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Recent advances in pharmaceutical dosage forms and devices using additive manufacturing technologies

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The era of 'one-size-fits-all' treatment approaches is becoming history for pharmaceutical manufacturing with the future encountering a revolution in drug development through the introduction of additive manufacturing technologies. The innovative elements of this disruptive technology will affect all shareholders of the pharmaceutical chain from the industrial sector to the dispensing facilities and, ultimately, the patient end-user. In this review, we provide an overview of the most recent advances in dosage forms and devices using additive manufacturing technologies, along with the regulatory landscape framing the development and safety requirements for 3D-printed drug products before entering the pharmaceutical market.

Introduction

3D printing (3DP) or additive manufacturing (AM) can be any manufacturing process used to transform a 3D digital model into a 3D physical subject by successive material deposition in a layer-by-layer mode. Some of these techniques [e.g., fused deposition modeling (FDM), stereolithography (SLA), binder jetting (BJ), powder bed printing (PBP), semi-solid extrusion (SSE) and inkjet printing (IP)] have been used during the past few years for the creation of pharmaceutical formulations, with the number of published papers increasing at an exponential rate since 2014 [1] (Fig. 1).

Although drug 3DP technology is still in its infancy, many steps toward the enrollment and optimization of different AM technologies in drug formulation and dosage forms have been taken. For instance, new pharmaceutical-grade polymers were found to be suitable for FDM 3DP operating at much lower temperatures (90 °C) than conventional FDM printing, enabling printing of thermolabile active pharmaceutical ingredients (APIs) [2], and a variety of biocompatible bioinks utilized in inkjet 3DP have been developed [3]. The main reason for this burst in AM is the fact that prices of 3D printers are declining steadily and rapidly. The low cost of FDM 3D printers renders them the most suitable candidate for equipping the community pharmacies and other small-scale healthcare provision facilities. Moreover, good manufacturing practices (GMP)-complying FDM printers and hot-melt extruders, for continuous and large-scale drug-loaded filament production, have recently been manufactured [4], highlighting the impending transition from proof-of-concept demonstrations toward real-life applications.

Oral delivery

Per os administration, although generally preferred for medication intake, is not ideal for the administration of APIs with a narrow therapeutic window or APIs that exhibit dose-dependent severe adverse reactions, because the commercially available dosage forms cannot cover the specific dosage needs of each patient. There is an unmet need for the development of formulations with a wide variety of dosage strengths while at the same time oral solid dosage form market drives towards the delivery of API's with high potency [5] and drugs targeting niche markets (e.g. orphan drugs) [6]. AM technologies enabling 'fine-tuning' of the API dose might bridge this gap, meeting individual patient idiosyncrasy and creating relatively small batches of personalized formulations, a trend depicted in the recent burst of published research articles on oral 3D-printed formulations (Fig. 2).

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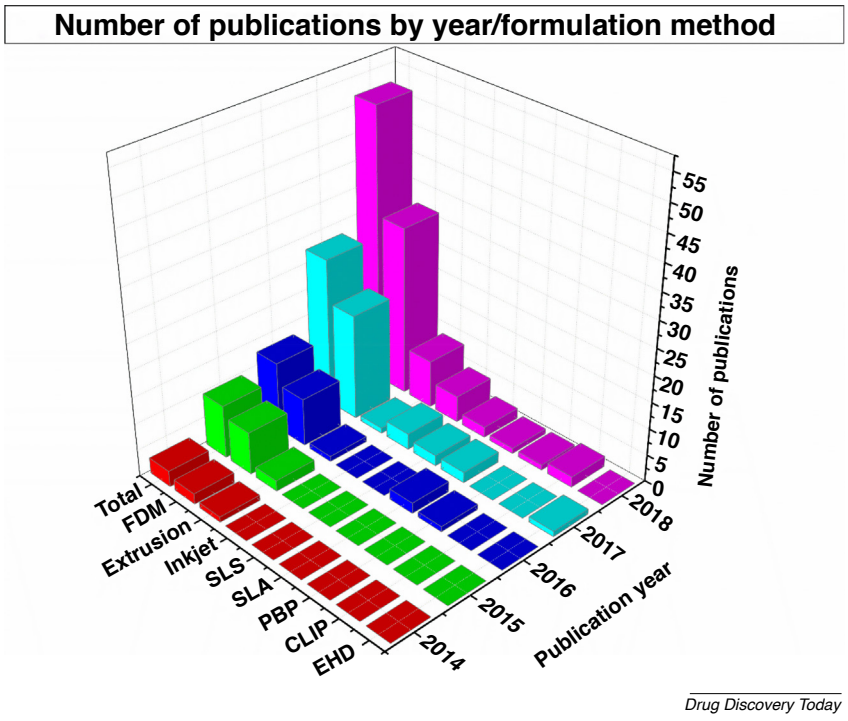

