. However, DoD, like any other 3DP technology, faces challenges regarding accuracy, consistency, and overall effectiveness. One specific challenge is related to drug loadings. DoD may be best suited for high-potency or low-dose drug delivery systems due to its precise control over the deposition of materials. Achieving uniform drug distribution in formulations with high drug loadings can be more complex and may require fine-tuning of the printing parameters to ensure consistent dosing throughout the printed object. Table 4 provides additional examples of recent advances in SODFs manufactured using the different types of 3DP technologies discussed in this section.

4. 3DP for early clinical development applications

The process of drug research and development (R&D) within the pharmaceutical industry is a complex, multistage procedure that is both time-consuming and costly to test efficacy and ensure quality. On average, it takes 10 to 15 years to develop a new drug, from the initial discovery phase to regulatory approval (Kulkarni et al., 2023). Unfortunately, this lengthy time to market presents a significant challenge for both the industry and, more importantly, to patients who may require access to life-saving treatments. Therefore, it is crucial that drug development timelines are accelerated. Due to being dose inflexible and expensive (Seoane-Viaño et al., 2021b) traditional manufacturing processes often hinder the rapid progress through the early-stage drug development process, which includes preclinical and first-in-human (FIH) clinical trials. It is of note however, that the use of 3DP can significantly reduce the time and cost associated with drug development by enabling the rapid production of formulations with excellent dose flexibility **(Fig 5).** Furthermore, 3DP has the potential to aid formulation development by allowing for the rapid production of product iterations for testing purposes, such as excipient compatibility and drug release. Given these benefits, incorporating 3DP technology into early-phase drug development has the potential to streamline or assist the drug development process and improve the pharmaceutical industry's overall efficiency.

4.1 Drug release

Drug release is a critical parameter for pharmaceutical dosage forms as it determines the rate and extent to which a drug is released from its formulation and becomes available to its site of action in the body. Drug release affects the pharmacokinetics of a drug, including its absorption, distribution, metabolism, and excretion (Wang and Ouyang, 2022). Therefore, understanding and controlling drug release is important in designing and developing drug delivery systems (DDSs), that can ensure optimal drug efficacy and safety. Furthermore, drug release studies are essential for regulatory approval of SODF's. Conventional manufacturing methods, such as tabletting and encapsulation, have limitations in terms of controlling drug release from SODF's. Tabletting, for example, frequently relies on compressive forces to make solid tablets, which can limit the incorporation of certain drugs or affect the uniformity of drug distribution within the tablet matrix. This compression-based approach may not allow for precise control over drug release kinetics, especially for drugs with complex release profiles

Table 4. Selective examples of recent advances in SODFs manufactured using 3DP technologies. Each study highlights the 3DP technique employed, the API and the polymers utilized to form the matrix.

Study performed	3DP technique	API	Polymers	Refs
Lego ® inspired capsular to allow multi modal release for treatment of sleep disorder	FDM	• Caffeine • Melatonin	• Hydroxypropyl cellulose (HPC) • Hypromellose acetate succinate (HPMCAS)	(Ghanizadeh Tabriz et al., 2023)
Praziquantel loaded 3D minicaplets produced	FDM	• Praziquatel	• Eudragit® EPO	(Bhatt et al., 2023)
Development of Timapiprant IR 3D printed tablet	FDM	• Timapiprant	• HPC • HPMCAS • Polyvinyl alcohol (PVA) • Kollicoat® IR (KIR) • Kollidon® VA (KVA) • Soluplus® • Polyethylene oxide (PEO)	(Uboldi et al., 2023)
Manufacturing of personalised HIV paediatric 3D printed tablets	DPE	• Ritonavir • Lopinavir	• Hydroxypropyl methylcellulose (HPMC) • Polyethylene glycol (PEG)	(Malebari et al., 2022)

Creation of a Budesonide loaded mini tablet for the treatment of eosinophilic colitis in paediatric patients	DPE	• Budesonide	• HPMC	(Pistone et al., 2023)
3D printed Gastro-floating tablets manufactured	SSE	• Famotidine	• HPMC	(Yang and Kim, 2023)
3DP of extended-release tablets of theophylline	SSE	• Theophylline	• HPMC	(Cheng et al., 2020)
Fabrication of sustained-release 3D printed tablets	SLS	• Acetaminophen	• Polyvinyl acetate (PVA) • Polyvinylpyrrolidone (PVP)	(Giri and Maniruzzaman, 2022)
3D printed sustained release printlets	Binder Jetting	• Acetaminophen	• HPMC	(Tan et al., 2023)
Formulation of IR SODF with zolpidem tartrate	DLP	• Zolpidem tartrate	• HPMC • PEG	(Adamov et al., 2022)
3DP to create custom tablet geometries encapsulating novel biocompatible photochemistry ascorbic acid	SLA	• Ascorbic acid	• PEG Dimethacrylate (PEGDMA)	(Karakurt et al., 2020)

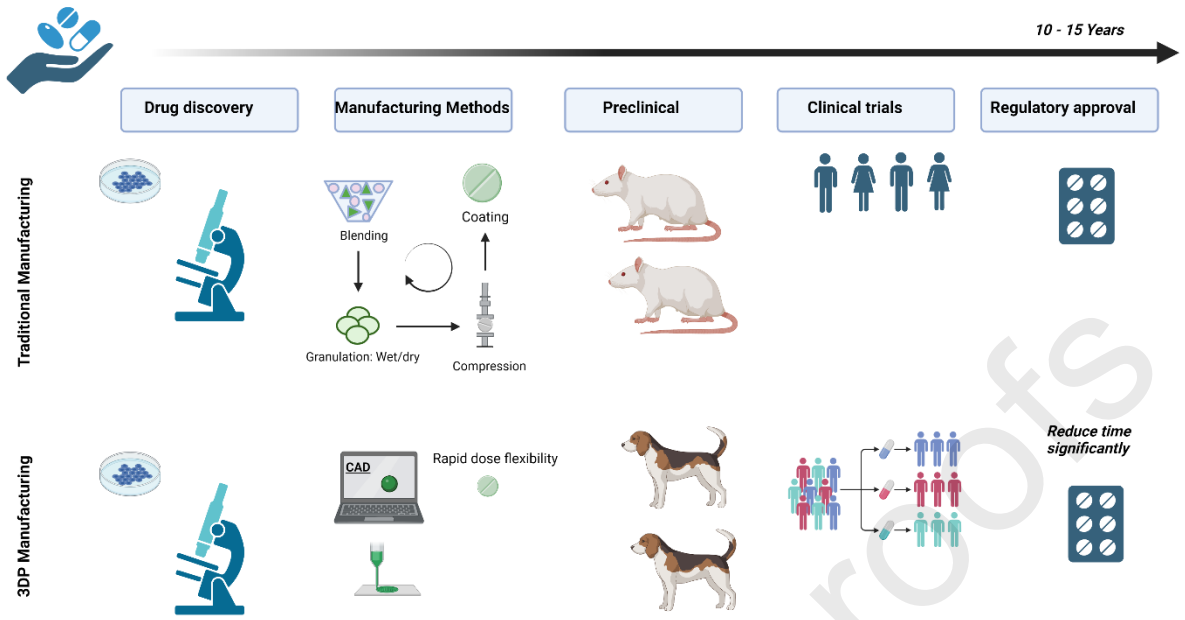

Fig 5. Traditional manufacturing of SODF's in comparison with 3DP, from the time it takes from initial drug discovery to regulatory approval. 3DP could significantly reduce the time and cost associated.

or those requiring extended-release formulations. One of the main issues with conventional manufacturing is the lack of dose flexibility and dose-sparing platforms, particularly for drugs with narrow therapeutic windows, can be attributed to various factors, including the minimum batch size requirements associated with manufacturing methods like HME and Spray Drying. 3DP technology has the potential to address these current issues, In preclinical studies, drug candidates are typically administered to animals to assess their efficacy, toxicity, tolerability, safety, and pharmacokinetic behaviour. During these studies, it is crucial to have a flexible and dose-sparing platform for drug administration. 3DP can address these needs, as for example, 3DP can be used to print tablets with precise drug dose and release profiles. This is particularly relevant for small-scale production for drugs with low solubility or bioavailability such as through the formation of an ASD, where conventional methods may be challenging or costly.

