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REVIEW ARTICLE

The promising role of semi-solid extrusion technology in custom drug formulation for pediatric medicine

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Abstract

The long-standing issue of inadequate medicine formulations has been a focus of regulatory bodies and pharmaceutical research, particularly in adapting medicines for children's unique requirements. The pediatric population presents diverse challenges in pharmacotherapy due to their varying age-related physiological differences, and taste and dosage form preferences. Conventional formulations often fail to meet these needs, leading to a high prevalence of off-label medication use and modifications by caregivers, which can compromise drug efficacy and safety. The well-known challenges of managing children's medication are similar to those in geriatrics, both of which require dose adjustments to accommodate the patient's pathophysiological characteristics and prevent deglutination problems. This paper explores recent innovations in drug formulations, highlighting the shift from traditional liquid formulations to solid dosages through three-dimensional (3D)

printing technology. Recent advancements in 3D printing technology offer promising solutions to these challenges. Additive manufacturing (AM), or 3D printing, facilitates the creation of complex objects (e.g., drug formulations) directly from digital models, allowing for high precision and customization. 3D-printed formulations have displayed considerable promise in improving palatability, adherence, and dose accuracy for pediatric use. Innovations like chewable tablets and taste-masked formulations make medications more acceptable to children. Moreover, the ability of 3D printing to adjust drug release profiles and doses offers a personalized approach to pediatric and geriatric pharmacotherapy, which is essential for managing conditions that require precise therapeutic control. The paper discusses several case studies using the semi-solid extrusion (SSE) process for producing personalized dosage forms, along with various technical and regulatory challenges associated with implementing this process in hospital-based drug manufacturing. In conclusion, while 3D printing in pediatric and geriatric pharmacotherapy addresses many challenges of traditional drug formulations, ongoing research and adaptation of regulatory frameworks are necessary to expand its application, ensuring safer, more effective, and more acceptable medication.

***Keywords*:** Unlicensed preparation; 3D printing; Pediatrics; Semi-solid extrusion; Hospital preparation; Personalized medicines

1. Introduction

The lack of availability of appropriate medicines for children has been an extensive and well-known problem for many years.[1] Children require medicines that are adapted to each age group, due to the remarkable heterogeneity of this population, which ranges from premature infants to young adults. Some medicines are not suitable for young children, and even less so for premature infants.[2–4] Furthermore, differences in the pharmacokinetic and pharmacodynamic profiles of children and adults necessitate different dosage strengths for children. Moreover, the preferred dosage form for children evolves with age and must be adapted to account for varying weights, forms, and taste preferences, which can differ from country to country.[5] Consequently, there is a strong demand for medicines that are suitable for children, easy to administer, use non-toxic excipients, reduced dosage frequency, good palatability, and flexible dosing.[6,7] When developing a medicine, the choice of pediatric forms is most often made in favor of oral liquid forms, despite their limitations, including stability issues, difficulty in achieving controlled-release formulations, the need for multiple-day dosing, exposure to potentially harmful excipients, poorer palatability, and higher costs. From an industrial perspective, these constraints represent a significant challenge.[8–11]

Numerous incentives from the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA), such as Pediatric Investigation Plans, are mobilized in order to develop new formulations adapted for children with specific indications, allowing them to achieve Pediatric-Use Marketing Authorization (PUMA) status. In contrast, pediatric formulations of drugs already on the market typically receive only hybrid generic status and are priced similarly to the original drug. Between 2007 and 2016, 267 new medicines and 43 new dosage forms for children's use were authorized. Unfortunately, despite these incentives, only seven PUMAs have been obtained since 2006.[12] Pediatric medicines remain underdeveloped, particularly in areas such as anticancer drugs, cardiology, or diseases affecting only children.[10,13–19] To achieve better results, Europe is in the process of amending its incentive rules (Regulation 726/2004 and Directive 2001/83/EC) and the legislation on medicines for children and rare diseases (Regulation 1901/2006 and Regulation 141/2000/EC, respectively).

Children are a particularly vulnerable patient group with limited pharmaceutical treatment options. Drug shortages have been associated with higher relapse rates in children with cancer, the use of less effective agents, off-label use, and a greater risk of both short- and long-term toxicity.[20] Drug shortages negatively impact patients by affecting drug therapy, causing delays in medical procedures or therapy, and contributing to medication errors.[21,22] Therapeutic alternatives, where they exist, are often associated with higher cost, lower efficacy, increased side effects, off-label use, and medication errors due to inexperience and lack of knowledge.[23,24]

Despite efforts by health authorities to promote the development of pediatric medicines, many medicinal products are authorized only for adults and are not currently available in formulations suitable for administration to the pediatric population. As a consequence, off-label or even unlicensed practices are frequent and their prevalence has been estimated to range from 3.2% to 95% overall, 26–95% in neonates,[25–27] 2.7–51.2% in outpatients, and 9.0–79.0% in inpatients.[28,29] Caregivers or parents often modify off-

label medicines before administration, such as crushing tablets into powder, opening capsules and diluting the powder in a liquid, or drinking injectable drugs. However, such modifications can have potentially harmful consequences for a pediatric patient.[30] These practices may affect the efficacy and safety parameters of the medicinal product by altering its absorption characteristics, stability, and palatability.[31–33] Such manipulation presents a risk of medication errors in dose calculation or preparation, leading to inaccurate dosing and undetermined effects on the product's stability.[30,34] Additionally, crushing tablets or opening capsules exposes caregivers or family members to chemical risks associated with the active substance, particularly when it is carcinogenic.

Due to the lack of appropriate medicines for children, compounded medicines (i.e., unlicensed preparation) can play an important role in addressing needs unmet by commercial medicines or during drug shortage.[35,36] Unlicensed preparations are produced by the community and hospital pharmacies, offering capsules or oral liquid formulations adapted to patients' needs. The need for adapted treatment through compounding is significant, especially in conditions with narrow therapeutic margins, long-term treatments, and medications where non-adapted dosages or non-compliance can jeopardize patient survival, such as cancer, autoimmune diseases, and cardiology.[10,34] For example, a recent study on hospital preparations in oncology by the European Society for Paediatric Oncology (SIOPE) and the European Society of Oncology Pharmacy (ESOP) identified 28 formulations for 13 different active pharmaceutical ingredients (APIs) used in chemotherapy and 35 formulations for 16 different APIs used in supportive therapy, each with a sufficient level of evidence.[37] In some cases, more sophisticated formulation strategies, such as encapsulation of drug particles or 3D medicine printing, are highly promising and have demonstrated a significant benefit over traditional extemporaneous preparation.[37] Such robust and adaptive techniques could facilitate access to personalized therapy for all pediatric patients.[38,39] Scientific publications and recent industry strategies indicate a clear shift from liquid dosage forms to novel solid dosage forms.[40] This new technology improves palatability, provides flexibility in the design of child-friendly dosage forms, and could enable cost-effective, individualized treatment options. However, further research in this field is evident.[41–43]

The common challenges of managing children's medication are similar to those encountered in geriatrics. Similarly, geriatric patients require dose adjustments according to their physiological characteristics and galenic compounding to compensate for deglutination problems. Swallowing difficulties in older adults present challenges for medication management, particularly as polypharmacy is so common.[44] Therefore, geriatric patients require personalized treatment using compounded medicines, just as pediatric patients do.[45]

Overall, the use of unlicensed preparations has increased over the last 10 years, especially as they are also used to compensate for drug shortages, such as anesthetic drugs during the COVID-19 crisis or amoxicillin since 2022.[46]

Furthermore, unlicensed preparations can be tailored to individual patients or produced at a larger semi-industrial scale. Since compounding carries the risk of contamination and supra- and subtherapeutic errors,[47] it demands highly trained personnel and premises that are no longer available in all pharmacies in many countries. To ensure the quality of the preparations and their safe use, regulations must be adapted to these different production scales. For example, the FDA has revised its recommendations to provide more flexibility to hospital pharmacies and health systems in the distribution of compounded drugs, while emphasizing the importance of ensuring their safety and efficacy.[48] In France, new regulations allow for the production of medium-sized batches, with a corresponding increase in quality towards Good Manufacturing Practice (GMP) standards.[49] In this context, 3D printing emerges as a valuable tool for creating custom shapes and doses, enhancing the quality of pediatric preparations.[42]

Since the 2010s, there has been increasing enthusiasm among academic, hospital, and community pharmacies, as well as the industry, for additive manufacturing (AM) of drugs.[50,51] Better known as 3D printing, AM is a process of creating a physical object by joining materials layer by layer from a digital 3D model.[52] All AM processes can be divided into a sequence of operations integrated within a digital chain, which comprises four distinct stages.[53–55] The first stage is computer-aided design (CAD), which involves creating a 3D digital model and converting its surfaces into a network of polygons, typically triangular facets. The positions of these facets are then translated into instructions for the 3D printer, written in G-code. The second stage is the preparation of the digital model prior to manufacturing, which involves optimizing and repairing the digital model before slicing it into layers. The third stage is computer-aided manufacturing (CAM), which involves manufacturing the physical object layer by layer. The fourth stage is post-processing, which is optional depending on the objects manufactured and the technology used. This stage consists of a series of steps carried out after the completion of a manufacturing cycle to ensure the finished product has the desired properties (e.g., support removal, drying, coating, polishing, coloring, smoothing, etc.).