FIGURE 1

Total number of research papers on 3D-printed formulations, sorted by method and year of manufacturing. Sources: Pubmed, Web of Science® and ScienceDirect®. Search terms used: '3D printing' OR 'additive manufacturing' AND 'dosage form' OR 'drug' OR 'tablet' OR 'drug loaded' OR 'drug eluting' OR 'pharmaceutical device'. Only papers referring to API-loaded formulations were included.

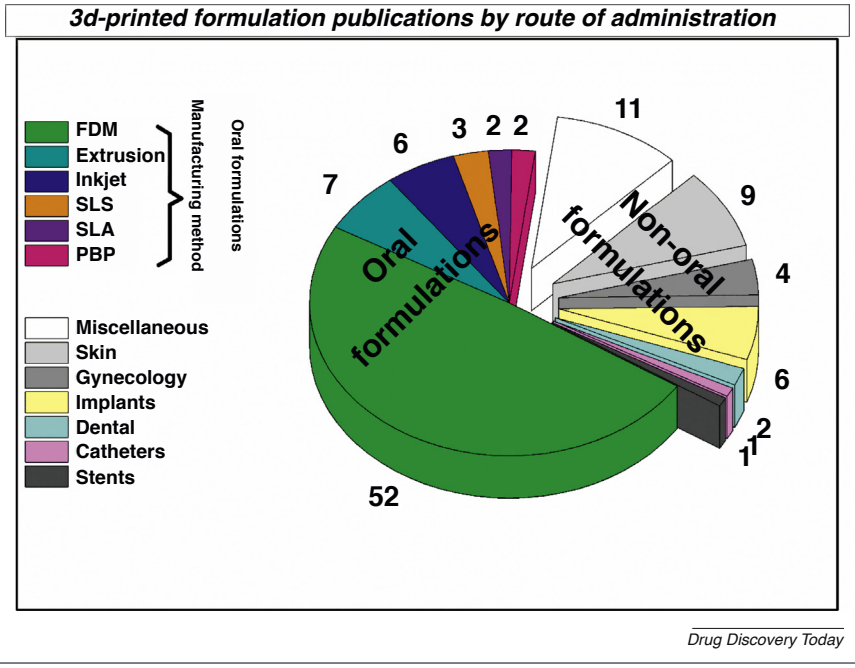

FIGURE 2

Total number of research papers on 3D-printed formulations sorted by route of administration (oral formulations also sorted by manufacturing method). Sources: Pubmed, Web of Science® and ScienceDirect®. Search terms used: '3D printing' OR 'additive manufacturing' AND 'dosage form' OR 'drug' OR 'tablet' OR 'drug loaded' OR 'drug eluting' OR 'pharmaceutical device'. Only papers referring to API-loaded formulations were included.

Controlled drug release

One of the most innovative aspects of AM is the ability of developing oral dosage forms with elaborate shapes and complex structures (like floating systems) [7,8], which were previously impossible to produce or required laborious and cost-ineffective procedures. Furthermore, dosage forms with more-sophisticated shapes and geometries can be easily manufactured via a wide spectrum of AM techniques including: (i) torus-shaped formulations achieving API zero-order release via FDM [9], SLA [10] or PBP [1] printing; (ii) dosage forms with an internal channeled [11,12], honeycomb [13], network [14] or gyroid [15] microstructure, where dimension adjustments could tailor drug release; and (iii) composite multilayered or shell–core formulations [16–19] that could deliver one or more APIs at different rates, depending on their specific structure and sequence of layers.