4.1.1. Immediate and modified release SODF's

In this context, within the pharmaceutical industry, "immediate" demonstrates a certain fluidity. According to the British Pharmacopeia (BP) ("Dissolution - British Pharmacopoeia," 2023) and the European Pharmacopeia (Ph.Eur) ("Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action," 2023) both require that immediate release (IR) formulations achieve at least 75% drug substance dissolution in vitro within 45 min. The United States Pharmacopoeia (USP) ("The Dissolution Procedure: Development and Validation," 2023) , on the other hand, requires that 85% of the drug substance be released within 30 to 45 min. The pharmacopeial standards differ because different regulatory bodies and countries have different guidelines and regulations for evaluating the safety, efficacy, and quality of drug products. Modified release formulations on the other hand are designed to release the drug in a controlled manner over a

specific period. Modified release formulations may adopt several forms including extended and delayed release, with coating systems frequently used in the development of these formulations. While coating is a widely adopted method in the pharmaceutical industry, its applicability depends on the specific drug and its properties. For some APIs, especially water-insoluble ones, coating systems may not offer precise control over drug release rates. Furthermore, it is critical to distinguish between cosmetic coatings used for appearance and functional coatings designed for protection or controlled release, as the necessity for coating can vary based on these factors (Nashed et al., 2021). In addition to coating systems, matrix systems are another approach to modified release formulations. In matrix systems, the drug is homogeneously dispersed within a solid matrix composed of polymers or other excipients. While matrix systems can provide sustained drug release, they may not offer the same level of fine-tuned control over release rates as coating systems do. The release rate in matrix systems often depends on factors like drug solubility, diffusion, and erosion, which may not be as predictable as with coating technologies. As a result, the choice between coating and matrix systems is influenced by a variety of parameters, such as the individual drug, its release requirements, and the intended release kinetics. 3DP as an alternative approach offers better control and consistency in the drug release. Using 3DP , drug release in dosage forms can be fine-tuned by varying excipients, structural and different thickness or coating variations. This technology offers the advantage of creating intricate release profiles, particularly beneficial when formulating tablets with multiple compounds, each with distinct release requirements. Furthermore, coatings can be strategically employed to further fine-tune these release profiles, adding an additional layer of control and customization to drug delivery systems. Saydam and Takka (2020) (Saydam and Takka, 2020) used 3DP technology to enhance the dissolution of rufinamide, an orphan drug for Lennox-Gastaut Syndrome. The study discovered that a combination of excipients and 3DP technology can improve rufinamide dissolution, resulting in significantly higher dissolution at therapeutic doses than Inovelon®.

As previously mentioned, FDM is currently the most widely used 3DP technology in pharmaceutical research and development. The tablets are constructed by layering nonporous filaments, leading to the creation of a solid mass where the API can be trapped within the tablet. The slow erosion process of the nonporous filaments leads to delayed drug release rates; therefore, making FDM 3DP SODF's suitable for sustained or delayed release formulations. Consequently, most studies utilising FDM were targeted towards these types of drug delivery applications. Several studies (Cheng et al., 2020; McDonagh et al., 2022; Skalická et al., 2021) have investigated various techniques designed to modify the release profiles for 3DP SODFs. One method relies upon alteration of the shape and geometries of the tablets, Fanous and colleagues (Fanous et al., 2021) explored the feasibility of FDM in the production of 3D printed tablets with rapid drug release of Biopharmaceutics Classification System (BCS) class IV compound lumefantrine as the model drug, utilizing Eudragit EPO as the matrix former. The team designed grid-like tablets for the paediatric population 6 years and older, varying the infill density with 5% lumefantrine drug load. They discovered that 65% infill density fulfilled the rapid release criteria, whereas 80% and 100% demonstrated slower dissolution. According to literature, reduction of the programmed infill density frequently accelerates drug dissolution rate for both lipophilic and hydrophilic drugs (Fanous et al., 2020). Interestingly, in this study, the infill density at 65% produced tablets with significantly different morphological characteristics, however, there were no major differences between the tablets printed at 80% or 100% infill. Overall, Fanous and colleagues' research shows that 3D printing has the potential to accurately customise drug release profiles through tablet geometry and infill density modifications, providing a personalised approach to pharmaceutical dosage forms.

A group of researchers employed a novel design approach in order to accelerate drug release using FDM (Patel and Serajuddin, 2021). They fabricated haloperidol tablets with rapid drug release, high drug-polymer miscibility and at the same time reducing the printing temperature by applying the novel acid-base super solubilization (ABS) principle. The ABS principle involves a unique approach to enhance the solubility of poorly water-soluble drugs by utilizing acid-base interactions. In the context of 3D printing, ABS offers significant advantages. It enables the creation of tablets with improved drug solubility, which is crucial for achieving rapid drug release. Additionally, ABS can enhance the compatibility between the drug and the polymer used in the printing process, ensuring better miscibility.

This innovative approach not only accelerates drug dissolution but also allows for the reduction of printing temperatures (Abdella et al., 2021). The team pointed out that previous research had found that FDM 3DP did not consider drug compatibility with polymeric carriers or whether they remained in a crystalline state, which could have a significant impact on the dissolution and bioavailability of poorly water-soluble drugs in FDM 3D printed tablets. To achieve a rapid dissolution rate and maintain supersaturation, it is crucial that poorly water-soluble drugs are formulated with polymeric carriers as amorphous solid dispersions (ASD) during 3DP. ASDs are a common strategy employed to enhance the solubility and dissolution rate of poorly water-soluble drugs, ultimately improving their bioavailability and therapeutic efficacy. In recent years, a growing number of research papers have been published where FDM 3DP of ASD have been used to enhance the solubility and dissolution rate. As highlighted by Patel and Serajuddin (Patel and Serajuddin, 2021), since the FDM 3D printed tablet is essentially an ASD, it is crucial that drugs remain miscible with the polymer in the tablet. This likeness, however, raises an important question: is it advantageous? While the similarity to ASDs has the potential to enhance drug solubility and dissolution, it also poses potential limitations. In cases where the ASD like formulation exhibits poor manufacturing or tabletting properties, not being able to make modifications may hinder the development process. Haloperidol was converted to the amorphous form by interacting with glutaric acid during HME, and the drug remained amorphous under high temperature and humidity conditions and was freely miscible with the polymers HPMC and Kollidon VA64 utilized by the group. Their studies revealed that elevating the amount of HPMC in the formulation slowed the release of the drug from the formulation. Duranovic and team (Đuranović et al., 2021) also demonstrated that the polymer in the 3DP formulation plays a crucial role in obtaining SODFs with the desired drug release properties. They produced paracetamol printlets utilizing HME and FDM 3DP, comparing three types of polymers; Polycaprolactone (PCL) and Polyethylene oxides (PEO) 100 K and 200 K were used, while Arabic gum was used as a plasticizer to facilitate the material flow and Gelucire® 44/14 as an enhancer of drug release. It was observed that PEO-based filaments presented challenges in the printing process due to print core clogging. However, the resulting PEO-based printlets displayed significantly faster drug release rates when compared to printlets made from PCL-based filaments. Despite this difference, both types of printlets exhibited prolonged drug release, with PCL-based printlets achieving 50% release in 8 hours and PEO-based printlets achieving complete release in 4 hours.

Other studies have explored the use of multi-compartment SODFs to achieve different release profiles for different drug substances, with binder jet 3DP being utilised by Hong et. al. (2021), for the development of levetiracetam-pyridochloride (LEV-PN) multicompartmental structure dispersible tablets. The unique aspect of this research is that the powder mixture contained LEV, while the ink contained PN, and a specific amount of PN was directly injected into a particular section of the tablet (Hong et al., 2021). The team addressed the issues of drug photo instability with partition control and the “coffee ring” effect associated with binder jet 3DP which often results from drug migration during the curing and molding stages of 3D-printed multicompartmental preparations was improved by modifying the drying techniques. The partitioning approach addressed the issue of drug photostability, which is a common challenge in pharmaceutical formulation. Directly injecting the photolabile drug, LEV-PN, into a particular section of the tablet allowed for protection against light-induced degradation. This partitioning strategy ensured that LEV-PN would be shielded from potential photodegradation, maintaining its stability and efficacy within the tablet. The 3D-printed compound dispersible tablets were made of 50 layers, each containing a 180 μm thick layer of powder. Characterizations demonstrated that all tablets had excellent surface morphology and internal structure characteristics, indicating that the ink droplets were accurately jetted during the printing process into specific regions according to the model design, which could achieve fine printing. The loose pore structure enabled the two drugs in the tablet to disintegrate in the mouth quickly and achieve rapid release. However, the incorporation of an API into the printing ink can influence the physicochemical properties of the ink fluid, potentially resulting in difficulties with the ink jetting process. As a result, careful consideration must be given to the selection of printing ink to ensure appropriate control of factors such as viscosity and surface tension. In this study, a 4.5% (w/w) PN (API) loading was added to the blank printing ink, enabling for precision jetting of low-viscosity printing inks. Although the team were able to develop a

micro drug system by adjusting the number of printing layers in the model and enabling modulations of drug doses as low as within 200 µl, it is limited to precise jetting of low-viscosity printing inks.

Russi and Gaudio, focused on developing multicompartmental capsules made of PVA through FDM for time-dependent release of drugs (79). Three different designs of the capsule were investigated, each with a varying number of reservoirs (e.g., single, double, and triple). The model drug used was curcumin, and *in vitro* dissolution testing was carried out to assess the release of the drug from the different capsule designs. Prior to the dissolution testing, thermal characterization was carried out to evaluate any possible changes due to the FDM printing process. The results showed no substantial differences. The dissolution testing confirmed the expected stepwise release profile, with the single reservoir releasing the drug in 180 min, double reservoir in 240 min, and triple reservoir in 360 min. Although, the study concluded that the 3D-printed multicompartmental capsules had potential for drug delivery applications, some caution is warranted regarding the polymer of choice. Specifically, the melting temperature of the PVA and the degree of crystallinity before and after FDM fabrication, were lower than typically reported for PVA. The decrease in crystallinity from 13% to 10% would suggest that the FDM process disrupted the ordering of the polymer chains, resulting in a less crystalline structure. This is likely due to the heating and cooling cycles of the FDM process, which can cause the polymer chains to become less ordered as they melt and solidify. It is important to note that changes in crystallinity can have implications for the physical and mechanical properties of the printed object. While a more amorphous polymer may be more flexible and less brittle, it may also be weaker and more susceptible to deformation under stress. Therefore, it is crucial to understand the effect of 3DP on the crystallinity degree to optimize the printing process and ensure that the final printed object possesses the desired properties.