Additive manufacturing (AM) processes offer several advantages over traditional methods. They enable complex objects to be manufactured with high precision and enable flexible modifications to the object's characteristics by adjusting the parameters of the digital model. This capability allows the creation of various versions of the same model. Therefore, AM processes are well-suited for the on-demand production of small batches.

This review presents a brief overview of the various technological aspects and materials used in the 3D printing of drugs, utilizing the Web of Science (WoS) and PubMed bibliographic tools. It provides a state-of-the-art bibliographic overview (2021–2024) of the latest advances in the field, focusing on drug 3D printing using semi-solid extrusion (SSE) technology, which is one of the most promising technologies for 3D-printed medicines. The aspects related to the manufacturing processes and post-treatment of the preparations are addressed. Finally, the application of SSE-printed compounds in a hospital setting is discussed.

2. Additive manufacturing processes for drugs

2.1. Processes overview

Additive manufacturing (AM) processes have been classified by ISO/ASTM 52900 into seven families according to the binding or solidifying agent, the raw material (polymer, metallic, ceramic, and composites), and the material distribution technique used (Figure 1).[56] The processes applicable to drug product manufacturing utilize polymers or photopolymers (resins). Five families using polymers or resins as raw material have been researched for drug manufacturing: powder bed fusion, material extrusion, material jetting, vat photopolymerization, and binder jetting (Figure 1).[57–59] The remaining processes, directed energy deposition and sheet lamination, are not designed for drug manufacturing but are instead for metallic parts manufacturing. Each process has its respective characteristics, advantages, and drawbacks that influence the quality and printability of drugs, as well as the organization of the production process.

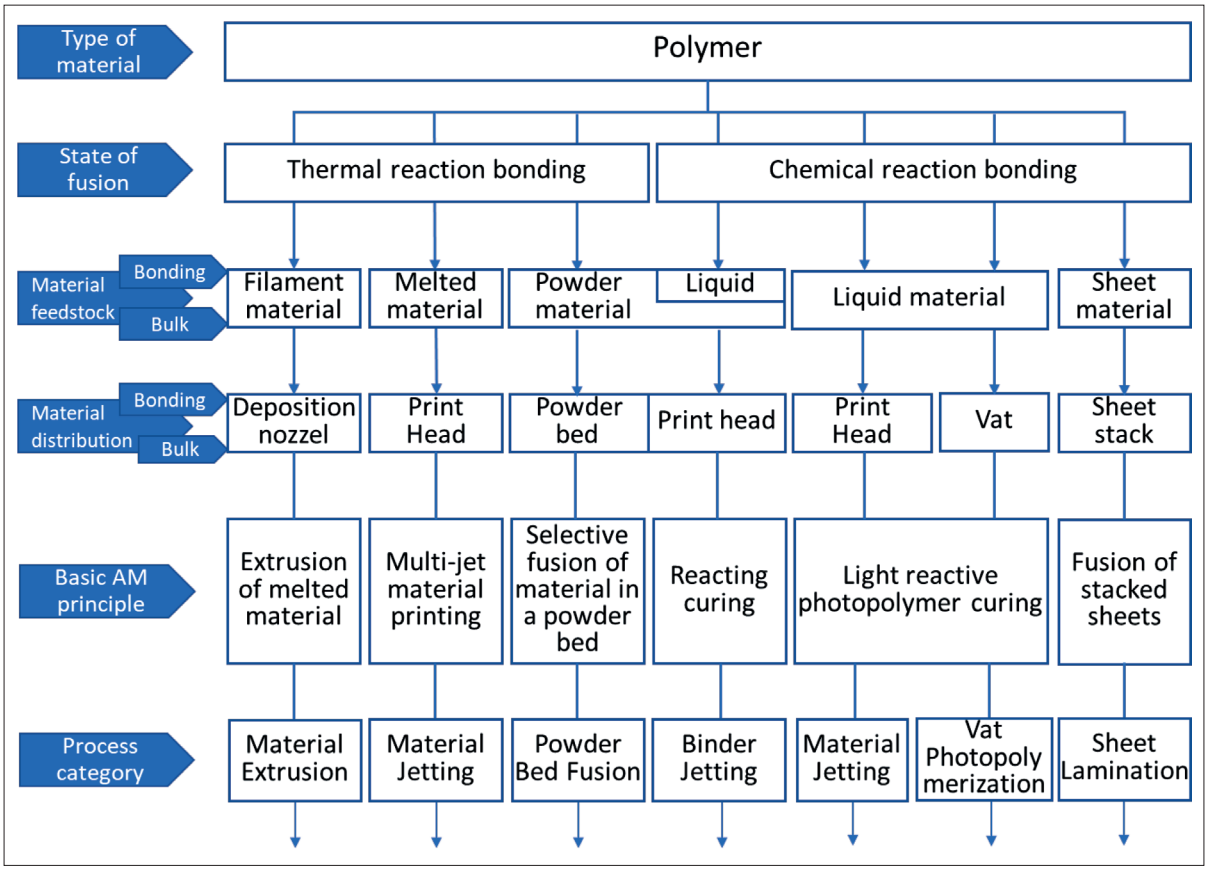

Figure 1. Diagram of additive manufacturing processes according to the ISO/ASTM 52900 nomenclature. Adapted with permission from ref.[52] Copyright © 2021 ISO/ASTM.

The processes can be divided into three major groups, depending on the characteristics of the raw material and the manufacturing requirements[60]: (i) powder agglomeration processes with powder bed fusion and binder jetting; (ii) liquid material solidification processes with material jetting and vat photopolymerization; and (iii) extrusion processes from solid or semi-solid materials.

To determine which of these processes would be most suitable for hospital and community pharmacy use in the coming years, the process should meet the following criteria:

(i) The process must be perfectly suited for manufacturing a wide range of different products, with minimal cleaning constraints and a low risk of cross-contamination between batches. This is crucial for hospital confounding, where equipment is used to produce various medications tailored to individual patient needs. If this criterion is not met, the process is excluded.

(ii) The materials used in the process (i.e., equipment and pharmaceutical raw materials) must be well-established for clinical use. The process should utilize a variety of excipients that are biocompatible and readily available. The process should be capable of handling and processing thermosensitive or photosensitive APIs or excipients.

(iii) The process must enable the manufacture of dosage forms suitable for specific populations. Considering oral dosage forms particularly suited for children, mini-printlets (mini 3D-printed tablets), orodispersible, fast disintegrating printlets, and chewable printlets have to be printable. These shapes must be appropriately sized for children's mouths and esophagus to ensure ease of administration. Suppositories are another type of solid dosage form suitable for children that are administered rectally. In addition, the selected process should ideally facilitate the production of drugs with different API release kinetics (immediate and controlled release). The process is excluded if this criterion is not met.

In the following sections, we will discuss the different criteria for each process. Processes that are unsuitable for manufacturing printed medicines in hospitals are excluded from the evaluation, with justification for their exclusion. Finally, we will identify and detail the most appropriate process.

2.1.1. Powder agglomeration processes

Powder bed fusion involves using thermal energy (e.g., scanning laser) to selectively melt areas of powder which is placed in excess within a container.[52,55] This process does not meet the aforementioned criteria. Firstly, it is not suitable for manufacturing multiple different products for various patients. The use of a large quantity of powder implies significant constraints for product changeovers, with extensive cleaning required for the powder container. Therefore, the risk of cross-contamination is high. This process is better suited for large-scale industrial production of a single product. In addition, hospital premises would need to handle the use and storage of large quantities of powder in controlled atmosphere zones, requiring extensive personal protective equipment, particularly for chemotherapy drugs, which present a major risk to operators. The process also does not accommodate heat-sensitive materials. Furthermore, only a small proportion (10–15%) of the powder is sintered during the process.[61,62] The rest is recovered, but not all of it can be recycled. Each pass through the 3D printer deteriorates the quality of the powder, necessitating the mixing of recycled powder with approximately 50% or more fresh powder,[61,62] resulting in significant material loss. For all these reasons, this process may not be suitable for manufacturing drug products in hospitals.

Binder jetting involves selectively depositing a liquid binding agent on a powder bed to agglomerate the powder particles.[52,55] This process is used to produce Spritam®, the first and only 3D-printed medicine commercially available in the United States of America (USA). Spritam® is prepared using the patented ZipDose® technology,[63] which allows the drug formulation to disintegrate extremely rapidly.[64] Binder jetting is similar to the powder bed melting process, except that it uses a solvent to bind the powder instead of thermal energy. The powder is also placed in excess in a container. Unlike the powder bed melting process, thermosensitive or photosensitive materials can be used, as binder jetting does not require thermal energy or a light source for production. However, like powder-bed fusion, the substantial use of powder is not suitable for hospital compounding, but rather for industrial manufacturing. Therefore, this process is excluded.

2.1.2. Liquid photoreactive material solidification processes

Vat photopolymerization is an AM process where a liquid photopolymer is placed in a vat and selectively exposed to a light source to create an object via light-induced curing.[52,55] However, this process has two main issues. First, there are limited biocompatible photopolymerizable materials available for drug production,[65] and there is insufficient information on their safety for human consumption. There may also be a risk of undesirable chemical reactions between the API and photopolymers.[65,66] As a result, the process may not yet be for drug manufacturing. Second,

the need to place the raw material (in liquid form) in large quantities in a tank and cure it with ultraviolet (UV) light precludes the use of photosensitive materials and complicates product changeovers. This results in extensive cleaning requirements and an increased risk of cross-contamination. For these reasons, this process is also not suitable for drug manufacturing in hospitals.