One-step formation of multicompartment and matrix dosage forms

An intriguing potential of AM is the creation of complex matrices and scaffolds allowing the incorporation of APIs or drug-loaded formulations. This arrangement enables the creation of conventional carriers like capsules (with distinct compartments, having the ability to incorporate different APIs and release them independently) [20] or the manufacturing of modifiable containers that enclose drug-loaded alginate beads [21], polymeric nanocapsules [22] or self-nanoemulsifying drug delivery systems (SNEDDS) [23]. Nevertheless, creation of customizable capsules via FDM appears to be beneficial compared with injection molding (IM) for the production of small individualized batches or at the set-up of the design of the capsular system manufactured by IM, because of longer processing times and increased costs [20]. By contrast, the conversion of multiparticulate systems into personalized oral solid dosage forms could combine the advantages of both systems (dose accuracy and convenience coupled with targeted delivery, less risk for dose-dumping and better distribution and dispersion in the GI tract) toward improved drug administration. An additional interesting feature of AM is the feasibility of simultaneous creation of a carrier matrix and its filling with drug-loaded solutions or suspensions [24]. This approach can be time-effective and ensure dose accuracy.

Site-specific delivery

3D-printed oral formulations can target different sites of the GIT, such as the intestinal [25] and colonic environment [21], by incorporating protective pH-responsive layers. The ability of 3D printers to provide precise drug dosing is crucial for this type of formulation, avoiding splitting, which in turn could affect the structural properties of the dosage form depriving them of their functional properties. The advantage of AM procedures in introducing distinct features like orifices and cavities (e.g., osmotic pumps [26], floating systems [7]) and coatings for controlled or taste-masking purposes, simultaneously with the fabrication of the dosage form core, enables site-specific drug delivery. Such formulations could be significant for the pharmaceutical industry, because continuous procedures and elimination of production stages have a crucial role in cost lowering.

Dosage forms for special groups

Dose adjustment of oral formulations is a crucial factor in pediatric dosage forms. This has been highlighted by Scoutaris et al., who developed attractive candy-like formulations by imitating Starmix® sweets and achieved taste-masking by coupling 3DP with hot-melt extrusion (HME) – a combination that could in turn increase adherence and compliance of pediatric patients (2–11 years old) to the prescribed medication [27].

Nowadays, polypharmacy among the elderly patient population is a common phenomenon. Incorporation of multiple APIs into the same dosage form will enhance patient compliance and reduce administration errors [28]. Creation of such polypills has been achieved recently by utilizing different AM techniques such as FDM (i.e., antidiabetic dosage form [29]) and SSE (i.e., a five-in-one cardiovascular treatment regime [30], an osmotic pump coupled with sustained-release layers for controlled-release of three distinct APIs [26] and antidiabetic core–shell, multilayer and gradient structures [17]).

3DP orodispersible and orally disintegrating dosage forms

Orodispersible and orally disintegrating dosage forms are enticing patient compliance in populations with swallowing incompetence. Spritam® (levetiracetam, a landmark in drug 3DP technology), a rapidly disintegrating tablet, is the only FDA-approved 3D-printed oral medicine so far. FDM 3DP has been employed to fabricate aripiprazole orodispersible films [31], as well as fast-dissolving single- and multi-layered films with taste-masking properties and rapid disintegration times as short as ~50 s [32], and SLS printlets demonstrated even shorter disintegration times (4 s) [33].

In vivo *studies*

Although all 3D-printed systems have presented acceptable *in vitro* performances, there are limited studies exploring their *in vivo* efficacies. Successful floating of a 3D-printed hollow dosage form was confirmed, ensuring suspension in the gastric environment for 10 h [7]. The *in vivo* behavior of a sealed 3D-printed dual-loaded oral dosage form was found to be significantly different from *in vitro* experiments, possibly because of the unsealing of the dosage form or the faster dissolution rate of the formulation, caused by the mechanical stimuli and biofluids of the GIT [34]. In another study, diltiazem-loaded hydroxypropyl methylcellulose (HPMC) tablets with various shapes and infill patterns revealed that the oral absorption profiles were closely correlated to the *in vitro* studies [35]. Finally, *in vivo* release of warfarin from a dosage form based on a cationic immediate release polymer was found to be significantly slower than in *in vitro* experiments, possibly owing to the different pH values of the rat's gastric environment, compared with the dissolution apparatus, hindering the erosion of the cationic polymer [36].