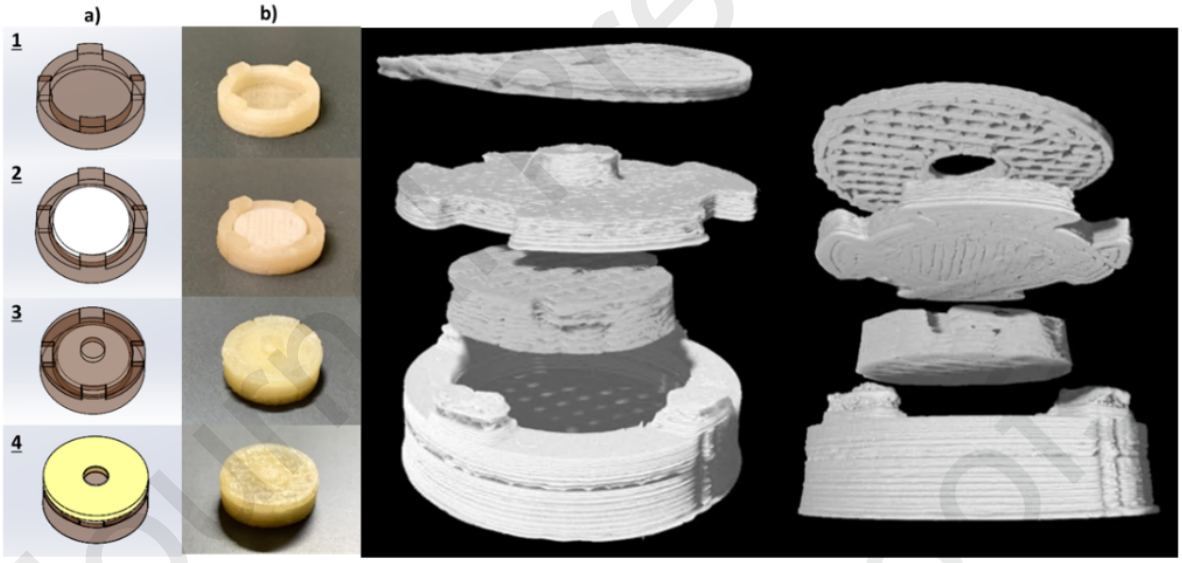

Fig. 6. (a) Design, (b) 3D printed and (c) X-ray CT rendering of the 3D printed compartments of the solid dosage form. From left to right, bottom compartment of the placebo section, top compartment of the placebo section, caffeine compartment and Melatonin compartment. Reprinted with permission from (Ghanizadeh Tabriz et al., 2023).

In addition, 3DP SODF's may be engineered with a view to combining two different release mechanisms demonstrating complex release profiles. This included tablets with two different sections presenting immediate and extended-release profiles. Tabriz and colleagues, recently reported on the development of LEGO®-like tablets **(Fig 6)** that allowed the use of FDM to deliver customised release profiles of melatonin and caffeine for the treatment of sleeping disorders (Ghanizadeh Tabriz et al., 2023). The modular units and filament compositions allowed for precise control over the release

kinetics, with immediate melatonin release followed by variable lag times and controlled caffeine release. Furthermore, specialised LEGO® compartments made of pH-dependent polymer (HMPCAS-AS-LMP) were used to further customise caffeine release. At pH values above 5.5, these pH-dependent compartments dissolved. This complete technique demonstrates 3D printing's capacity to construct complex release profiles by carefully planning the formulation and adjusting compartment thicknesses.

Thicker dimensions of the compartments led to slower caffeine release, consistent with the findings of another study demonstrating the ability to alter wall thickness to regulate drug release (Melocchi et al., 2020). This provides an intriguing possibility in which the thickness of these compartments could serve as an effective alternative to existing coating approaches for achieving controlled drug release.

Achieving consistent drug release from batch to batch, using 3DP can prove to be quite a challenge. However, this group has demonstrated that the optimization of filament fabrication and print parameters is essential to achieving reproducible and consistent drug release from batch to batch when using 3DP technology. Overall, these studies demonstrate the ongoing interest and progress made in the adoption of 3DP technology being developed to fabricate SODFs, and in achieving the necessary precision of control over drug release kinetics.

4.2. Dose flexibility

SODF's with varying drug concentrations can be created using 3DP, allowing for dose customization, based on factors such as a patients age, weight and medical history. Dose flexibility is also an essential advantage within preclinical drug development, as the evaluation of a wide range of doses is necessary for pre-clinical development and FIH trials (Shen et al., 2019). With the use of 3DP, a diverse range of dosages can be produced to accommodate the specific needs of a study. Animals used in preclinical studies frequently differ in size, weight, and metabolism, which can affect drug absorption and distribution. Researchers can ensure that each animal receives the correct dose based on its individual characteristics by using 3DP to create customised doses for different animal models. Modifying the physical dimensions or infill percentage of tablets, might allow for an easy dose manipulation with 3DP. For example, it is possible to decrease the tablet size while maintaining the same infill density, or in this scenario, keep the tablet size the same but decrease the infill density to reduce the amount of drug in each tablet. It demonstrates how it is totally feasible to customize the dose based on the needs of individual patients, without having to create an entirely new formulation or manufacturing process. In a 2021 study, researchers used 3DP to create ketoprofen tablets with varying dose and dissolution profiles from a single feedstock filament (Pyteraf et al., 2021). According to the findings of the study, modifying the physical dimensions or infill percentage of tablets allowed for flexibility in dose manipulation by application of 3DP. However, the study has certain limitations that should be noted. For instance, the range of API content in the filaments tested was limited, with the study only testing filaments containing ketoprofen content of 20%, 40%, and 50%. This may not fully represent the range of API concentrations that could be used for customized dosing. Furthermore, the team encountered difficulties when attempting to produce 50% ketoprofen-loaded filaments due to the plasticizing effect of the API causing high elasticity, making printing difficult. It should also be noted that the study focused solely on a single drug and formulation, and therefore, the results may not be generalizable to other drugs or formulations. Further research may be required to investigate the feasibility and limitations of using 3DP for customized drug dosing in a broader range of drug products.

4.3. Drug design

The utilization of 3DP technology provides an innovative and versatile approach when applied to the manufacture of allowing, as it does, the ability to enhance overall appearance, size, and structure integrity, as required. In contrast to conventional manufacturing methods, 3DP technology allows for precise control of the geometry, internal structure, and surface area that impact dissolution kinetics (Cui et al., 2021). However, the level of control may vary among different 3DP methods, for example with SLA and DLP excelling in geometry and structure precision, while FDM provides for accurate geometry and internal structural control via infill density modifications. It also provides the potential to customize SODF designs, targeting individual patient needs, including those of the paediatric population. Notably, this ability to provide more attractive dosage forms has been shown to increase patient compliance and treatment adherence within this demographic. Consequently, 3DP technology presents a promising avenue for the development of personalized dosage forms that can improve therapeutic outcomes and enhance patient experience. Bogdahn et. al., (Bogdahn et al., 2021) conducted a study aimed at exploring the swallowability of FDM 3D printed SODF's of various shapes but comparable size. The team developed a multi-nozzle system to enhance the efficiency of the printing process, which enabled the production of 576 printlets and facilitated the attainment of statistically meaningful results. In this study, 12 healthy subjects participated in a blinded design and evaluated six 3D printed placebo objects (e.g., oblong, round, pyramid, football, cuboctahedron, and sphere) alongside two traditionally compressed (oblong and round) placebo reference objects. The results of the swallowability study showed that both the 3D printed and compressed oblong tablets were the most easily swallowed, while the pyramid and cuboctahedron were the most difficult. These findings confirm the results of a previous study by Goyanes and colleagues in 2017 (Goyanes et al., 2017), which found that geometries with corners and edges are challenging to swallow. The study conducted by Bogdahn et. al., provides evidence that large tablets with elongated geometries were significantly easier for the participants to swallow.

There is more design freedom with 3DP, allowing the production of dosage forms to provide the appropriate size and geometry and containing precisely tailored dosages. This is particularly significant in the formulation of mini tablets, which are commonly utilized in paediatrics. With the ability to manipulate the diameter (<5mm) and quantity prescribed, the behaviour of mini tablets, including drug release and dosing, can be controlled with a high degree of accuracy with 3DP. Additionally, their small size makes them an attractive option for administering drugs to rodents and

other small animals in preclinical studies. The ability to titrate doses slowly is also a particular advantage of 3DP, customisable doses can be used to avoid splitting conventional SODF's to achieve a required strength, and doses of medication can be titrated at intervals lower than is possible with existing products. A recent study carried out by Buyukgoz and team in 2022 (Gorkem Buyukgoz et al., 2022), investigated the robustness of 3DP mini tablets as a platform for administering mg dosages for age-specific therapy, without the need for tablet splitting. The drug Griseofulvin, a poorly water-soluble

drug, along with HPC and kollicoat as polymers to prepare filaments through HME at drug concentrations ranging from 1% to 20%. As shown in **Fig 7**, 3D printed minitablets measuring 2mm were produced, achieving a reliable dose titration within the range of 0.19-3.91 mg with high accuracy. These mini tablets with cylindrical shapes exhibited excellent uniformity and label claim values that were within the acceptable range, demonstrating that HME followed by 3DP not only has the advantage of manufacturing a variety of strengths, but it also assures consistent dosing, potentially reducing the need for tablet splitting However, the release profile of the single unit mini tablet showed slight differences, likely due to the low drug concentration in a single tablet, but the release profiles of mini tablets with varying drug concentrations were found to be statistically similar for composite units ranging from 5 to 20 counts. The study did show, however, that using solidified HPC and the dense matrix of FDM 3D-printed tablets aided in achieving comparable release profiles from composite unit mini-tablets. Overall, the study demonstrated that 3DP mini tablets with the ability for dose titration can be advantageous for preclinical studies, leading to increased efficiency.