Material jetting is an AM process that involves spraying a liquid onto a substrate in droplets, triggered by either piezoelectric or thermal stimulation. This process includes two main types: (i) continuous inkjet printing (where ink flow is continuous) and (ii) drop-on-demand (where ink is jetted on demand).[67] Depending on the technology used, the drops could either solidify spontaneously or with the aid of heat or UV light.[65] Among the reported dosage forms, oral and buccal films have demonstrated significant promise for this technology.[67,68] In 2024, material jetting meets most of our criteria except the second one. Inkjet 3D printers currently used in pharmaceutical research are still in the early stages of development[68] and are essentially derived from conventional desktop printers, which are not yet suitable for clinical use. Therefore, despite its potential, this process is also excluded for hospital and pharmacy use.

2.1.3. Extrusion processes

Extrusion is a mechanical manufacturing process where the material is forced through a small hole (the die) under pressure, transforming it into a homogeneous, plastic, semi-solid mass, known as the extrudate (typically a filament). In AM based on extrusion processes, the raw material is passed through a nozzle orifice and selectively deposited layer by layer.[52] The raw material may be in solid form or semi-solid form. All extrusion-based AM processes follow the same successive operations[55]: material loading, liquefaction, pressure application to move the material through the nozzle, extrusion, and controlled layer-by-layer deposition along a predefined path, followed by bonding the successive layers. The specifics of SSE are discussed in the next section.

In fused filament fabrication (FFF), also known as fused deposition modeling (FDM), the material is a solid thermoplastic filament obtained through hot melt extrusion (HME). HME uses a heat input to melt thermoplastic materials, which may initially be in various forms, such as powders, granules, flakes, pastes, etc. The extrudate is produced continuously, and the size and shape of its cross-section are defined by those of the die.[55] Established in the pharmaceutical industry in the 1980s, HME is used to produce a variety of dosage forms (e.g., pellets, granules, implants, etc.).[60] HME can also be used to produce controlled-release forms and increase the apparent solubility of APIs by promoting the formation of amorphous solid dispersions.[60,69] Additionally, HME can be used to produce solid thermoplastic filament suitable for FFF/FDM. In FFF/FDM, the filament is fed through a print head with a heated nozzle that melts the material and deposits it layer-by-layer on the manufacturing platform.[52,53,55] Among the AM processes discussed, FFF/FDM is one of the least costly and easiest to operate, providing good precision and versatility,[60,64,70–78] and remains the most frequently used AM process in the market.[55]

Fused filament fabrication/fused deposition modeling (FFF/FDM) offers several significant advantages. First, it uses solid filament that can be easily stored and handled during production, making it easy to set up on hospital premises. The filament is consumed precisely by the 3D printer for parts manufacturing, minimizing waste and simplifying cleaning, which involves only the nozzle and build platform onto which the material is deposited. This helps manage the risk of cross-contamination. Moreover, HME has long been used in the pharmaceutical sector, providing access to a wide range of biocompatible excipients for use in FFF. The process does not require light exposure, enabling the use of photosensitive materials and eliminating the need for post-printing treatments.

However, this process has significant limitations. Firstly, filament manufacturing by HME can be challenging to manage within hospitals due to the complexity of achieving homogeneous distribution of APIs, making it difficult to achieve at the point of care. The API can be incorporated either with the excipients in the extruder or post-extrusion, which complicates the process.[70] Additionally, HME equipment is costly and bulky. FFF also has a low printing speed, i.e., 2–5 min to manufacture a single tablet, or >1 h for a single batch of 30 prints.[70] It is difficult to improve this speed due to the constraints of filament flow, which requires a balance between low viscosity for extrusion and high viscosity for layer adhesion.[60,70,76] Another drawback is the need for high temperatures to melt the thermoplastic filament, typically ranging from 100 to 250°C,[70] which makes it difficult to manufacture drugs containing heat-sensitive APIs.

In terms of feasible dosage forms suitable for children or the elderly, the FFF process is well-suited for manufacturing solid dosage forms for swallowing, including chewable forms, such as the mini-tablets developed by Parulski et al.[79] However, formulations produced using this process often result in dosage forms with high hardness and melting temperatures higher than 100°C, which makes them unsuitable for suppositories or orodispersible forms.

In view of these drawbacks, we consider that the FFF process is not currently the most suitable option for compounding in pediatric oncology hospitals.

2.2. Semi-solid extrusion

2.2.1. Process overview

The other extrusion-based AM process is SSE. Unlike FFF, SSE uses a semi-solid (or semi-molten) raw material, usually placed in a syringe or cartridge and extruded at low temperatures,[80] generally between ambient temperature and 80°C (Table 1).[81] The material is extruded by applying sufficient pressure in two main ways. The first approach is pneumatic extrusion, whereby the piston of the syringe containing the pharmaceutical ink is pushed by compressed air pressure. The pressurized air is connected directly to the syringe body, whose nozzle can incorporate a valve to control the air channel into the printhead via an on-off switch, closing the channel when the valve is switched off[80] (Figure 2). The advantages of this system are high precision in material extrusion, fast response time as the syringe body can be instantly pressurized, and suitability for viscous materials (as the gas can reach high pressures without compromising system integrity). However, it is less effective for low-viscosity materials and is more complex compared to mechanical systems.[80,81] The second approach is mechanical extrusion, utilizing either a piston or a screw controlled by stepper motors to push the material through the nozzle (Figure 3). Mechanical extrusion is more affordable and easier to transport than the pneumatic system, as it does not require an air compressor. Furthermore, syringes can be replaced quickly and easily, speeding up the printing process. However, it is not suited for high-viscosity materials.[80]

The quality of dosage forms manufactured by SSE is influenced by three categories of parameters: material parameters, operating parameters, and machine parameters. These parameters interact with each other and influence the quality of the finished products, including API content and uniformity, release kinetics, mass and mass uniformity of printed products, product appearance, and mechanical properties (e.g., surface roughness, dimensional accuracy, hardness, etc.). Material parameters refer to the formulation, particularly the material's rheological properties and, to a lesser extent, its thermal properties. Operating parameters are those that can be modified during print production, i.e., numerical parameters and physical parameters. Numerical parameters enable modulation of the dosage and kinetics of print release from the 3D model; physical parameters designate the selection of optimal temperature, pressure, and print speed as a function of material and numerical parameters. Machine parameters are the characteristics of the equipment used to print the drug, such as the design and number of printheads or the diameter of the nozzle.

2.2.2. Dosage form design by computer-aided design

Operating parameters affect the quality attributes of the finished product. The design of the dosage form mainly includes its geometry, dimensions, and infill density. Design geometry is an editable parameter, where the exchange surface can be adjusted to modify the API release kinetics. Different dosage form dimensions can alter the quantity of API in the finished product (e.g., larger dosage forms contain more API). Additionally, the size of the dosage form is strongly correlated with its mass.[110] The infill density of the dosage form can be varied to obtain different properties and release profiles. Generally, porosity is retained to facilitate API release; thus, infill density rarely reaches 100%. By adjusting these parameters during drug production via SSE, it is possible to tailor the dosage form to meet the specific needs of the patient, ensuring precise control over the drug's characteristics and performance.

2.2.3. Pharma-ink and dosage forms

The 3D printing material, also called the Pharma-ink (a mixture of drugs and excipients), should possess several ideal characteristics: it should be easy to prepare without using heat, adhere minimally to facilitate packaging in the 3D printer while ensuring sufficient adhesion of the semi-solid mass to the printing bed, be smooth and free of lumps, and be easily incorporated into a syringe. Finally, the dynamic viscosity of the ink must be sufficiently high, with shear-thinning properties, to be printable without collapsing once extruded.[110] Table 1 provides a non-exhaustive literature review of articles published between 2021 and 2024 on drugs manufactured via SSE. The most common dosage forms are solid oral forms, predominantly swallowable dosage forms (films or tablets). Other solid oral dosage forms produced by SSE include orodispersible and chewable forms. One advantage of SSE over FFF is its ability to manufacture solid dosage forms with a soft texture, allowing for the creation of chewable printlets. For example, gummies made by Rouaz-El Hajoui et al. contain gastro-resistant pellets with the API,[100] enabling the modified release of the API while still allowing chewing of the dosage form (Figure 4). While most of these solid oral dosage forms are designed for systemic pharmacological action, there are a few examples intended for local action in the stomach, such as gastro-floating devices. Other notable forms include mucoadhesive films like vaginal ovules made by Teworte et al.,[123] rectal forms, such as infliximab suppositories made by Awad et al.[121] (Figure 5), and medical devices impregnated with active substances,

Table 1. Commented bibliographical review (2021–2024) on the use of 3D printing for semi-solid extrusion (SSE) according to the different pharmaceutical forms produced and their composition (active pharmaceutical ingredient [API] and excipients)