3D-printed pharmaceutical medical devices

The assets of AM technology to fully customize geometric dimensions and medication dosing have been valorized to disengage the current 'one-size-fits-all' treatment approaches and endorse the on-demand fabrication of patient-specific models. Toward that direction, drug-loaded medical devices are being designed to fulfil these requirements. The effect of excipient composition has been examined as a regulating factor on drug-release properties of FDM

3D-printed constructs [37,38] with drug content being recognized as an additional factor to impact drug release [39]. In the exploration of new materials in FDM 3DP, different grades of ethylene vinyl acetate polymers have been utilized in fabricating implantable T-shaped intrauterine systems (IUDs) and subcutaneous rods [40].

Suppositories and vaginal rings

Progesterone-eluting poly(lactic acid) PLA/polycaprolactone (PCL) vaginal rings designed with different shapes demonstrated sustained release kinetics over 7 days with the device geometry affecting the rate of drug release owing to the distinctive surface-area:volume ratio of each design [41]. Similar extended release patterns were obtained from hormone-eluting PCL constructs, FDM-printed donut-shaped, Gellhorn-shaped or IUD geometry [42].

Wearable devices

In the first-in-human study, a wearable oral device in the form of a mouthguard was 3D-printed based on the anatomical imprint of the volunteers. Minor discomfort was reported by the volunteers while wearing the device, necessitating further optimization of the printing resolution [43]. To redefine the utility of a common polymer [poly(methyl methacrylate); PMMA] in dental prosthesis, 3D-printed PMMA dentures were functionalized with antifungal-containing microspheres with the potential to further advance denture performance with multiple functionalities [44].

3D-printed patches

Implantable patches for pancreatic cancer

A polymeric patch was fabricated containing a high 5-FU payload and geometry adjustable to the site of administration [45]. The patch enabled controlled drug release kinetics over a 4-week period, effective suppression of pancreatic tumor growth after direct application at the tumor site in an orthotopic pancreatic cancer model minimizing systemic drug exposure and the incidence of severe side effects [46].

Drug-eluting patches for transdermal application

The exquisite precision of 3DP combined with 3D scanning has been leveraged to produce anatomically adaptable patches for personalized transdermal applications. In a comparative study, SLA was found to outrank FDM technology in manufacturing antiacne devices with salicylic acid in terms of higher resolution, drug-loading capacity and thermal stability, as well as faster drug diffusion across the device, whereas 3D scanning of the application area facilitated full customization of the printed device to the patient's anatomical requirements [47]. In the same notion, personalized PCL dressings loaded with antimicrobial metals were fabricated against scanned templates of a target wound, showing prolonged release kinetics, a feature desirable in clinical practice to minimize the frequency of medical intervention in the treated area [48]. Antimicrobial PCL/polyvinylpyrrolidone (PVP) patches fabricated using electrohydrodynamic (EHD)-printing-enabled manipulation of tetracycline hydrochloride release kinetics based on the fiber pattern and composition [49].

3D-printed microneedle arrays

Microneedles (MNs) have been implemented in transdermal drug delivery as a minimally invasive method to enhance small and macromolecular drug permeation across the skin barrier. Inkjet-printed insulin-xylitol coatings on SLA-printed pyramid/cone resin MNs showed a rapid insulin release while retaining protein integrity [50]. Continuous liquid interface production (CLIP) has been used as an alternative approach to coat polyethylene glycol (PEG)-based MNs with model proteins, facilitating spatial control over the coating pattern [51]. In an attempt to optimize MN geometrical properties, chemical etching was adopted as a post-fabrication step of biodegradable PLA MN arrays [52]. A novel approach in personalized drug delivery was attained with a MN splint customized to fit a patient's skin curvature to treat trigger finger [53]. A bioinspired needle design was based on the barbs of honeybee stingers, intending to decrease the insertion and extraction forces during percutaneous application by varying the design parameters of the barbs [54]. The spectrum of 3D pharmaceutical formulations referred to above is summarized in Fig. 3.

Patient acceptability

AM as a disruptive and innovative technology has introduced the meaning of personalized medication with high impact on the efficiency, quality and cost-effectiveness in the production of patient-centric pharmaceutical formulations. AM managed to bridge the gap between utilizing a standardized manufacturing process while retaining a customizable output. Nevertheless, the novelty elements of this technology would be futile if patient acceptability was not taken into consideration. The influence of the shape, size and color of different placebo FDM 3D-printed tablets (Printlets^{TM}) on end-user acceptability was evaluated in a single-site, open-label trial with 50 adults aged 18–45 years [55].