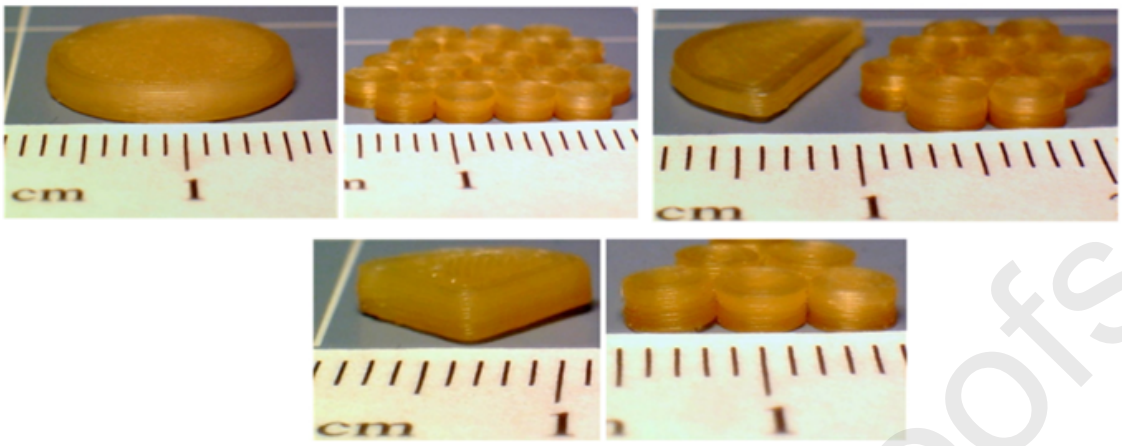

Fig 7. Digital images of: Full tablet vs. twenty mini tablets, half tablet vs. ten mini tablets, and quarter tablet vs five mini tablets. Reprinted with permission from (Gorkem Buyukgoz et al., 2022)**.**

4.4. Personalized medicine

Due to the "one-size-fits-all" approach, with its failure in considering the unique needs of individual patients, conventional mass manufacturing of dosage forms has a success rate of only 30% in achieving the intended therapeutic outcomes (Khalid and Billa, 2022). This issue is particularly acute in the case of SODF's, where the only way to change the dose is by splitting or crushing tablets. However, this can result in insufficient medication or damage to the film coating, because of this deficiency, there is a growing interest in developing more efficient medicines that can be tailored to each patient's specific needs. Although the use of 3DP within the area of producing personalised medicine in tablet form is still in its relative infancy, several studies have been conducted to explore the potential benefits and challenges of using this technology in pharmaceuticals. **Fig 7** provides an overview of SODFs that have been produced. A particularly promising application is for the formulation of SODF's which require precise, tailored dosages for neurological disorders such as attention deficit hyperactivity disorder (ADHD) and Parkinson's disease (PD). ADHD is considered a chronic disorder of significant impact, being typically diagnosed in childhood and which may remain active into adulthood. Stanojevic and colleagues (Stanojević et al., 2021), examined the possibility of

manipulating tablet thickness and drug loading to customise drug release rates, ranging from immediate to prolonged release. In conjunction to this, the researchers aimed to create predictive models for atomoxetine (ATH) release rate from tablets printed using DLP 3DP technology. They formulated a photoreactive mixture of poly(ethyleneglycol)diacrylate (PEGDA), poly(ethyleneglycol) (PEG) 400, water, a photo initiator, and ATH as the model drug. The ratio of PEGDA to PEG 400 was constant at 3:1, but the amount of ATH varied from 5% to 20% (w/w). They used this mixture to create 3D cylindrical-shaped tablets with the same diameter but different thickness. They were able to create tablets with doses ranging from 2 mg to 37 mg, which had both immediate and modified release profiles. The researchers encountered difficulties in selecting the appropriate hydrophilic polymer and achieving the desired API release rate, while maintaining the 3D-printed dosage form's printability and reproducibility. These challenges may have impacted upon the overall success and feasibility of this study if had not been able to optimize the formulation and excipient combination. This highlights the significance for careful formulation development and optimisation in 3D-printed DDS design. The choice of appropriate excipients, API loading, and printing parameters can have a significant impact on the quality attributes and performance of the final product. The difficulties encountered by the researchers in this study highlight the complexities of designing 3DP drug delivery systems, as well as the need for a systemic approach to overcoming these difficulties. Proper optimisation and validation are critical to achieving the desired therapeutic effect while maintaining product quality and stability.

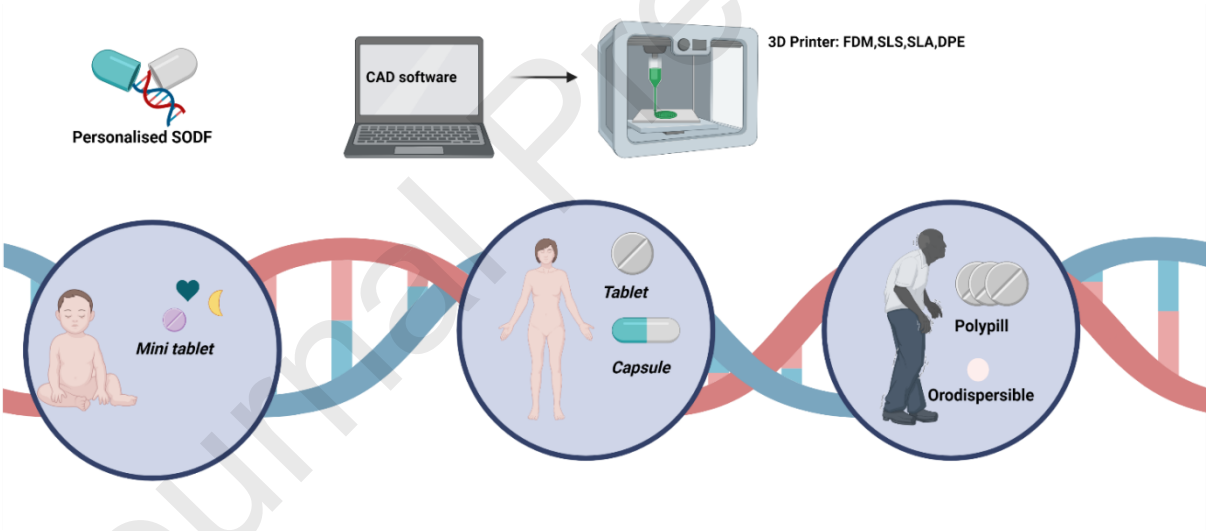

Fig 8. Schematic overview of 3DP SODFs within the area of personalised medicine: process involves developing a digital model of the tablet or capsule using CAD software, the model is then sent to a 3DP. 3DP can produce mini tablets or customised shapes that is attractive for the paediatric population. The technology can produce customized SODFs that are tailored to an individual patient's needs, such as the specific drug dose, release rate and combination of API's.

Conversely, in 2022 Gultekin et. al., (Gültekin et al., 2022) utilized FDM 3DP in the preparation of dosage forms with variable release properties for the treatment of PD. PD is a diverse and complex neurodegenerative disorder, affecting approximately 10 million people worldwide. The symptoms and progression of Parkinson's disease may vary greatly between patients, making it difficult to develop effective treatments that would prove effective for everyone. Typically, PD is treated with medications

that target the disease's symptoms, such as levodopa (LD), dopamine agonists, and MAO-B inhibitors. Unfortunately, patient responses to these drugs can vary greatly, with some patients perhaps experiencing adverse effects or requiring higher doses to achieve the same effect. The team developed a 3DP SODFs manufactured of commercially available (0.25 and 1 mg) and intermediate (0.375, 0.5 and 0.75 mg) doses of pramipexole with Eudragit EPO and POLYOX N80 polymers. For all doses of pramipexole, 3D-printed tablets demonstrated reproducible physicomechanical and *in vitro* drug release properties. The optimal 3D-printed oblong tablet formulation's stability was evaluated and found to be comparable to that of conventional tablets, with the formulation remaining stable for 12 months at 25°C in 60% relative humidity (RH), and 6 months at 40°C in 75% RH. Notably, there is a lack of published literature on the stability of 3D-printed tablets, highlighting the need for additional research in this area to ensure the long-term efficacy and safety of these personalised medicines.