Formulation type	Formulation details and properties	API	Excipients	Commentaries	Ref.
Oral dosage forms					
Swallowable printlets	Immediate release printlets	Caffeine	Sodium alginate; HPMC; sodium croscarmellose	Development of caffeine-containing printlets for neonates suffering from apnea of prematurity	[82]
	Immediate release printlets	Cranberry leaf extracts	Polyethylene oxide	*In vivo* assessment (in rats) of L-arginine-loaded cranberry leaf extract bioactivity on insulin resistance and development of 3D-printed dosage forms	[83]
	Immediate release printlets	Sildenafil citrate (10 mg)	Gelucire® 48/16; glycerol	Bioequivalence assessment of solid oral dosage forms of sildenafil manufactured by SSE within hospital pharmacy vs. industrial sildenafil tablets; sildenafil was selected for its treatment of pulmonary arterial hypertension in children, which requires a low dosage that can be adapted from one individual to another according to their pathophysiological characteristics	[84]
	Gastro-resistant delayed-release printlets	Octréotide acetate (3.4%)	Carbopol 974P NF, HPMC 2910, corn starch	Evaluation of the ability of SSE to manufacture swallowable dosage forms containing biological macromolecules	[85]
	Immediate-release printlets with porous geometry	Paracetamol	HPMC	Evaluation of the effects of solid drug particles in inks on the quality of printed parts with porous geometry	[86]
	Controlled release re-dispersible 3D-printed nanomedicines	Resveratrol, curcumin	Carboxymethyl cellulose sodium, glycerin, water, poly(ε-caprolactone), medium chain triglycerides, polysorbate 80	Feasibility assessment of manufacturing oral solid dosage forms containing two API co-encapsulated in polymeric nanocapsules using SSE; different *in vitro* release profiles were obtained depending on the polymer used, the infill density, and the presence/absence of a channeling agent	[87]
	Immediate-release printlets	Flurbiprofen (15%)	Sodium alginate, mannitol	Evaluation of the effects of pre-crosslinking alginate ink-gel on preventing matrix collapse after drying the printed dosage form	[88]
	Immediate-release printlets	Albendazole	Polyethylene glycol 1500, propylene glycol, poloxamer 188, ultrapure water	Inclusion of nanocrystals within printlets made by SSE and MESO-PP	[89]
	Swallowable printlets with several drug release profiles	Tranexamic acid or paracetamol	HPMC, PVP, SiO_2	Printability assessment of different formulations (particularly their rheological properties) and the impact of structural design and formulation on the quality of printed dosage forms (drug release kinetics, dimensions, mass)	[90]
	Gastric floating delivery system with 8 h sustained-release and immediate and prolonged floating (>10 h)	Clarithromycin	HPMC K15M CR, EC 20, PVP k30, poloxamer 188, carbomer 934P, nano-$CaCO_3$	Evaluation of the effects of a core-shell system made using multi-nozzle SSE 3D printing on the floating time and drug release	[91]

Continued

Table 1. Continued

Formulation type	Formulation details and properties	API	Excipients	Commentaries	Ref.
Swallowable printlets	Gastric floating delivery system	Propranolol hydrochloride (12.5%)	Sodium alginate, hydroxyethyl cellulose, calcium chloride, Tween 85	Formulation of a floating drug delivery system in a single step with coaxial SSE 3D printing using ionotropic gelation of sodium alginate	[92]
	Controlled-release intragastric floating printlets	Furosemide and sildenafil citrate	Polysorbate 80; Gelucire® 48/16	Manufacturing parameters and quality control of 3D printed dosage forms based on EP; the study demonstrated the suitability of testing for dissolution, uniformity of mass, and content uniformity according to EP tests.	[93]
	Controlled-release gastro-floating printlets	Famotidine	HPMC; alpha-lactose monohydrate; microcrystalline cellulose; PVP	The dosage form demonstrated sufficient buoyancy after 10 h	[94]
	Gastroretentive printlets	Niclosamide	Gelucire 50/13	Dosage form made using MESO-PP	[95]
	Gastro-floating printlets	Ricobendazole	Crosslinking ink: water; ethanol; calcium chloride; hydroxyethyl cellulose; Tween®85 Alginate ink: sodium alginate solution	Co-extrusion of crosslinking ink and sodium alginate ink feeds	[96]
Chewable printlets	Pectin-based drug-loaded gummies	Simethicone	Pectin, sorbitol, citric acid anhydrous, maltitol	Formulation of sugar-free gummy dosage form for adults and children	[97]
	3D-printed chewable medicines containing amino acids	Isoleucine or valine or citrulline	Sucrose, pectin, maltodextrin, water, maltitol, flavorings (lemon, vanilla, peach), colorants, citric acid	This study evaluated the efficacy and acceptability of 3D-printed drugs (made in a hospital setting) vs. conventional compounded medicines in six children; the printed drugs were well-accepted and displayed improved adherence	[98]
	Emulsion gel for solid dosage forms (immediate release)	Fenofibrate	Formulation 1: Water, soybean oil, Maisine® CC, stearic acid, silica suspension, Methocel™ A4M, Methocel™ E4M, Ac-Di-Sol SD-711 (croscarmellose sodium) Formulation 2: Water, soybean oil, Maisine® CC, Tween 85, stearic acid, silica suspension, Methocel™ A4M, Ac-Di-Sol SD-711 (croscarmellose sodium)	This study evaluated a lipid-based formulation within an emulsion gel stabilized with solid particles and a surfactant; the aim was to develop a formulation adapted for poor water-soluble API for SSE 3D printing	[99]
	Formulation of gastro-resistant chewable printlets from enteric omeprazole pellets	Omeprazole (7 mg)	Formulation 1: omeprazole powder, carboxymethyl cellulose, carrageenan, xanthan gum, sodium bicarbonate, glycerol, liquid sweetener, essence, purified water Formulation 2: omeprazole pellets, gelatine, carrageenan, xanthan gum, liquid sweetener, essence, lemon juice, purified water	Comparison of formulation 1 (3D-printed hydrogels with dissolved omeprazole powder) vs. formulation 2 (3D-printed hydrogels loaded with gastro-resistant omeprazole pellets); both demonstrated appropriate properties for 3D printing (especially rheological properties) and conformed with pharmacopeia specifications for content and mass uniformity; formulation 2 exhibits high gastro-resistance	[100]
	Immediate-release printlets for pediatric use	Isoniazid	Corn starch, distilled water	Development of a pediatric-friendly formulation in low-resource settings	[101]

Continued

Table 1. Continued

Formulation type	Formulation details and properties	API	Excipients	Commentaries	Ref.
	Immediate-release printlets for pediatric use	Amlodipine besylate	D-mannitol, maltitol, carboxymethyl cellulose sodium type 800 mPa/s, sodium starch glycolate type lippin, sucralose, methylparaben, soybean oil, anhydrous citric acid, sodium citrate, FD&C yellow n°5	Evaluation of the feasibility of SSE 3D printing hospital preparations for children	[102]
Chewable printlets	Immediate-release gummy chewable printlets for pediatrics	Propranolol hydrochloride	Sodium carboxymethyl starch; gelatin; carrageenan; γ-aminobutyric acid	Evaluation of different gum formulations; gelatin improves printability; carrageenan improves thermal stability and disintegration rate of dosage forms	[103]
Polypill (printlet)	pH-responsive polypills for delayed drug release	Bovine serum protein	Carboxymethyl chitosan, sodium alginate, PEGDA, TPO	Development of a dosage form for API release, modified by modulating the carboxymethyl chitosan/sodium alginate ratio and the filling density using SSE 3D printing	[104]
Swallowable films	Swallowable films with several modified drug release profiles	Hydrochlorothiazide	Copolymer PVA/PVAc	Evaluation of five PVA/PVAc copolymers with different ratios of PVA to PVAc monomers to adjust API release rate	[105]
	Immediate-release printlets	Loratadine	Cellulose; manitole; CMS-Na; PVP	Preparation of orodispersible printlets containing water-insoluble and thermally unstable drugs	[106]
	Immediate-release swallowable films	Eucalyptus extract	Tween 80, esters of polyglycerol and stearic acid, Eumulgin SMO 20, polyethylene oxide	Formulation of a stable aqueous nanoemulsion based on modified lipophilic eucalypt extract applicable in the SSE 3D printing process, without losing the antimicrobial activity of the original eucalyptus extract.	[107]
	Sustained release swallowable films	Triamcinolone acetonide	Carboxymethyl cellulose 4000, tetraethyl orthosilicate 98%, pluronic P123	Feasibility assessment of producing pharmaceutical films using a hydrophilic ink containing mesoporous silica with nanostructured pores as a drug carrier for hydrophobic API	[108]
	Films with four different structures based on carboxymethyl cellulose ink from durian rind wastes	Theophylline	Carboxymethyl cellulose derived from durian rind wastes	The aim of this study was to assess the recyclability of agri-food waste (durian rind) as an excipient used in the manufacture of films by 3D printing	[109]
	Immediate-release films of nano-piroxicam via supercritical carbon dioxide technology	Nano-piroxicam (7.5%)	HPMC, Tween 80, eau purifiée, glycerol	The aim of the study was to produce a printable ink that stabilizes API nanoparticles to conserve API original polymorph	[110]