The personalized element of AM can create a positive social impact in terms of improving the healthcare experience of sensitive patient groups, such as the pediatric and geriatric populations, by actively involving them in the decision-making process. Customization of the composition and the organoleptic and textural properties of medication to individual specific health requirements, as well as preferences, can in turn increase patient acceptability, compliance and adherence [56].

At the same time, pharmacoprinting will introduce patients to a more engaging role within the pharmaceutical chain, rather than being the last recipient of the distribution chain. Patients will be authorized with more responsibilities regarding medication design, which will inevitably increase self-motivation to comply with medication intake. This reorganization, however, will require the training of the patient population to new principles to enable a smooth and safe transition from traditional to personalized medicine [56].

Regulatory landscape

The exponential pace at which AM research and technology is advancing in healthcare product manufacturing demands that regulatory agencies remain commensurate with this progress and sculpt the normative framework for product manufacturers. The FDA has recently issued a guidance draft regarding the design and manufacturing as well as device-testing considerations, addressing the regulatory requirements for 3DP medical device manufacturers [57]. However, these are not generalized to all 3D-printed medical devices, because an individual assessment of safety and efficacy might be required, especially for

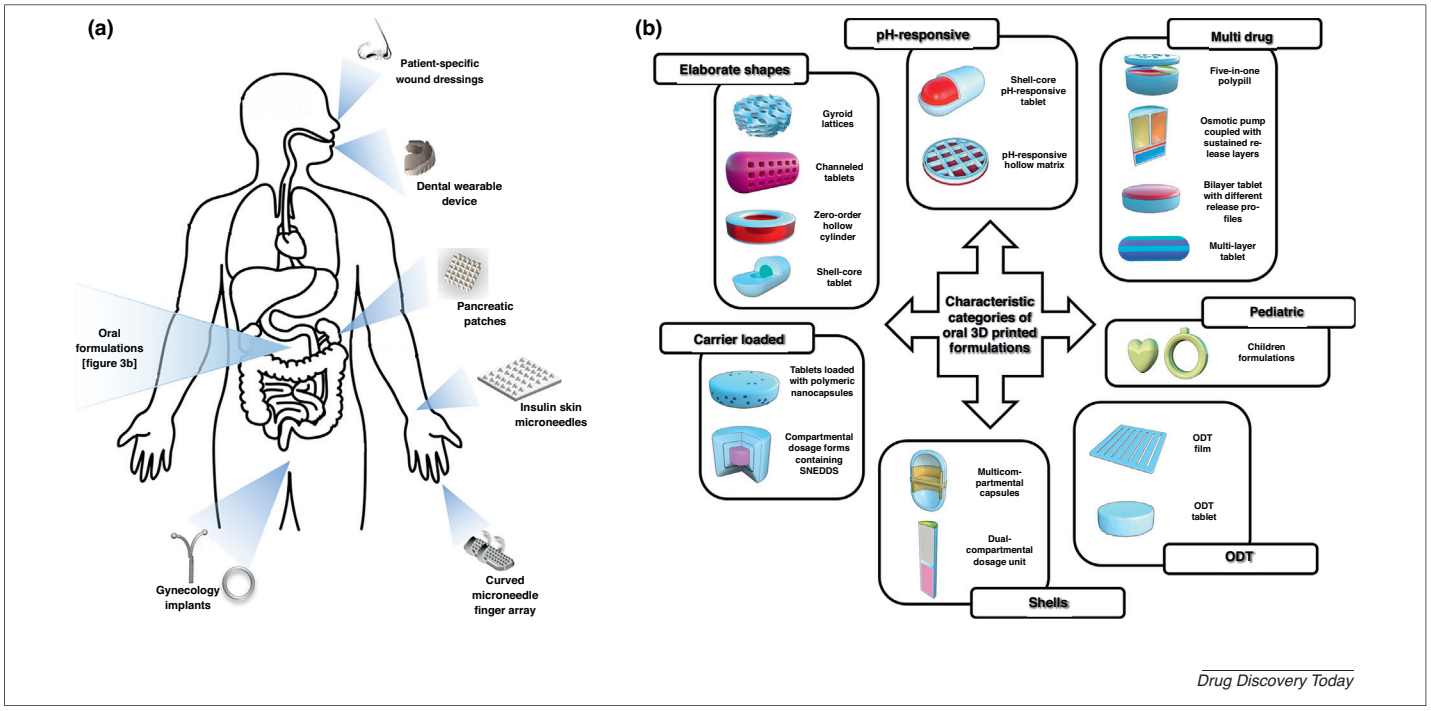

FIGURE 3

Characteristic categories of 3D-printed formulations with distinct features and administration routes. **(a)** Overview of all routes of administration and **(b)** orally administered solid dosage forms.