Windolf and colleagues (Windolf et al., 2022), conducted a study utilizing FDM to create a personalized mini-floating polypill for PD. FDM was used with HME to produce two different compositions into filaments; pramipexole (PDM) and PVA for rapid drug release and a fixed combination of LD/BZ (benderazide) in ethylene-vinyl acetate (EVA) copolymer matrix for prolonged drug release. Since LD is absorbed in the upper gastrointestinal (GI) tract, a formulation that floats in gastric fluid was desirable, with the aim of prolonging API absorption. Using the FDM 3DP process, different polypill geometries were printed from both filaments with variable dosages. The dosage forms ranged from 15 to 180 mg LD and exhibited similar release rates ($f2 > 50$). Additionally, a mini drug delivery dosage form was printed that released 75% LD/BZ within 750 min and could function as a gastric retentive drug delivery system, due to the floating properties of the composition. The LD/BZ dose was reduced to 15/3.75mg per mini tablet, and the PDM dose was set to 0.375mg. Such advances in drug delivery technologies emphasise the need for more adaptable dosage forms that go beyond the limitations of traditional tablet splitting or crushing.

The studies mentioned above have highlighted the potential of 3DP technology to significantly advance drug delivery and improve treatment outcomes for SODFs. Despite this, there are still several challenges that need to be addressed, including formulation, quality control (QC) and manufacturing scalability. It is worthy of note that a large percentage of newly developed drug molecules (70-90%) show poor aqueous solubility, posing a significant challenge in drug delivery. As a result, it highlights how the importance of further investigation as to whether the approaches described in these studies can be effective for APIs classified as BCS Class II or IV, and their inherently low solubility.

4.4.1. Paediatric populations

Paediatric patients differ from adults in many aspects of pharmacotherapy, including capabilities for drug administration, taste preferences and drug related toxicity. In general, the paediatric population is not homogenous; therefore, oral formulations are primarily focused on the patient age, weight, and physiological condition. Conventional manufactured SODF's have garnered an unfortunate association with limited dose flexibility and the risk of choking, due to the size and shape of the tablet or capsule. In the pharmaceutical industry, the paediatric population still presents as the greatest challenge in terms of developing flexible and appropriate drug dosage forms, with a marked lack of said dosage forms adequate for a child's age and size, considering their enormous weight range, from approximately 0.5 kg to 100 kg. This would dictate the requirement for a range of different doses of medicines to be made available, to provide for these variations, deemed an important task for conventional tablets or capsules as previously mentioned. This is one of the main reasons why liquid formulations are favoured as the first choice for children. But the popular belief that children should not or will not swallow tablets is a false one; research studies have demonstrated that children as young as four years old have shown a preference for tablets that could be swallowed or chewed, as opposed to taking liquid formulations (Bracken et al., 2022).

In 2022, Malebari and colleagues (Malebari et al., 2022), explored the feasibility of producing spherical mini tablets of ritonavir and lopinavir combined with HMPCAS with PEG 4000 through the use of DPE 3DP, for Human Immunodeficiency Virus (HIV) treatment. By using this method, the tablets could be made small (6 mm spherical), making them easier for children to take, with their solid state would improving the bioavailability of the drugs when taken orally. The study also aimed to compare this technique with HME and FDM to determine if it was a more convenient method. The printlets were analysed and compared to Kaletra, a commercially available drug that also contains ritonavir and lopinavir. The mini tablets fabricated by HME followed by FDM led to a significant drug degradation (>30%) at 120 °C the temperature required to obtain printable filaments. When this technique was replaced with DPE, the temperature was reduced to 80 ˚C, and the residence time inside the heating barrel of the extruder was much shorter (<10 min). This allowed for an enhanced control of the printing process and avoided drug degradation. The minitablets were slightly smaller in weight and diameter when compared to the lopinavir ones, although there was no statistical significance observed between the two tablets. The recommended dose for HIV treatment is 16 mg of lopinavir and 4 mg of ritonavir per kg of body weight. The current tablets have a drug content of 25%, which is equivalent to 40 mg. Therefore, to treat an HIV-infected child weighing 10 kg, four minitablets of lopinavir and one minitablet of ritonavir are needed. While the dose can be readily adjusted by changing the tablet diameter or the number of tablets administered, this may affect patient compliance. Furthermore, the drug release studies were performed separately for lopinavir and ritonavir, which may impact their overall solubility and dissolution profiles. Despite these limitations, the study demonstrated that the 3D-printed minitablets could maintain a sustained release profile, which is critical for ensuring adequate drug exposure and efficacy. The same HME and DPE 3DP method was used by a group of researchers in the same year (Boniatti et al., 2021). Boniatti et. al., used a mixture of kollidon VA 64 and surfactants to create child-friendly praziquantel tablets. Praziquantel has long been used to treat schistosomiasis, a disease that affects over 250 million people. There is, however, no treatment for children, and adults' tablets are frequently split for use. The 3DP tablets were studied and found to increase praziquantel release by fourfold. Characterisation tests showed that the 3DP tablets improved the release of praziquantel four times, as this technology does not require the use of filaments and can help with the current issues with praziquantel like poor solubility, unpleasant taste, and varying dose requirements. However, there were limitations to the study, including the pellets and powders produced. Using pellets demonstrated inconsistent flow into the printer and the milled materials, on the other hand, provided a more continuous flow and a better printing process, but the drug load in the system affected the feed rate. Although there were limitations, the study demonstrated the potential of printing with high drug load materials obtained by HME, which is an important step forward. SEM and palatability analyses were not performed due to the limitations and as the study indicated that the taste masking capabilities of this 3DP technology without the need for additional taste masking excipients are an advantage, palatability studies could have further evaluated this aspect.

Most of the studies involving paediatric dosage forms have gone down the route of mini-tablets or gummy candy style formulations. Though it was of interest that Karavasili and colleagues (Karavasili et al., 2020) developed a chewable chocolate-based dosage form using 3D extrusion printing in 2020. They used both a lipophilic (ibuprofen) (IBU) and a hydrophilic (paracetamol) (PCT) as the drugs of choice and the study provided successful results. Different shapes ranging from simple structures to cartoon characters, were designed to increase the appeal for children. Recently, the same team using the same drugs used cereal (Nestle honey Cheerios') to develop a drug loaded ink for SSE 3DP (Karavasili et al., 2022). The team aimed to create a platform method for the administration of both hydrophobic and hydrophilic drugs to hospitalized paediatric patients through breakfast consumption. Different 3D printed designs, including numbers and letters, were created as illustrated in **Fig 9**. The study proposed that concealing drug administration under the auspice of an essential daily eating habit could help overcome adherence barriers to medication intake by paediatric patients within a hospital setting. However, the development of candy-like or breakfast-cereal-like oral dosage forms does come with ethical and safety implications. Children may not be able to distinguish between medicine and candy, potentially leading to an overdose. As Karavasili noted in the study, oral dosage forms like this should be administered in a clinical setting. Chewable oral formulations hold promise, but numerous challenges

must be addressed before they can be widely accepted by the pharmaceutical industry and pharmacy practice for personalized medicine (Herrada-Manchón et al., 2020).

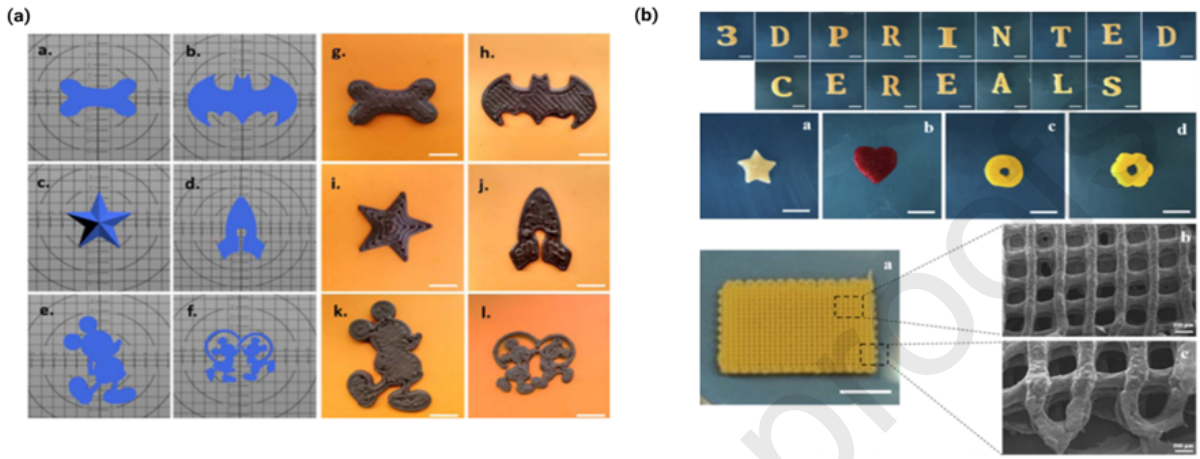

Fig 9. (a) Schematic of .stl files and 3DP chocolate-based dosage forms (Karavasili et al., 2020). (b) Number and letters of the alphabet, star, heart, torous, and a flower 3DP cereal (Karavasili et al., 2022). Reprinted with permission.