Continued

Table 1. Continued

Formulation type	Formulation details and properties	API	Excipients	Commentaries	Ref.
Orodispersible dosage forms	Immediate release printlets from emulsion gels.	Fenofibrate	Capmul MGM EP, Captex 355 EP/NF, Kolliphor EL, purified water, Methocel A4M, Ac-Di-Sol SD-711	Quality assessment of SSE additive manufacturing of lipid-based emulsion gels for poorly water-soluble drugs; printlets that disintegrate within 3 min are considered orodispersible	[111]
	Immediate release printlets	Hydrochlorothiazide	Lactose monohydrate, croscarmellose sodium, PVP, flavoring essence	Comparative study of the suitability of the molding for SSE 3D printing to produce pediatric dosage forms	[112]
		Carbamazepine	Ac-Di-Sol; Kollidon® 30; lactose monohydrate; sucralose; water	Development of small dosage forms (mini-tablets) for pediatric use	[113]
	Orodispersible films	No API used	HPMC; PVA; glycerol; sodium starch glycolate; porogen agents (Aeroperl® 300, Fujisil®, Syloid® 244 FP, Syloid® XDP 3050, Neusilin® S2, Neusilin® US2, and Neusilin® UFL2)	Multi-layered films with porous structures used as substrates for inkjet printing	[114]
		No API used	Maltodextrin; sorbitol; hydroxyethyl cellulose; purified water	Evaluation of different drying times on the properties of orodispersible films made by additive manufacturing	[115]
	Fast-disintegrating tablets	Phenytoin sodium	HPMC E15; sodium starch glycolate	Feasibility assessment of manufacturing fast-disintegrating tablets via SSE that were filled in dosing syringes	[116]
Others dosage forms					
Mucoadhesive films	Mucoadhesive buccal films	Estradiol	D-sorbitol; polyoxyethylene sorbitan monooleate; acetonitrile; glycerin; gelatin; polyethylene glycol; hydroxypropyl cellulose; transcutol P oil.	Different release rates observed depending on the infill pattern (rectangular, honeycomb, and plain); plain infill had the lowest drug release rate; rectangular infill had the highest drug release rate	[117]
	Mucoadhesive films	Apigenin	Ethanol; water; carboxyvinyl polymer; poloxamer; HPMC	Development of apigenin-loaded printed films to prevent carcinogenesis in patients suffering oral leukoplakia	[118]

Continued

doi: 10.36922/ijb.4063

Table 1. Continued

Formulation type	Formulation details and properties	API	Excipients	Commentaries	Ref.
Suppositories or ovules	Suppositories made with laponite-alginate hydrogel	Methylene blue as the drug model	Laponite; alginate	Feasibility assessment of manufacturing suppositories using SSE, with post-printing API loading via adsorption	[119]
	Suppositories for local multidrug delivery	Tofacitinib citrate; budesonide	Lauroyl macrogol-32 glycerides (Gelucire® 44/14); coconut oil; N,N-dimethylacetamide	Poor water-soluble drugs; good self-emulsification; printing temperature (29°C) close to ambient temperature; an evaporative air cooler placed in front of the printer to ensure printing consistency	[120]
	Suppositories for local drug delivery	Infliximab	Gelucire® 44/14 or Gelucire® 48/16; coconut oil; purified water	Successful printing of well-defined suppositories containing biological, thermosensitive, and hydrosensitive API	[121]
	Vaginal ovules	Metronidazole	Polycaprolactone; Gantrez™-AN119	Disc- and mesh-shaped intravaginal devices developed for the sustained release of antibiotics; the aim was to reduce the frequency of administration	[122]
	Vaginal mucoadhesive ovules	Pirfenidone	Sodium alginate; HPMC; aqueous solution: HEPES, $CaCl_2$ crosslinker	Ovules demonstrated sustained release with mucoadhesive properties	[123]
Medical devices	Skin patches for wound application	Not available	Corn starch; β-glucan water suspension; glycerol; distilled water	Extrusion over an alginate support of the corn starch-based ink for wound treatment by SSE	[124]
	3D-printed silicone scaffolds for sustained release (intravaginal use)	Metronidazole	Mixture of vinyl-terminated polydimethylsiloxane (70%) and vinyl-methyl-modified silica (30%); methylhydrosiloxane-dimethylsiloxane copolymer, trimethylsiloxane	Successful sustained release (14 days) of metronidazole contained within a 3D-printed silicone-based scaffold for intravaginal use	[125]
	Anti-infective urinary catheter	Secnidazole	PVA; sodium alginate; methylcellulose; polyethylene glycol	Characterization of stability and suitability of secnidazole-impregnated PVA-based urinary catheter; the device demonstrated anti-biofilm activity	[126]

Abbreviations: EC, ethylcellulose; EP, European Pharmacopeia; HPMC, hydroxypropyl methylcellulose; MESO-PP, melting solidification printing process; PEGDA, polyethylene glycol diacrylate; PVA/PVAc, poly(vinyl alcohol-co-vinyl acetate); PVA, polyvinyl alcohol; PVP, pyrrolidone; TPO, Diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide.

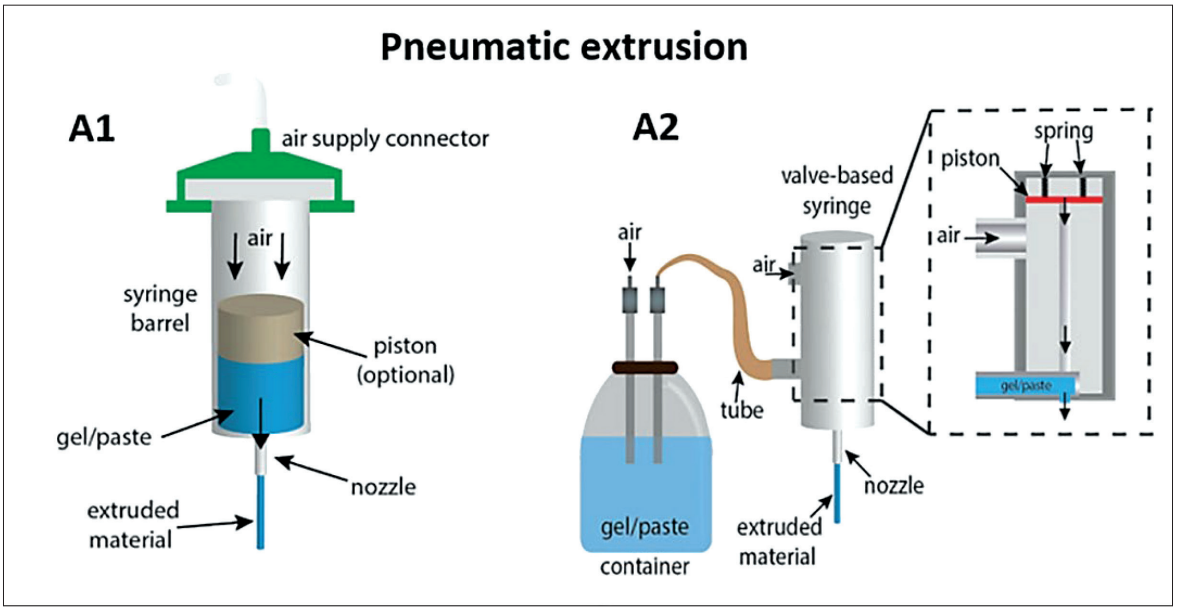

Figure 2. SSE 3D printing extrusion mechanisms: pneumatic extrusion including (A1) valve-free and (A2) valve-based. Adapted with permission from ref.[80] Copyright © 2024 Elsevier.

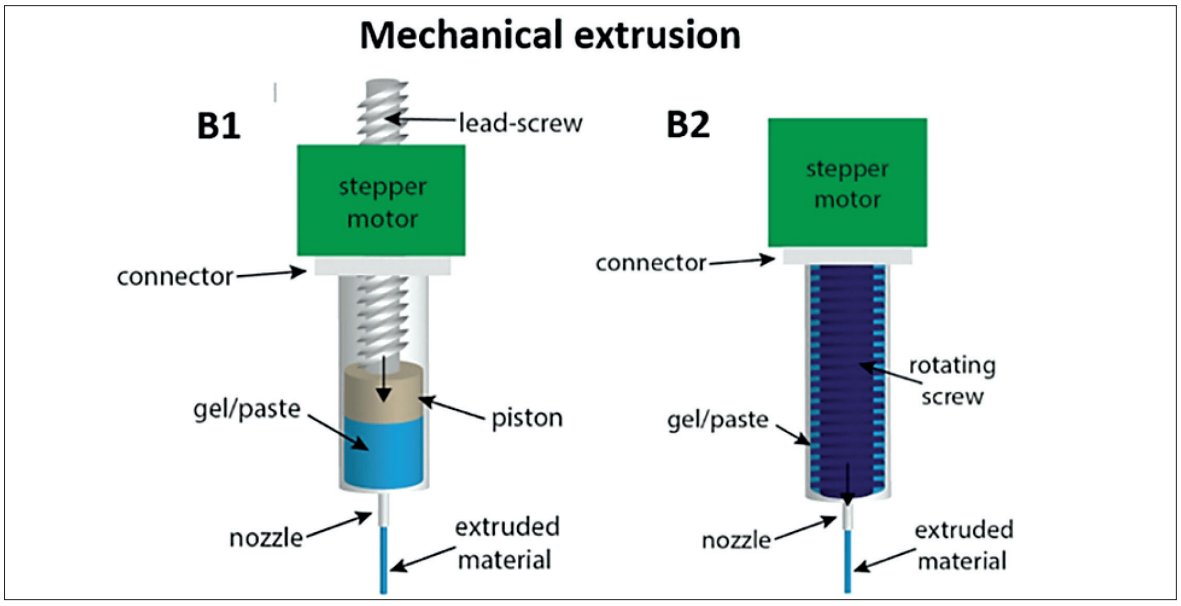

Figure 3. SSE 3D printing extrusion mechanisms: mechanical extrusion including (B1) piston- or (B2) screw-driven. Adapted with permission from ref.[80] Copyright © 2024 Elsevier.

like the anti-infective drug-loaded urinary catheter made by Archana et al.[126] The articles reviewed report different drug release kinetics (immediate or controlled release), demonstrating the versatility of SSE for producing variants of the same drug. Except for orodispersible forms, which are primarily advantageous for their rapid release of APIs, controlled release kinetics are found among all the solid oral dosage forms (Table 1), including chewable formulations. For example, Rouaz-El Hajoui et al.[100] developed a gastro-resistant form produced by SSE from a hydrogel loaded with pellets containing an API sensitive to the stomach's acidic pH. This example demonstrates that the formulation of a chewable form is compatible with modified release kinetics.