patient-matched products. So far, >100 FDA-reviewed 3D-printed medical devices are on the market but only one FDA-approved pharmaceutical product has been marketed by Aprecia Pharmaceuticals – as a tablet for oral suspension (Spritam®) indicated in adults and children with epilepsy. Nevertheless, guidelines for 3DP dosage form manufacturing have not been issued yet by any regulatory agency. It remains unknown whether regulatory approval will only apply to the final product or a set of baseline compliance requirements will appertain to all components and stages of designing and manufacturing a final product. Because personalized AM will inevitably scale-down the batch size of industrial manufacturing, packaging and labeling will also have to adjust to meet the manufacturing needs of small-scale and individualized medicine.

The patent landscape of 3D-printed-related products and processes has been shaped in accordance to the advances in AM technology. Although earlier applications mainly focused on the utility of 3DP in prototype manufacturing, only lately has there been a progressive escalation in applications related to the direct fabrication of pharmaceutical dosage forms by AM [58]. Aprecia Pharmaceuticals in its patent: US20140271862, discloses a rapid disperse dosage form containing levetiracetam, a process for preparing the dosage form and its use for conditions that are responsive to the use of the specific active [59]. The University of Central Lancashire reports on the broader range of the use of fused filament fabrication (FFF) 3DP to produce solid-dosage forms [60]. The National University of Singapore claims to have printed drug tablets with fully customizable release profiles for personalized medicine. The invention relates to dosage forms comprising an erodible polymer of specified geometry and an active pharmaceutical compound, and release from the dosage form is affected by the polymer's geometric shape [61]. Grünenthal relates to a floating pharmaceutical dosage form with a density lower than the density of gastric fluid, aiming at achieving predictable and enhanced drug absorption [62]. The dosage form contains the active ingredient and a cavity and contains claims on the preparation of the dosage form comprising a 3DP step. Merck filed a patent application identifying a process for the manufacture of a solid pharmaceutical administration form using a contactless 3D-laser-printing process and a composite layer usable in this process [63]. The inventors disclose claims not only on the final product but also on intermediate products, the manufacturing process, the apparatus employed and the starting or intermediate materials. Claims can be further extended to hardware and software covering different aspects of AM technology, because it is essential to protect from any intention to put an invention into effect. Another crucial issue that also needs to be addressed is whether these patents apply only at an industrial level or are extended to community pharmacies, because in countries like the UK extemporaneous pharmacy preparations are exempted from patent infringement [58].

Especially because digital elements are an integral part of AM, IP infringement of an idea or a design might be laborious to prevent or even identify among thousands of designs circulating across an equal number of websites with digital file sharing. IP owners can obtain copyright protection over their designs and CAD files, which, although not as broad as a patent, provides a substantially long-term protection. But how effective can any precaution be when the broad commercialization of 3D printers renders any individual with a 3D printer a potential infringer, intentionally or

not? This issue might also affect quality monitoring of the final products bearing the trademark of the brand owner, for which, however, the development of good AM practices will provide a straightforward path in product manufacturing and quality assurance.

Although advances in the field are still preceding legislation and because AM will not be the last in the long line of innovative technologies, the regulatory mechanisms will have to sharpen their reflexes and create a protective shield for inventors and patients. In that sense, authorities should support digital risk management and develop data frameworks to regulate data accessibility and balance data openness and IP protection.

Safety considerations

One of the primary considerations stemming out of the implementation of AM in the development of pharmaceutical dosage forms relates to specific safety requirements, regarding environmental health issues and material biocompatibility concerns. The main hazards associated with the 3DP process derive from the generation of hazardous airborne materials as a result of heating, extrusion or fusion of thermoplastic materials usually used as feedstock materials and can potentially act as respiratory or skin irritants and sensitizers. Compliance with the manufacturer's specific installation and operation guidelines (i.e., SOPs) is the minimum effective precaution to be applied to effectively minimize exposure to health and safety hazards associated with 3DP processes [64].