4.4.2. Geriatric populations

Geriatric patients, like paediatric patients, have unique dosage requirements that often differ from those of typical adult patients. Additionally, many elderly patients may have difficulty swallowing medication or be hesitant to do so due to dysphagia. Traditionally, crushing, or splitting tablets with higher drug doses was necessary to achieve the optimal dosage. However, 3DP technology provides a solution to this problem by enabling the creation of tablets with swallowability in mind and can be customized to meet the specific needs of geriatric patients. This technology also allows to produce tablets with slow-release formulations, which is particularly advantageous for medications requiring consistent, controlled release over an extended period. Elderly patients typically take more medications, making it valuable to combine multiple drugs, dosages, and/or drug-release profiles into a single formulation. However, conventional manufacturing processes do not currently support the individualization of "polypills," producing only fixed-dose combinations. Windolf and colleagues, have previously demonstrated the advantages of 3DP technology in this regard. In addition to the above benefits, 3D printed tablets are non-compressed and can be layered, making them befitting for orodispersible tablets (ODTs) that melt in the mouth, making them easy to swallow. This has resulted in an increase in the popularity of their use, as evidenced by several studies. A recent study (Tranová et al., 2022) utilized the FDM technique to produce 3DP ODTs of paracetamol and domperidone. Filaments containing API matrix-forming polymer, super-disintegrant, and plasticizer were created using HME. The printing process induced amorphization in the case of all tablets containing paracetamol and those containing domperidone without mannitol. Five different spatial shapes were successfully printed, with the crown shape with infill of 15% tablets for domperidone and paracetamol, respectively, reaching the shortest disintegration time, fulfilling the Ph. Eur. limit of within 3 min. During the dissolution studies, approximately 80% of APIs were released from printlets within 15 minutes, confirming the tablet's immediate release properties. However, the printability and properties

of the orodispersible tablets were significantly influenced by the API properties, particularly in high drug-loaded formulations. The rough and porous surface of the domperidone tablets could have an impact on the aesthetic and functional aspects of the printed product. It is difficult to create universal, fast-disintegrating formulations that can accommodate the properties of various APIs is a challenging task. Nonetheless, 3DP technology provides a promising solution for addressing the unique medication needs of geriatric patients.

5. Defect Detection and Quality Issues in 3D Printing

A primary concern within the landscape of 3DP revolves around the pervasive challenges associated with defect detection and the resulting impact on product quality. Unfortunately, defects are frequently occurring, and their control incurs significant expenses For example, problems with tablet porosity, layer misalignment, and inadequate excipient fusion are examples of defects in SODFs that make it difficult to maintain pharmaceutical product quality (Nazir et al., 2023). These defects not only compromise the mechanical properties of the final dosage forms but also present significant obstacles in meeting stringent regulatory standards. The presence of microstructural flaws, such as insufficient compaction resulting in tablet capping or lamination, can have a significant effect on the end product's structural integrity. These defects may result in variations in drug release profiles, affecting the bioavailability of the API and potentially compromising the therapeutic efficacy of the medication. Defect control has proven to be an expensive commitment, partly due to the lack of comprehensive process knowledge, hindering the ability to predict and prevent defects accurately. To address this, researchers are exploring advanced process monitoring techniques. For instance, in laser powder bed fusion processes, in-situ monitoring using high-speed cameras and thermal imaging has shown promise in identifying defects in real time(McCann et al., 2021). These techniques lower the possibility of errors and reduce the need for expensive post-process checks. The incorporation of roadmaps into this strategic framework serves as a crucial tool in directing efforts aimed at preventing defects. By aligning 3DP advancements and defect mitigation strategies within a roadmap, pharmaceutical manufacturers can establish a comprehensive and forward-looking plan. This roadmap-driven methodology expedites the development of workable solutions while simultaneously enabling the real-time discovery of problems using sophisticated monitoring mechanisms. Furthermore, a significant obstacle in the production workflow is being caused by the inadequacy of current monitoring tools to identify anomalies and faults in real time. Real-time monitoring is made more difficult by material inconsistencies, changes in the surrounding environment, and printing problems (Delli and Chang, 2018). The integration of continuous manufacturing into the 3DP workflow offers a promising solution to these challenges. Continuous manufacturing involves uninterrupted, end-to-end production processes, enabling real-time adjustments and enhanced control over the manufacturing process. This methodology is consistent with the fundamentals of Quality by Design (QbD) and enables the establishment of durable and dependable production procedures that satisfy regulatory requirements. Utilizing machine learning algorithms is becoming more and more common as a solution. These algorithms can forecast outcomes and find patterns linked to the production of defects by examining large datasets produced during the printing process. For example, in polymer-based 3D printing, machine learning models have proven effective in anticipating problems with layer adhesion, enabling real-time corrections to avoid structural

weaknesses(Xu et al., 2021). Due to these obstacles, the 3DP industry is forced to rely more heavily on costly testing and qualification procedures, which has negative financial effects.

6. Utilizing simulation and optimization in 3D printing for SODF development

Simulation and optimisation techniques can be used in 3DP to improve the manufacturing process and to ensure the quality of the dosage forms produced. Researchers can predict how materials will behave during the printing process and can identify potential issues or opportunities for process optimisation by using simulation software. The process parameters and materials used can then be refined using optimisation techniques, resulting in greater efficiency, consistency, and quality in the manufacturing process. However, the reliability and validity of these simulations can vary based on the specific software, models, and parameters used. The accuracy of the simulation software's models and assumptions is critical in determining their validity, and the dependability is dependent on the simulation software's robustness and the quality of input data (Robinson, 2023). To optimise the design and manufacturing of 3DP SODF's, mathematical modelling is an important tool. Researchers can predict and control the behaviour of the drug and tablet during manufacturing and in vivo performance by developing mathematical models based on the physical and chemical properties of the drug and the 3DP process. By controlling printing parameters such as nozzle size, layer thickness, and infill density, mathematical models may be adapted with a view to optimising the porosity, density, and release rate of the tablet. They can also simulate and predict drug dissolution and absorption in the gastrointestinal tract and systemic circulation. Mathematical modelling is a powerful implement for the task of speeding up the development and regulatory approval of 3D technologies. Thakkar et. al., (Thakkar et al., 2020) published a study in 2020 that demonstrated just that. The study looked at the effect of fill density on the performance of 3D printed dosage forms, specifically ASDs of a BCS class II drug prepared with HPMC-AS polymers. The researchers discovered that the rate of drug release was determined by the polymer's solubility and rate of hydration, which was influenced by the fill density of the tablets, rather than the intrinsic properties of the drug. The potential of mathematical modelling in developing a robust formulation strategy for 3D printed dosage forms is highlighted in this study. Other researchers have uncovered some association between infill and release, but it is crucial to determine the significance and correlation statistically of this association to further justify the release behaviour. Although some previous studies have reported a relationship between infill density and drug release behaviour in 3D printed dosage forms, the statistical significance and correlation of this association needs to be established to validate its impact on release behaviour.

Machine learning (ML) and Artificial intelligence (AI) are promising techniques that have demonstrated an ability to enhance the development and optimization of 3D printed SODF's. By analysis of the large amounts of data generated through various aspects of the 3DP process, such as formulation, printing parameters, and drug release behaviour, ML/AI algorithms can identify important relationships and patterns that may not be apparent through traditional statistical methods. In recent years, several studies have demonstrated the potential of ML/AI in optimizing 3DP processes for drug delivery. For example, Wang et. al., (Wang et al., 2020) used a ML/AI algorithm to predict the release behaviour of 3D printed tablets containing metformin, based on the printing parameters and formulation characteristics. Recently, Ong and colleagues (Ong et al., 2022), used a combination of in-house and literature-mined data on HME and FDM 3DP formulations to improve the predictive performance of ML/AI models. The dataset included 1594 formulations. The optimised models were successful in predicting printability and filament characteristics with higher accuracy, and HME and FDM printing temperatures within a more precise temperature range than previous models. Overall, ML/AI has the potential to significantly improve the efficiency and effectiveness of 3DP for drug delivery, by providing insights into complex relationships between various factors and enabling rapid optimization of the printing process. **Fig 10** provides an overview of the different types of ML that have been applied to 3DP procedures.