Figure 4. Pictures of 3D-printed gummies. Adapted with permission from ref.[100] Copyright © 2023 The Authors. Published by Elsevier B.V.

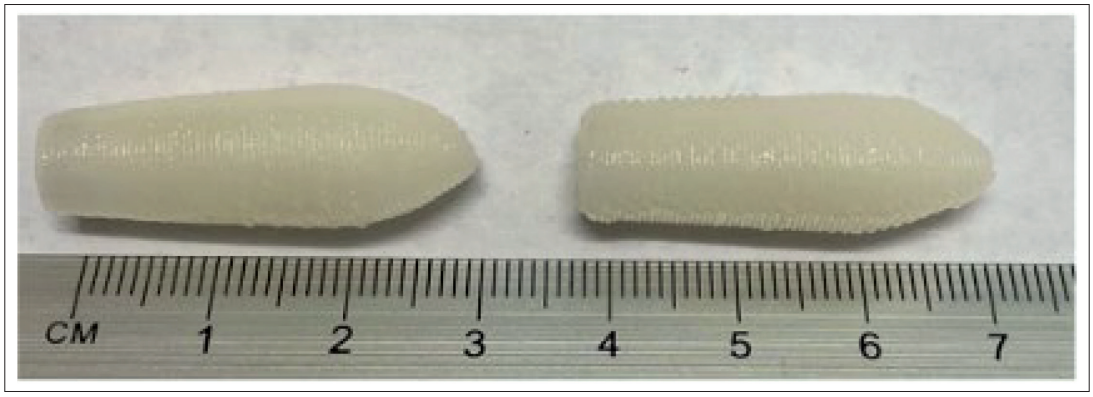

Figure 5. Picture of 3D-printed suppositories. Adapted from ref.[85]

2.2.4. Rheological properties

The rheological properties of the material are central to the successful execution of the SSE process and to obtaining finished products of the desired quality.[80] A notable prerequisite for successful printing is that the raw material should ideally be shear-thinning[80,110,85,108,118] (i.e., the viscosity of the material decreases as shear strain increases) and without thixotropy[80,85,127,128] (i.e., the viscosity of the material should not decrease under constant stress over time). The absence of thixotropy is important because the viscosity of the material should not be time-dependent, and the successive layers should recover their initial structure within a few seconds after extrusion.[80,85,127,128] A thixotropic material is likely to have a viscosity that decreases as printing progresses, causing the dosage form to collapse. Shear-thinning behavior ensures uniform extrusion with smooth extrudates,[85] preventing nozzle clogging. Conversely, if the viscosity is too low, there is a risk of collapse of the dosage form.[81,118] Therefore, it is necessary to formulate a semi-solid raw material with appropriate viscosity, neither too high to impede extrusion nor too low to prevent collapse. The viscosity of the material should allow extrusion only when pressure is applied and ensure a consistent extrusion rate so that the dosage form obtained meets specified

requirements (e.g., API content, release kinetics, etc.).[80] Rheological properties also influence the nozzle and print bed temperatures: higher viscosity typically requires higher printing temperatures for extrusion. Compared to FFF, SSE has two main advantages: the required temperatures are lower, generally between ambient temperature and 80°C[81] (Table 1); and the printing rate is generally faster. For instance, Hu *et al.* reported that 50 dosage forms can be printed in 13–15 min.[113] To facilitate technology transfer between teams, it is important to translate these rheological properties into force parameters for the printer system. This data allows for the calibration of the printers to obtain consistent results.[129,130] Additionally, it is crucial that the pharma-ink remains stable in terms of its rheological properties in the cartridge before printing, enabling on-demand printing without the need to prepare the pharma-ink each time.

2.2.5. Printheads and nozzle

The nozzle diameter must be sufficiently precise to achieve high resolution for the dosage form, ensuring accurate dosage and API release kinetics while minimizing the risk of obstruction due to the size of the raw material components or the rheological properties of the material.[80,85] Consequently, the mean particle size of the API should be smaller than a few hundred micrometers.[80]

The number of print heads determines the range of printed products that can be produced by the machine. Each nozzle can only handle one filament. Machines with at least two nozzles are particularly advantageous for multi-layer printed products (also known as polypills). These machines can alternate between layers containing two different APIs or between an API and an excipient. There are several examples of polypills produced using SSE technology.[131,132]

2.2.6. Extrusion pressure

Pressure is a critical parameter in the SSE process.[81] The pressure applied to the top of the syringe containing the raw material increases progressively until a certain threshold is reached, at which point the material begins to be extruded. The extrusion rate is directly correlated with the pressure applied, making it essential for this pressure to remain constant with only slight fluctuations to ensure the quality of the finished product.[81] Poorly controlled pressure would lead to inconsistencies in material flow, potentially affecting API content. Therefore, pressure must be accurately measured using sensors integrated into the 3D printer. These sensors can detect process problems, e.g., a clogged nozzle would be signaled by an unexpected increase in pressure or the presence of air in the syringe that would be indicated by an unexpected drop in pressure.[81] In general, pressure measurement can be used to establish correlations between pressure and critical quality attributes of the finished product (e.g., mass, dimensions, etc.).[81]

2.3. Post-processing steps

Post-processing is an optional stage in the 3D printing process. For SSE, when post-treatment is necessary, it is almost always drying (Table 2). Drying involves removing water or other volatile liquids from a product, either in a free or adsorbed state. This step is often critical depending on the quality attributes of the dosage form.[80] The need for drying depends on material parameters, i.e., the quantitative and qualitative composition of the pharma-ink, as well as the thermal and rheological properties of the material. It also depends on the printing temperature.

Drying influences the residual moisture content, which affects various parameters of the product. For example, the limits of residual moisture content for orodispersible films are in the range of 3–6%.[133] The moisture content within orodispersible films influences their chemical and microbiological stability, as well as properties like stickiness, tensile strength, flexibility, and disintegration time.[115] Microbiological stability is a particularly important parameter, given the transition from a semi-solid gel containing a significant amount of water to a solid oral dosage form, where the water activity must be reduced to less than 0.6 to minimize the risk of biological contamination.[111,134]

In the reviewed articles, three possibilities regarding post-processing are noted: (i) obtaining a finished product without post-processing[83,84,89,93,95,100,101,103,107,120,121]; (ii) drying is necessary (Table 2); and (iii) other post-treatment operations, besides drying, are necessary, such as crosslinking the printed parts,[104,123] adsorption of the active substance[119] or coating.[126]

The most common drying method is open-air drying at room temperature, with drying times generally between 12 and 48 h. Drying is also carried out in an oven (sometimes under vacuum), at low temperatures (20–80°C), for periods ranging from a few hours to 24 h. The printing bed is sometimes used to dry printed materials, with temperatures of 60–70°C for 10 min to 2 h. Desiccators or freeze-drying are sometimes used. Some studies combined different drying techniques. Falcone et al. used a combination of open-air drying, a low-power microwave (200–400 W), an oven, and a desiccator.[92] Except for freeze-drying, most drying techniques are simple and do not require complex equipment, making them feasible to use with SSE in hospitals. However, these methods generally require several hours to complete.

Table 2. Drying conditions

Drying method	Temperature	Time	Commentaries	Ref.
(i) Air-dried at 22.2°C for 48 h (ii) Freeze-drying at -80°C for 15 min; 15 h vacuum			Long drying times can increase the risk of recrystallization	[110]
Freeze-drying	-80°C	Overnight	Freeze-drying creates a porous network accessible to water; hydration of the dosage form produces a thick gel, enabling longer active pharmaceutical ingredient (API) release	[85]
	-80°C	20 h	The drying step follows an ionic crosslinking step	[104]
Air-dried	Room temperature	24 h		86
	Room temperature	Until obtaining a constant weight		88
	Room temperature	48 h		108
	Room temperature	6 h		112
	Room temperature	Overnight		113
	Room temperature	Overnight		118
	Room temperature	24 h	Drying is necessary for the evaporation of acetone	[122]
	19.2 ± 0.9°C	48 h		87
	Ambient temperature	12 h		90
Oven-dried	37°C	24 h	Three drying conditions were tested: 70°C for 12 h, 40°C for 16h, and 37°C for 24 h; 37°C for 24 h demonstrated the easiest removal from printlet supports	[124]
	55°C	No data	The drying step is followed by dip-coating of the printed parts with 2% Eudragit E100 in methanol in order to prevent humidity uptake	[126]
(i) Oven-dried at 50°C for 4 h; then stored in the desiccator at 20°C for 24 h or refrigerated at 4°C for 72 h (ii) Oven-dried at 50°C for 24 h			Printlets dried at 50°C for 4h, followed by refrigeration at 4°C for 72 h demonstrated the highest sustained API release after 24 h and 14 days.	[125]
Oven-dried	50°C	4 h		91
	80°C	2 h		
Oven-dried	50°C	24 h		94
Vacuum oven drying	40°C	2.5 h	Dosage form cracking at > 40°C	[111]
Ventilated oven-dried	40°C	12 h		82
(i) Air-dried at room temperature (ii) Microwave 200 W for 15 min (iii) Microwave 300 W for 10 min (iv) Microwave 400 W for 5 min (v) Oven-dried at 40°C for 7 h (vi) Vacuum drying at room temperature for 6 h (vii) Desiccator overnight				92