Although the regulation landscape for 3D-printed medical devices from a safety standpoint is still gradually developing, the establishment of safety requirements for 3D-printed pharmaceutical dosage forms is still in its infancy. A comprehensive biocompatibility assessment of commercially available polymers utilized in 3DP of microfluidic and biomedical devices has been previously conducted employing five standard whole-organism biotests. Results raised biocompatibility concerns regarding the safety of the polymerized resins used in MultiJet (MJM) and SLA processes [65]. Similar safety concerns were brought up in another study assessing the toxicity of 3D-printed microfluidic devices fabricated with different commercial photopolymers using the fish embryo test (FET). Results suggested that a pre-treatment of the polymers combined with a post-treatment washing step of the devices might be beneficial in terms of decreasing the observed toxicity in zebrafish cultures [66]. This post-fabrication treatment approach employing multiple washing steps was adopted by Lim et al. after the fabrication of a MN splint [53]. The *in vitro* biocompatibility of the printed parts was tested in human dermal fibroblast (HDF) and human adult low calcium high temperature (HaCaT) cells profiling their safety for use in human dermal cells.

The widespread use of commercial thermoplastic filaments (e.g., ABS, PLA, PET) in FDM commonly requires printing under elevated temperatures, which might result in feedstock material partial decomposition into toxic degradation products. However, there is a scarcity in the assessment of the safety profiles of commercial and custom-made filaments subjected to heat-treatment during extrusion and FDM printing of pharmaceutical dosage forms. It is therefore of the utmost importance to implement standardized *in vitro* cytotoxicity studies that will provide a preliminary assessment on the biocompatibility of the materials in use. Evaluation of the levels of degradation products during the formulation process and establishment of degradation product acceptance criteria should be prerequisites to assure the safety and efficacy of the developed pharmaceutical dosage forms.

Based on their intended use, 3D-printed products require additional CE marking for the equipment, the software and the raw materials utilized, if aiming for medical or pharmaceutical application. However, custom-made 3D-printed medical devices are only bound to ex-post controls by designated authorities and are exempt from conformity assessment and CE marking [67]. In case of damage caused by defective products, it might be challenging to impute responsibility on a single entity, because the liability burden will have to be identified among the software, printer and product manufacturers. This might prove even more challenging owing to the decentralization of the AM infrastructure, necessitating new legislation to ensure the safety of the end users and consumers. Quality assurance and product liability issues might also emerge from 3D printer operators in hospitals and pharmacies, who might not have the same technical background as an industrial operator.

Concluding remarks and future perspectives

Although 3DP of dosage forms and devices is moving rapidly from infancy to maturity, many steps should be made before this disruptive technology becomes an everyday tool in patient therapeutics. A necessary precondition for the deployment of AM technologies in community and hospital pharmacies is the creation and commercial distribution of industrially manufactured drug-loaded filament spools or bioink cartridges, because it would be cost-inefficient for these facilities to acquire and operate high-precision equipment to create quality feedstock material (under GMP conditions) for their 3D printers. Progress in materials science is crucial for developing raw materials with advanced properties and optimized performance under the operating conditions of AM techniques while promoting sustainability and ecofriendly practices in materials use and in AM processes. Priority should be given to standardizing the characterization techniques employed in testing 3D-printed objects and starting materials to create an international database of baseline performance metrics. That would simplify quality assessment and increase reproducibility and safety of the final products. Equally important is the development of computer software that could calculate the dimensions and design the desirable formulations by only inputting the required strength of the dosage form and the composition of the drug-loaded filament or bioink. Such software should be approved by regulatory authorities and design the dosage forms according to acceptable and rigorously proven specifications.