6.1.1. Implementation of Quality by Design (QbD) and Process Analytical Technology (PAT)

QbD and PAT implementation can significantly improve the quality and efficiency of 3DP for 3D printed SODF production. QbD and PAT are regulatory initiatives aimed at ensuring consistent product quality throughout the product development process. QbD entails identifying critical quality attributes (CQAs) of the final product, and in the design of a process capable of consistently meeting those attributes. QbD in 3DP entails optimising the formulation (i.e. critical material attributes), printing parameters (i.e. critical process parameters), and post-processing steps to ensure that the final product meets the desired CQAs. 3DP could ideally aid QbD by potentially shortening the time and API usage

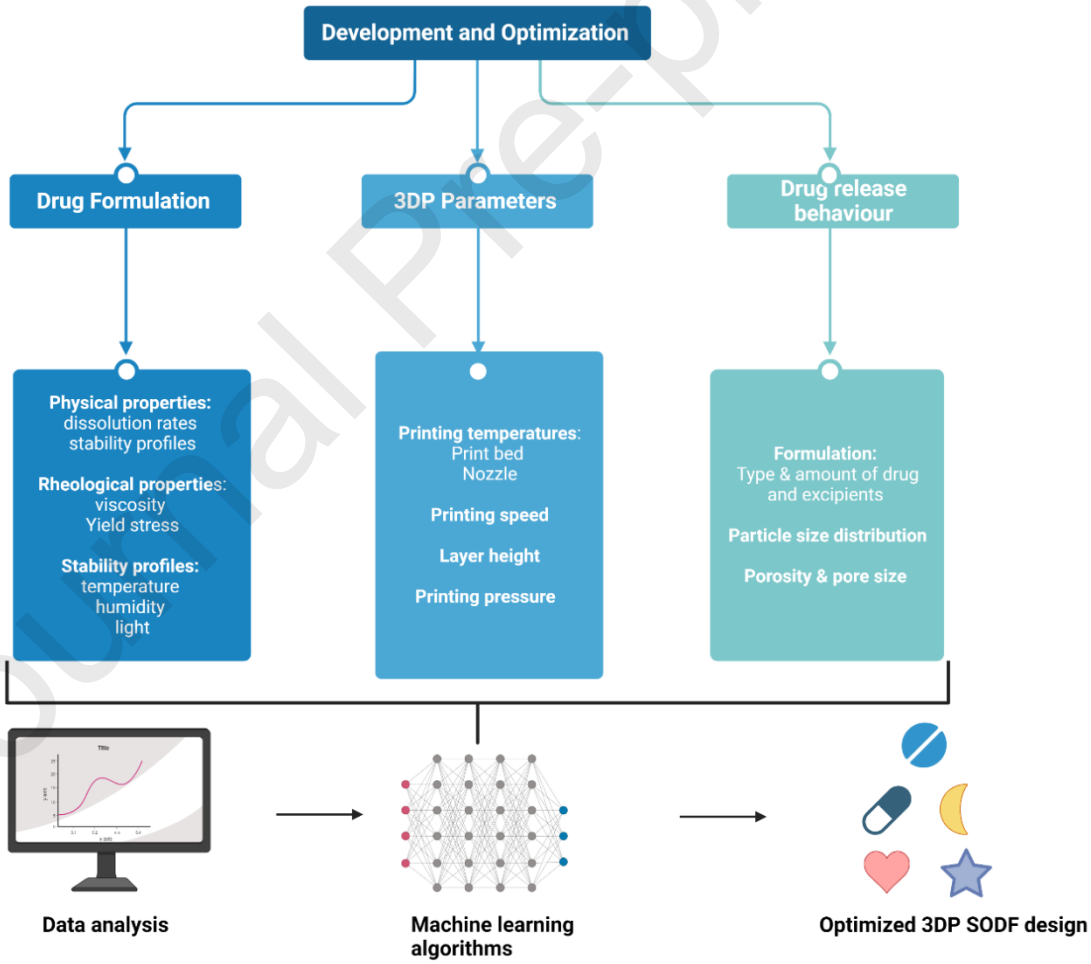

Fig 10. Schematic overview of machine learning applied to 3DP. Flowchart demonstrates data collection such as drug formulation, 3D printer parameters and drug release behaviour. This data is analysed using machine learning algorithms to identify patterns and relationships between the drug

properties and the 3DP parameters. Training the algorithms to optimize the design of SODF's, based on identified patterns and relationships.

required for product development. However, there are obstacles. A specific number of tablets, for example, may still be required for various studies, which can take time and resources. Furthermore, specifying a batch or run-time in 3DP can be difficult. Although it is frequently regarded as a continuous process, there may still be a minimum time required to complete a batch, particularly when data gathering, and analysis are considered. As this technology matures, it is critical to ensure that QbD and PAT can operate efficiently within the dynamics of 3DP. Henry et. al., (Henry et al., 2021) for example, investigated the effect of five print parameters (e.g., infill, overlap, number of shells, layer height, and layer pattern) on the CQAs of a fixed size 3D printed caplet containing Eudragit EPO, Polyox WSR N10, and zolpidem hemitartrate. They investigated the effect of each parameter on the mechanical properties, dimensions, weight, porosity, and dissolution characteristics of the 3D printed caplets using a Design of Experiments (DoE) approach. To assess the effect of five print settings on caplet properties, a fractional factorial design (resolution V+) with 20 experiments and four replicates was used. The researchers concluded that a higher level of the factors reduced deviation from the desired geometry, with overlap having the greatest impact. The infill was found to have the greatest influence on the weight of the caplet, followed by overlap and shells. Based on all the responses collected, infill was determined to be the most influential factor because it determines the mechanical properties of the caplet, its dimensions, weight, porosity, and dissolution behaviour.

PAT is a scientific, risk-based approach for ensuring product quality in real-time during manufacturing by integrating process understanding, control strategies, and in-line or at-line measurements of CQAs where feasible. By doing so, it allows manufacturers to move from the traditional approach of relying on laboratory-based testing of collected samples to real-time quality assurance. While not all parameters may be practically measurable using PAT (e.g., microbiology, which, in theory, can be predicted based on water content but still requires testing due to equipment cleanliness), it is applied to CQAs where implementation is viable. In the production of SODF's, near-infrared spectroscopy (NIR) and Raman spectroscopy (RS) have become universal tools for process monitoring and control. NIR and RS can be used to measure various parameters, such as API content, moisture content, and tablet hardness, without the need for destructive testing or sampling (Zhong et al., 2020). A group in 2022 (Trenfield et al., 2022), looked at how NIR and RS could be used to predict the amorphous content of itraconazole-loaded formulations. Calibration models were created using partial least squares regression, which successfully predicted amorphous content in the 0-20% w/w range. For predicting amorphous content, the NIR and Raman spectroscopy models demonstrated excellent linearity and accuracy. Overall, the study demonstrates SLS 3DP ability to produce solid dispersions containing a BCS II drug, as well as the use of NIR and Raman spectroscopy to quantify amorphous content as a non-destructive quality control measure at the point-of-care. Researchers can adjust the process to ensure that the final product meets the desired quality specifications by measuring these parameters in real-time during manufacturing.

7. Regulatory challenges and quality controls

In the pharmaceutical industry, navigating the complexities of regulatory frameworks and guaranteeing strong quality standards are critical, especially in the cutting-edge field of 3D printing for SODF development. The strategic planning encapsulated in roadmaps emerges as a key player in addressing these challenges. Roadmaps are crucial tools for navigating the challenging world of regulatory compliance, in addition to providing light on the route towards technical breakthroughs. By aligning strategic planning with regulatory and quality control objectives, roadmaps offer a systematic approach

to overcoming hurdles. They provide a structured framework that describes procedures for strict quality standards in addition to anticipating regulatory obstacles. This integration promotes a smooth transition from conception to commercialization by guaranteeing that the development and manufacturing processes follow legal requirements ("America Makes and ANSI Publish Standardization Roadmap for Additive Manufacturing Version 3.0," n.d.). Despite the successful manufacturing of different SODFs with various release profiles and geometries using different 3DP technologies and materials, only one has been approved and placed in the market. This is mainly due to the several challenges that still need to be overcome with 3DP technology in drug manufacturing, including regulatory limitations as there are currently no regulatory pathways for 3DP SODFs. In 2017, the FDA issued a draft guidance document titled "Technical Considerations for AM Medical Devices" to provide regulatory considerations for medical devices produced using 3DP technology. However, for 3D printed oral formulations parameters for quality requirements have not yet been clearly established. The BP does describe quality requirements for tablets, but it is unclear as to whether the current BP tests for tablets are also fully applicable to 3D printed tablets (Lafeber et al., 2021). Although 3DP follows different processes to that of conventional oral dosage forms, researchers follow the same guidelines and quality standards. Another regulatory issue concerns the materials used in 3DP. Traditional drug manufacturing processes typically use materials that are well-characterized and standardised, but 3DP involves a broader range of materials with varying properties, some of the materials used in 3D printing for pharmaceutical applications are approved for pharmaceutical use, while others are commonly employed in the field of polymer processing. The regulatory status of specific materials can vary, and regulatory agencies are working to evaluate their suitability for pharmaceutical applications. In 3D printed SODF manufacturing, quality control presents a significant challenge (fig 11). Because 3DP is a LbL process, there are concerns about the final product's consistency and uniformity. Standard Quality Control (QC) tests may not be suitable for 3D printed SODFs, necessitating the development of new tests and acceptance criteria. Furthermore, factors such as printer calibration, material properties, and printing parameters can affect the quality of the 3D printed SODFs, so the process must be carefully monitored and controlled to ensure consistent quality. Another regulatory concern is the requirement to demonstrate the consistency and reproducibility of the 3DP process. This includes the need to maintain the desired product properties while controlling the quality of the raw materials used in the 3DP process. By incorporating QbD and PAT into the manufacturing process of 3D printed SODFs, manufacturers can provide a more robust and comprehensive understanding of the product and the process used to produce it. This can help with regulatory approval by demonstrating that the final product is manufactured consistently within the specified quality range and meets all safety and efficacy requirements.