Continued

doi: 10.36922/ijb.4063

Table 2. Continued

Drying method	Temperature	Time	Commentaries	Ref.
Drying is mentioned but without specific data about the process				96
				97
(i) Vacuum oven	22°C	Overnight	Vacuum oven at 400 mbar pressure	[99]
(ii) Air-dried	Room temperature	24 h		
In-process drying with a heated bed	60°C	2 h		102
In-process drying with a heated bed	70°C	10 min		114
In-process drying with a heated bed	70°C	41–114 min post-printing		115

3. Discussion

3.1. Challenges

Based on the literature review on the SSE process for AM of drugs, it is evident that the SSE process is currently the most suitable and mature technology for manufacturing compounded preparations. The SSE process enables the manufacturing of many different products, allowing for easy product changeovers. Additionally, it offers easy-to-use technology with equipment and excipients adapted to clinical use. Finally, SSE makes it possible to design a wide range of dosage forms tailored to each patient's needs, mainly for oral administration, with immediate or modified release kinetics. Therefore, this technology could significantly benefit patients whose medical needs are unmet by existing industrial therapies or conventional compounding methods. Currently, the design and production of compounded medicines are subject to various constraints, which can be classified into three categories: (i) scientific and technical aspects, (ii) regulatory aspects, and (iii) personnel-related aspects (i.e., involved in design and manufacturing).[135]

3.1.1. Scientific and technical aspects

According to Pluta,[135] the scientific and technical aspects of compounded medicines encompass several critical factors: (i) formulation quality (i.e., ensuring the dosage form meets the patient's needs and is stable), (ii) formulation calculations (e.g., renal clearance, the half-life of the API, stability data, etc.), (iii) operating procedures, and (iv) post-preparation steps (e.g., control preparation, pharmacopeial standards, etc.). The SSE process introduces several technical challenges to these factors. The first challenge is related to the CAD, which is the model on which printed medicines are based. In particular, 3D modeling provides the flexibility to produce different dosages by modifying parameters, such as size or filling density. However, the resolution of the infill pattern is less precise compared to FFF, and the extruded gel tends to be more cohesive. This can make it difficult to obtain a porous dosage form, potentially affecting the release kinetics.

As a result, the computational aspects of compounding become more complex, with mathematical modeling playing a crucial role in the drug development process. This complexity highlights the importance of adopting a Quality by Design (QbD) approach, which integrates comprehensive modeling aspects and the use of experimental designs in drug development. In parallel, the formulation must not only be compatible with these numerical aspects but also satisfy rheological constraints. As highlighted in the technical aspects of SSE, formulations for drug production can be highly diverse and complex. In this context, the development of formulations using

SSE should be based on mathematical modeling, enabling adjustments of numerous variables to achieve desired outcomes, such as specific dosages and targeted drug release kinetics. Consequently, adopting the QbD approach is a key to the success of SSE in drug manufacturing. This approach involves developing a control strategy defined in ICH Q10 as "a planned set of controls, resulting from the understanding of the product and the manufacturing process, which ensures the performance of the process and the quality of the product."[136] The control strategy should ideally favor non-destructive quality controls conducted "in line" during the manufacturing process. Such controls are technically through the use of process analytical technology (PAT). PAT is defined in ICH Q8(R2) as "a system of design, analysis, and control of production through the in-production measurement of critical quality and performance attributes of raw materials and materials in use, with the aim of ensuring the quality of the finished product."[137] In essence, PAT enables the design, analysis, and control of pharmaceutical manufacturing processes by measuring process variables, ensuring that they conform to the parameters set by mathematical modeling and that the quality of the finished product meets the expected standards. The key advantage of PAT in the context of SSE is its ability to provide non-destructive controls. This is particularly valuable as the batches produced for each patient are often very small in size and may not be adequate for statistical analysis of the batch by representative sampling. For instance, in the SSE process, pressure sensors integrated into printers can measure extrusion pressure, facilitating control of the drug's quality attributes (e.g., dose, size, and weight).[81] On-line near-infrared spectroscopy can be employed to quantify API content.[138] Likewise, integrating an in-built balance within 3D printers allows for precise control over the mass of medicines manufactured.

3.1.2. Regulatory aspects

From a regulatory standpoint, current regulations in both Europe and the USA do not require compliance with GMP,[135,139] as they are designed to regulate the mass manufacturing of standardized products. Hospital preparations are typically made in small batches for a small number of patients. This approach allows for the control of associated risks and ensures the maintenance of an appropriate level of quality. However, the FDA and the French Medicines Agency have recently revised their quality recommendations, raising the required standards closer to those of GMP.[49]

As a result, batch-release controls for compounding are not required. However, the 3D printing of drugs at the point of care may necessitate regulatory changes. AM enables the production of highly sophisticated dosage forms with highly complex release kinetic profiles (e.g., different kinetics for different APIs) through a process based on digital technology. The benefit for patients lies specifically in the precision and flexibility of the products manufactured, which can vary significantly from one patient to another. Given these factors, it would be surprising if release quality controls were not implemented for printed drugs, as the risks to patient safety and drug efficacy are substantial. Therefore, incorporating PAT into 3D printers seems essential.

3.1.3. Personnel

Compounding requires qualified personnel with expertise in technical, scientific, and quality aspects. Drug AM via SSE will require in-depth training to fully understand and master the technology. Specific training on the machinery (particularly its use, control, cleaning, and maintenance) should be provided to all staff involved in this process. In addition, staff should also comprehensive training on slicing software that enables treatment customization to ensure the quality and safety of the drugs produced.

3.2. Manufacturing scenarios

Currently, "traditional" compounded medicines are manufactured at the point of care using pharmacy or hospital staff and equipment (and regulated by section 503A of the Federal Food, Drug, and Cosmetic Act). Bearing in mind what has been said above, the crucial question is whether hospital premises and the staff who work there can manufacture these SSE-printed medicines, guaranteeing their safety, efficacy, and quality. We can identify the following players involved in the development and production of printed dosage forms.

The structure responsible for drug development follows a Quality by Design approach, ensuring the development of the drug formulation, the design of the 3D digital model at the origin of the dosage form, and different calculations and mathematical modeling allowing the prediction of critical quality attributes of the product from input variables. This structure will thus oversee defining and validating the production procedure, ensuring the quality of the process, its reliability, and its performance. In the remainder of this text, this structure will be referred to as "structure (a)."

The structure responsible for manufacturing the intermediate pharma-ink (the gel or paste placed in a cartridge or syringe, mixture of drug and excipients). In the remainder of this text, this structure will be referred to as "structure (b)."

The structure responsible for 3D printing is the pharma-ink, the post-processing, and the batch release.

We have seen that generally post-processing consists of a simple drying operation in the open air or in an oven. Freeze-drying is probably the most sophisticated drying process found in the literature for SSE, but it remains little used (see Table 1). This is why it is very likely that the structure that prints the drugs is the same as that which carries out post-processing. In the remainder of this text, this structure will be referred to as "structure (c)."

We can identify different scenarios for pharmaceutical 3D printing at the point of care, which are being considered by regulatory agencies such as the FDA[140] or in other works such as Jørgensen et al.[141]

Development and production at the point of care: In this first scenario, the hospital or pharmacy the hospital would bring together the activities of structures (a), (b), and (c). Printed medicines would therefore be developed, manufactured, and distributed in the same way as other compounded medicines made within hospitals. The pharma-ink would be prepared at the point of care before printing the medicines. This would imply a certain number of constraints for hospitals, like maintaining qualified personnel for ensuring the development of printed dosage forms as well as maintaining the equipment in a state of qualification that ensures its operability and performance.

Point of care ensures only manufacturing of the final product: the second scenario separates the development and production of the pharma-ink from the production of the finished product between two different structures. In this case, we could imagine that a pharmaceutical company would bring together the activities of structures (a) and (b), and oversee the research and development (R&D) for printed medicines, in collaboration with health authorities, 3D printer manufacturers, and hospitals. Hospitals would only ensure that they manufacture the finished product. A case study carried out by Seoane et al. and published in 2023 studies the feasibility of decentralized production of printed medicines in hospitals based on 3D printer pharma-ink manufactured by a third party.[138] On this basis, a pharmaceutical company could take on the task of manufacturing the pharmaceutical ink and distributing it to hospitals. The commercialization of the pharma-inks may require the need for new regulations, as the pharma-in is not a final medicine nor a raw material.

Outsourced development and manufacturing: An alternative business model to the production of medicines in a hospital or pharmacy would be one where the hospital outsources the development and manufacturing of the printed drug to a third party that would be structures (a), (b), and (c) all in one. The latter is a traditional industrial manufacturer subject to GMP or another hospital that has the capacity to develop and manufacture the printed drugs.

These scenarios are likely to coexist, depending on the hospitals' ability to manage the development and manufacture of printed drugs. For a hospital, the use of a third party for the development and/or manufacture of pharmaceutical inks should be based on a risk assessment that will determine if the hospital can perform these activities while ensuring the quality, safety, and efficacy of the printed medicine.

3.3. Applications of 3D printing technology in the compounding unit

Chronic conditions have been estimated to affect 10–30% of children, depending on the criteria used.[142] Examples of chronic diseases include asthma, cystic fibrosis, HIV, congenital heart disease, diabetes, attention-deficit/hyperactivity disorder, depression, and cancer. For these patients, as with adults, personalized medication based on genetic and physiological parameters is increasingly feasible. However, this often requires adjustments to the treatment, risking non-adherence or sub/supra therapeutic effects. In many cases, it necessitates adapting the form and strength of a licensed medicine.[143] For example, in a phase I–II trial evaluating metronomic chemotherapy in patients with a relapsed or refractory Wilms tumor (MetroWilms), there was a need to administer adjusted doses of cis-retinoic acid or etoposide. The dosage forms in the market did not accommodate these adjustments, and patients were even required to drink an injectable solution of irinotecan due to the lack of an oral form for the product.[144] Changing the route of administration of a medicinal product is not a recommended practice, as it may have harmful consequences for pediatric patients.[30] Indeed, these practices may alter the efficacy and safety parameters of the medication by modifying its absorption characteristics, stability, and palatability.[31–33] For instance, in the MetroWilms clinical trial, the etoposide injection was unsuitable for children because it contained alcohol and had an unpleasant taste, which significantly reduced patient compliance.

To reduce this practice, hospital pharmacies are currently producing various capsules and liquid forms to meet patient needs with specific doses.[145] As described by Curti et al., compounding does not have high dose accuracy, which is a problem for drugs with a narrow therapeutic index.[146] With 3D printing, it is possible to manufacture medicines in more accurate doses for patients based on their weight, age, and specific needs.[147] The accuracy and flexibility of 3D printing have been studied for low-dose formulations for neonates[82] and high-dose medications to reduce the number of tablets required.[148] For certain anticancer drugs or medications used in cardiology with

a narrow therapeutic index, 3D printing could provide a viable solution.

3D printing can also improve patient compliance by reducing the number of tablets to be taken. For example, polypills that combine multiple APIs with different release profiles into a single dosage form offer a practical solution. An example is a polypill that incorporates nifedipine and captopril, both used to treat arterial hypertension in patients with type II diabetes, along with glipizide, which is used for the treatment of type II diabetes.[131] Incorporating all three drugs into a single solid dosage form would be highly beneficial in treating diabetic patients; however, the formulation would require the distinct release profile of each drug. Additionally, polypills that combine, for example, an antiemetic with an oral anticancer drug or two antibiotics in one dose could improve compliance, which is a major factor in managing pediatric chronic diseases.

One of the significant advantages of 3D printing is its ability to enhance adherence by developing novel dosage forms that are easy to administer and designed with child-friendly formulations.[149] These can include different flavors and color profiles,[80] addressing one of the major challenges in pediatrics, i.e., making medicines acceptable to children who are often reluctant to swallow bitter tablets. For example, BACTRIM® (40 mg/mL trimethoprim + 8 mg/mL sulfamethoxazole, oral suspension) and DALACIN® (75 mg/5 mL clindamycin granules for suspension) are marketed in liquid oral form but are often poorly tolerated due to their unpleasant taste and large volumes required for administration.[150,151] This can lead to non-compliance, increasing the risk of opportunistic diseases or the development of antibiotic resistance.

3D printing can make oral dosage forms more appealing for children by producing tablets with eye-catching appearances and favorable palatability. Some studies have produced chewable dosage forms, while others focused on taste-masking by adjusting excipients and incorporating pleasant flavors, which can increase adherence to treatment.[42] For example, Karavasili et al. produced pediatric-friendly chocolate-based dosage forms of paracetamol and ibuprofen, suggesting the possibility of encapsulating the drug paste within a matrix that masks its unpleasant flavor, as in the case of some bitter-tasting drugs.[80]

Following these strategies to make medicines more pleasant for children, 3D-printed gummies were fabricated with different shapes (heart, bear, and disc) and colors using mixtures of gelatin, carrageenan, xanthan gum, and sweeteners. Additionally, gelatin and hydroxypropyl methylcellulose (HPMC) hydrogels were used to prepare gummies with lamotrigine.[39] The viscosity and strength of the formulation were easily modified by varying the amounts of the two main excipients, HPMC and gelatin. Moreover, the production of dispersible film with personalized doses, such as hydrocortisone, can enhance dose accuracy while improving patient compliance.[152]

An important benefit of AM in drug manufacturing is the possibility to tailor treatments to individual patient requirements and adapt drug release profiles as needed. For example, ranitidine hydrochloride was used as a model drug, and it was observed that the addition of corn starch among the components resulted in a greater extended release of the drug. [153] Similarly, a study prepared immediate-release levetiracetam tablets to treat epilepsy, where the dose in pediatric patients is subsequently increased over time.[134] This flexibility offered by AM enables tablet preparation that can be easily modified to follow the required dosage regimen.[154] In France, for example, the preparation most frequently made in hospitals is an immediate-release melatonin capsule for various uses, such as alleviating stress before imaging exams or aiding sleep during hospitalization.[155] However, this formulation often requires adjustments (i.e., frequently opened) before administration, which can compromise the stability of the drug.

An alternative approach to enhance compliance involves preparing solid lipid tablets based on emulsion gels.[111] Unlike previous approaches where blends of lipid excipients are directly printed, these formulations are printed using preformed oil-in-water (O/W) emulsions loaded with the poorly soluble drug fenofibrate. The resulting formulations disintegrated in less than 15 min. Besides printing the tablets at room temperature, which is particularly useful for thermolabile compounds, these formulations are effective for poorly water-soluble drugs, as they help improve their oral bioavailability. The low temperatures required for material extrusion make this technique suitable for printing proteins and other thermosensitive drugs.[80]

Due to the lack of commercially available tacrolimus suppositories, these are commonly compounded in hospital pharmacy settings using a molding technique, which requires several steps and long periods of solidification. Suppositories loaded with the immunosuppressant tacrolimus, which are commonly used in patients with therapy-resistant inflammatory bowel disease (IBD), have already been prepared.[156] Using SSE and a suitable combination of lipid excipients, self-supporting suppositories were directly printed without the aid of molds. Moreover, the suppositories were fabricated in various sizes to accommodate patient comfort and dosage requirements. They were prepared using a mixture of Gelucire 44/14 or Gelucire 48/16 and coconut oil, the latter served as a plasticizer. Both pharma-inks displayed

good printability without the need for solid-phase carriers or a cooling system on the build plate. These active substances, for which pharmacies already produce various preparations, are excellent candidates for the approach.

The application of 3D printing in pharmaceutical manufacturing minimizes the need for excessive excipients. The two major components of a 3D-printed tablet or dosage form are the polymer matrix and drug component. Hence, the use of 3D-printed dosage forms for disease treatment reduces the risk of unwanted side effects and enhances therapeutic efficacy.[157] Personalized medicine demands tailored treatments, which can be provided by compounding. Besides an individualized dose, other specific patient needs, such as sensory processing disorders, food allergies, and dietary needs, can be accommodated by compounding.[158]

Due to their ease of administration, absence of toxic excipients, improved palatability, and flexible dosing, 3D printing has demonstrated its significant value across various pharmaceutical applications. 3D-printed tablets can be produced to avoid swallowing issues (chewable tablets), with different release profiles (e.g., immediate or controlled release), unique features (e.g., high drug loads), and better palatability that can be tailored to individual patient needs.[80]

Despite the technological challenges, several teams have successfully addressed these issues in real-world applications, particularly focusing on rare diseases with low therapeutic indices. This approach optimizes treatment effectiveness while reducing undesirable effects.[131,134,159] Although current technology exhibits limitations with regard to its applications, enhancements in printing velocity and the concurrent utilization of multiple printheads are expected to improve the quantity of material that can be produced.

In the forthcoming years, the capacity to optimize these parameters will prove pivotal in determining whether the focus remains on rare diseases, where the demand is high, or shifts to more prevalent diseases with similarly high demand. Nevertheless, the ability to meet the demand will remain a crucial consideration.

4. Conclusion

This review highlights significant advancements in pediatric pharmacotherapy through 3D printing technology. Traditional formulations have long struggled to meet the specific needs of the populations, leading to off-label use and potential safety risks. In contrast, 3D printing, particularly SSE technology, offers promising solutions by enabling the production of customized drug formulations tailored to individual patient needs. This technology addresses critical issues for small-scale production, such as dose accuracy, palatability, and ease of administration, thereby improving adherence and therapeutic outcomes.

The ability to produce polypills with varying release profiles and chewable, taste-masked formulations demonstrates 3D printing's potential to revolutionize medication for conditions requiring precise therapeutic control. Moreover, the flexibility and precision of 3D printing make it an invaluable tool for creating personalized treatments that traditional compounding methods cannot achieve with the same efficiency or safety.

Despite these promising developments, the practical production of these drugs will depend on the pharmacies' and hospitals' ability to manage the risks involved in production, considering the criticality of the drug and the hospital's resources for development and production. Furthermore, the successful integration of 3D printing into routine clinical practice requires ongoing research, as well as clarification of legislation and harmonization between countries. Ensuring the safety, efficacy, and quality of 3D-printed medications will involve robust quality control measures and specialized training for personnel involved in the drug manufacturing process.

The challenges associated with this novel production method include the need for personalization, ease of administration, and long-term patient compliance. It is of paramount importance to monitor patient compliance with these novel drugs, even if initial studies yield favorable feedback indicating that these personalized forms are well adhered to by patients.[98]

In conclusion, 3D printing technology represents a transformative approach to personalized medicine, addressing long-standing formulation challenges and paving the way for safer, more effective, and more acceptable medications. Continued innovation and regulatory support will be essential to fully realize its potential in improving patient care and outcomes.

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Conflict of interest

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