From an industrial perspective, investigation should focus on the feedstock material (i.e., mechanical properties of the filaments armamentarium), whereas novel characterization methods like μCT should be employed to evaluate the similarity of the 3D-printed dosage forms with their corresponding CAD drawings [29] (Fig. 4). Rheological studies on the characterization of molten polymer drug mixtures are expected to play a key part in materials characterization and filament printability [68]. Integration of nondestructive techniques that will allow quality control of the final product at the site of production will upgrade healthcare services and guarantee patient safety [69]. Therefore, technical

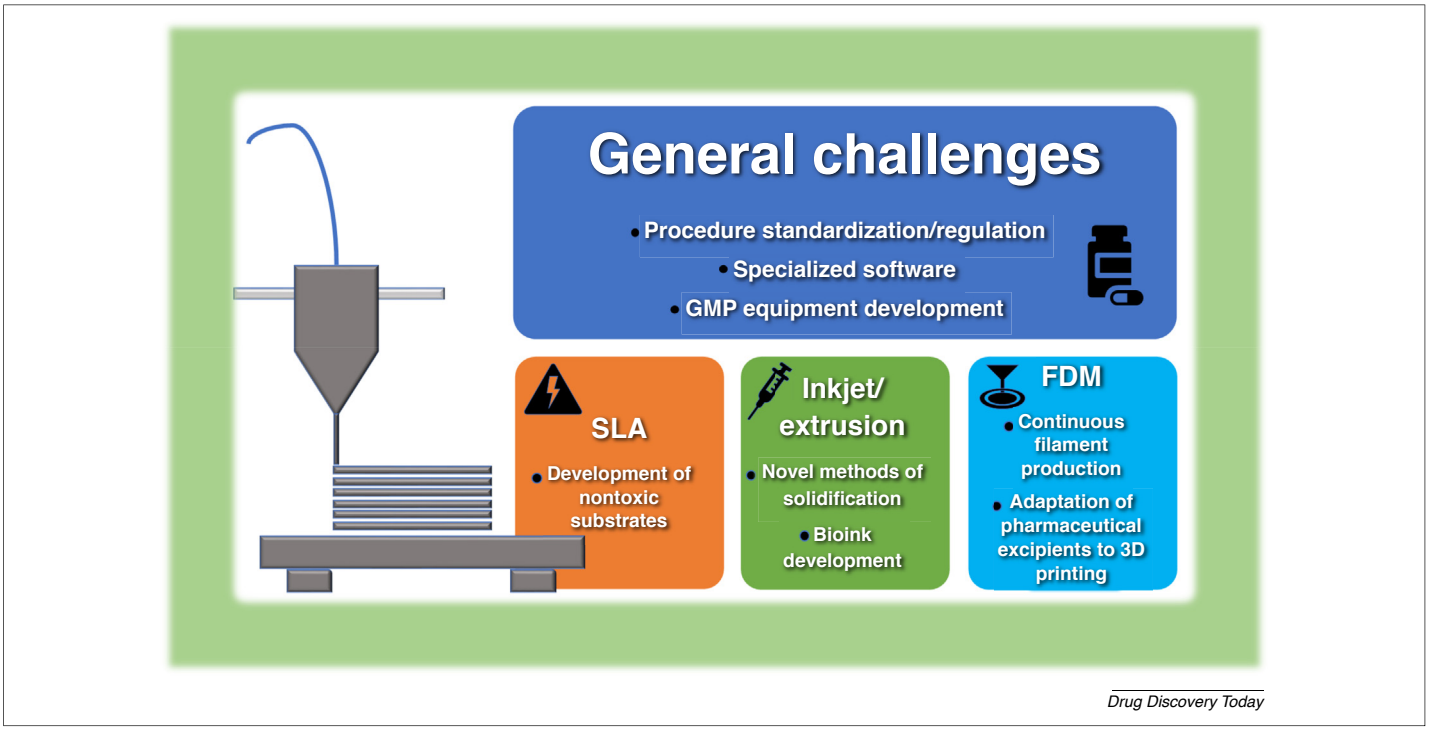

FIGURE 4

Future challenges in pharmaceutical 3D printing.

skill acquisition should be complemented with a more interdisciplinary education of the operators of AM technologies and quality control systems.

Public education, training and life-long learning are also fundamental to ensure public acceptance and proper integration to the new AM technologies [70]. Fast-forward, in-space manufacturing under zero gravity conditions will be the future of AM technologies, introducing the capability for on-demand manufacturing of any product especially for deep-space missions. Material and equipment performance in zero-G is currently being investigated, also providing significant information on AM on the ground [71]. When the above preconditions are fulfilled, pharmaceutical AM will have the potential to pave the way for future pharmacotherapy, which will be truly personalized, versatile and easily modifiable, benefiting its initial target first and foremost: the patient.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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