8. Challenges and future directions

3DP is an emerging technology (ET), possessing the potential to revolutionize the manufacturing of SODF's. However, there are still some challenges that need to be addressed before this technology can become widely adopted in the pharmaceutical industry. One of the challenges

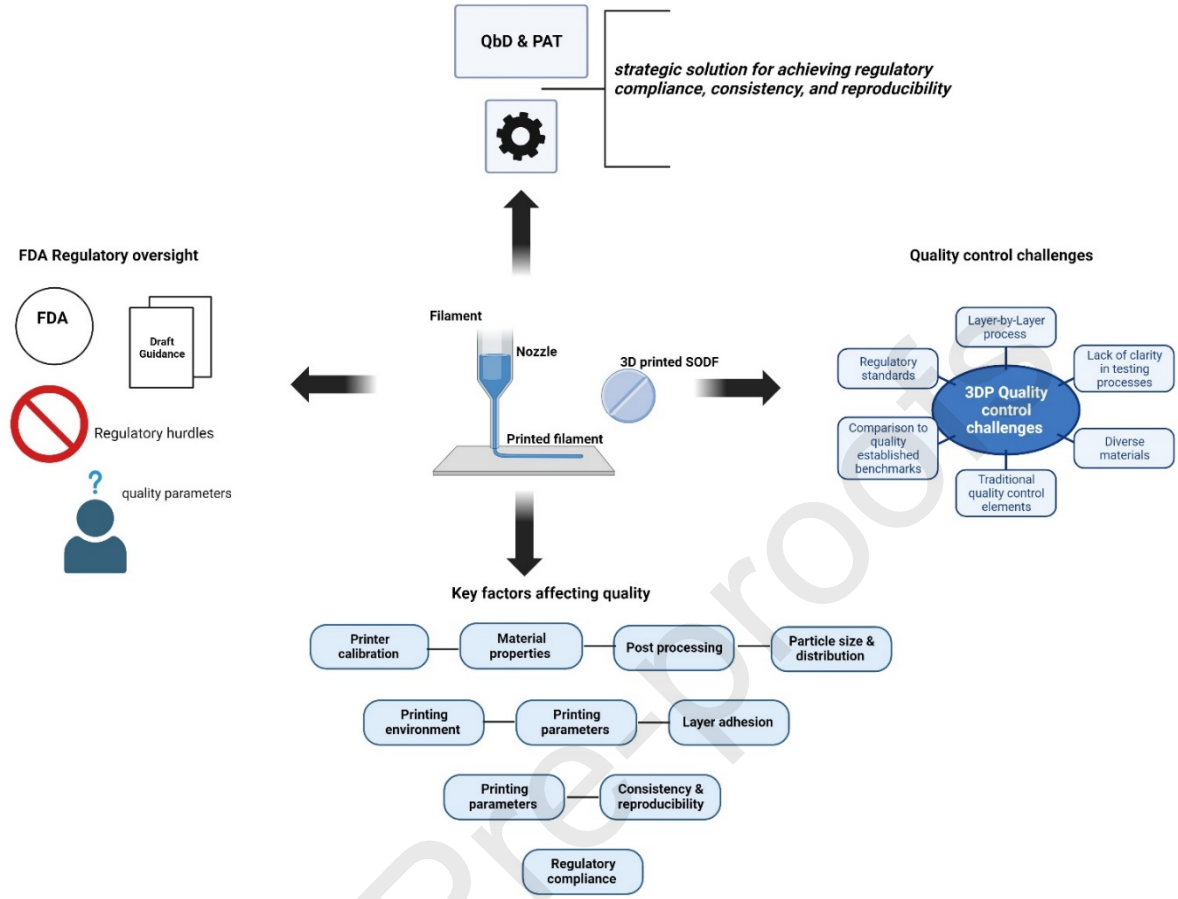

Figure 11, Navigating Regulatory Challenges and Ensuring Quality in 3D Printed SODFs. 3D-printed tablet symbolizing the 3D printing of SODFs. Left-hand side FDA regulatory oversight, draft guidance documents, and the absence of established quality parameters. On the right-hand side challenges in quality control specific to 3D printed SODFs. Below key factors affecting quality, including printer calibration, material properties, and printing parameters. Above emphasizes the integration of QbD and PAT as strategies to ensure consistency, reproducibility, and regulatory compliance.

encountered is the reproducibility of 3DP SODFs, particularly in technologies reliant upon a nozzle mechanism to build sequenced layers during formulation such as FDM. Clogging of nozzles in the 3D printer head can occur in powder-based 3DP, and the removal of excess powder can pose potential health and occupational hazards, necessitating the use of specialized laboratory equipment (Mostafaei et al., 2021). The use of natural and synthetic polymers, a new technique employed in the creation of a 3DP dosage form, involving their incorporation into the dosage form's structure or formulation. This approach is reported to alter the drug release rate and enhance API stability. Notably, when working with natural polymers such as gelatine or chitosan, the specific characteristics of these materials can significantly influence the selection of crosslinking agents. Crosslinking agents are frequently chosen based on their compatibility and reactivity with these natural polymers, considering variables such as solubility, reactivity, and cytotoxicity. Many research projects are turning to synthetic polymers like HPMC to overcome cytotoxicity problems and ensure compatibility. One of the biggest challenges in this field relates mainly to the paucity of adequate filaments, composed of pharmaceutical grade materials. A significant drawback is the need for thermoplastic polymers for FDM printing, although

the majority of the pharmaceutical grade polymers are not thermoplastic (Quodbach et al., 2022). And most of the time, 3DP formulation filaments are prepared at high extrusion temperatures, which may possibly lead to instability of thermolabile drugs. Also of concern is the presence of residual solvents in some 3DP dosage forms, which require drying of the dosage forms at high temperatures to allow for the removal of the solvent (Annaji et al., 2020). These solvents can originate from various stages, including drug substance manufacturing, excipient and polymer processing, and the 3D printing process itself. This is in accordance with the International Conference on Harmonisation (ICH) guidelines, which specify certain acceptance limits for solvents. The physical appearance of finished products of 3DP has raised some doubts, particularly when there is involvement with paediatric studies where a child-friendly appearance and taste are of utmost importance for successful formulation. Some studies have reported that the use of certain 3DP technologies, such as FDM or SLS, has led to the creation of printlets with rough or imperfect surfaces that are unappealing to patients of any age. This poor appearance can also lead to poor patient compliance, which is a significant concern in the pharmaceutical industry.

From a purely business perspective, 3DP technology may not be considered as the most suitable application for mass production, mainly due to limitations in production speed, cost, and regulatory requirements. That is not to say it has little positive to offer, as it still provides significant benefits when used within certain applications. Traditional manufacturing methods, for example, can be costly and time-consuming in the preclinical space, where small batches of drugs with specific design variations are required. As research in the field has shown, 3DP technology can be a cost-effective and faster solution for producing customised drugs with precise dosages and formulations in such cases. As a result, while 3DP technology may not be a replacement for traditional manufacturing methods in mass production, it can still be a useful tool. The development of robust protocols and methodologies is an essential component of any scientific research, including 3DP technology in pharmaceutical manufacturing. It is of importance to note that 3DP technology development for SODF's is an active and ongoing area of research, with a considerable involvement of researchers and institutions, working to improve and optimise the process. As a direct result, there may be variations arising, within the protocols and methodologies as applied by different groups. Presently, there is a current lack of consensus with regards to what would be the most appropriate and effective 3DP technology methods for generating accurate and reproductible preclinical models for drug development. A need for rigorous testing and validation of 3DP models is therefore required, and addressing this will require collaboration between researchers, industry, and regulatory agencies, when it comes to the establishment of best practices and standards for 3DP in preclinical drug dosage form development.

9. Conclusions

3DP technology integration into the pharmaceutical industry solid dosage forms is still in its early stages, although there is evidence that significant progress has been made. Although 3DP has demonstrated great potential, it is still limited, and the traditional drug delivery system remains the industry standard. 3DP technology is expected to provide the greatest benefits in personalised medicine, although it appears unlikely to replace conventional manufacturing for mass production. The 3DP method, on the other hand, is capable of producing small batches of specific design variations to aid in clinical studies for example researchers can quickly and accurately produce customised dosage forms with different drug release profiles and other desired characteristics. This enables rapid prototyping of drug formulations, which can then be tested in early clinical trials for efficacy, safety, and bioavailability. While 3DP technology integration into the pharmaceutical industry for solid dosage forms is still in its early phases, significant progress has been made. Though it may not replace conventional manufacturing for mass production, 3DP is well-suited for rapidly producing small batches of custom dosage forms with precise characteristics, aiding in early clinical studies for efficacy, safety, and bioavailability, thereby accelerating development timelines and reducing costs within the context of early clinical development

Aside from the benefits of speed and cost, the literature provided in this review shows that 3DP can also provide greater flexibility in the development process. It allows the development of complex drug formulations and customised DDSs that would otherwise be difficult or impossible to achieve using traditional manufacturing methods. This review article focused on the applications of 3DP in SODFs for early clinical development stages in the pharmaceutical sector, highlighting the technology's benefits and limitations. Overall, 3DP technology appears to be a promising avenue for the pharmaceutical industry, and it remains likely that we will see more and more applications of 3DP in SODFs in the future.

Author Contributions: Conceptualization, D.A.L. & S.K.A.; resources, D.A.L. & S.K.A.; writing—original draft preparation, R.L.M.; writing—review and editing, R.L.M., T.Q., S.K.A., and D.A.L.; supervision, D.A.L. All authors have read and agreed to the published version of the manuscript.

Funding: This paper was not funded.

Acknowledgements: The authors would like to thank Queen's University Belfast and Janssen for the PhD scholarship to R.L.M.

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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: