Practical Application of 3D Printing for Pharmaceuticals

Subjects: Medicine, Research & Experimental

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Three-dimensional (3D) printing is an unrivaled technique that uses computer-aided design and programming to create 3D products by stacking materials on a substrate. 3D printing technology is used in the whole drug development process, from preclinical research to clinical trials to frontline medical treatment. From 2009 to 2020, the number of research articles on 3D printing in healthcare applications surged from around 10 to 2000. Three-dimensional printing technology has been applied to several kinds of drug delivery systems, such as oral controlled release systems, micropills, microchips, implants, microneedles, rapid dissolving tablets, and multiphase release dosage forms.

3D printing additive manufacturing personalized medicine

1. Printing Materials Used in Pharmaceutical 3D Printing

1.1. Lactose

Lactose can be used as a filler or diluent in 3D powder bed printing, or SLA, for pharmaceuticals. It can enhance the compactability, physical stability, and drug solubility of the powder mixture used in 3D-printed tablets [1][2]. Generally, a lactose monohydrate binder blend is preferred for 3D powder bed printing due to the fact that a proper binder can enhance the mechanical properties of the tablet. A hydrophilic and hydrophobic API was successfully formulated into a printed tablet using lactose as a diluent due to its high solubility.

1.2. Polylactic Acid (PLA)

PLA is a biodegradable polymer that is often used in the 3D printing of implants, scaffolds, and drug delivery systems. It is accepted by the United States Food and Drug Administration (FDA) and is considered safe for use [3]. PLA has sufficient thermoplastic properties to be printed using the fused deposition modeling (FDM) technique [4][5]. The proper grade and molecular weight of PLA, together with a proper plasticizer, can be prepared for the filaments. PLA can be formulated with various drugs and excipients to achieve the desired release kinetics. However, PLA has a slower rate of degradation, making it suitable for sustained drug release [6][7].

1.3. Polyvinyl Alcohol (PVA)

PVA is a water-soluble thermoplastic polymer that is often used as a filler or binder in 3D printing tablets due to its biodegradability, biocompatibility, and dissolvability. It can improve the mechanical strength and drug release properties of the printed dosage forms. PVA can be printed using extrusion-based [8] or inkjet-based techniques [9]. For example, Goyanes and his team manufactured personalized oral caplets via fused deposition modeling using PVA filaments loaded with paracetamol or caffeine [10]. Kampanart and his colleagues also used PVA to produce tablet housing in order to control the drug's release profile and allow for zero-order release, as well as to lift the core tablet on gastric fluid for at least eight hours [8]. In addition to oral dosage forms, 3D-printed PVA is applicable to suppository dosage forms. Tatsuaki and his colleagues have developed a water-soluble polymer (polyvinyl alcohol) suppository shell for controlled drug release [11].

1.4. Hydroxypropyl Methylcellulose (HPMC)

HPMC is a cellulose-based polymer that is commonly used in 3D-printed dosage forms as a binder, diluent, supporting structure, and sustained-release agent. In comparison to other 3D printing materials, HMPC is distinguished by its dissolvability and low toxicity. Generally, HPMC can be printed in three dimensions using an extrusion technique [12]. Prashant and co-workers applied HPMC and methyl cellulose as biodegradable support structures. It was discovered that HPMC can be printed while maintaining the hollow structure of the primary printed product, and it can be easily removed from the building material by dissolving it in water [12]. Yiliang and his team used an extrusion-based 3D printer to prepare semi-solid tablets with different drug-loading dosages at ambient temperature. The active pharmaceutical ingredient, theophylline, was incorporated into hydrogels prepared with HPMC K4M or E4M for a prolonged drug release profile [13].

1.5. Gelatin

Gelatin is a natural protein-based biopolymer derived from collagen, which is typically derived from bovine or porcine skin and bones. Due to its biocompatibility, biodegradability, and simplicity of processing, it has been used for decades in a number of pharmaceutical formulations. Gelatin can be used as a bio-ink [14] or a printable material in 3D printing to construct complex structures and drug delivery systems [15]. Due to the gelatin's pliability, elasticity, and hydrophilicity, it has been utilized as a 3D-printed biodegradable excipient in gummy antiepileptic drug formulations for pediatric patients via the extrusion base technique [15].

1.6. Polyethylene Glycol (PEG)

PEG is a versatile polymer that can be used in 3D printing in pharmaceutical applications. It is a water-soluble, biocompatible, and biodegradable material that offers several advantages for drug delivery and tissue engineering [16]. Hsin-Yun Hsu used the drop printing technique to prepare naproxen/PEG 3350 solid dispersions with PEG coatings of different molecular weights, resulting in precise dosages and predictable compositional uniformity of API in three-dimensional structures [17].

2. Journey of 3D Printing in Pharmaceutical Application

The pharmaceutical industry has used 3D printing technology for several decades, but it has only recently begun to gain widespread adoption. One of the early pioneers of 3D printing was Charles (Chuck) Hull, who filed a patent application in 1986 for the use of UV lamps to cure photosensitive resin layer by layer to create small custom parts [18]. Therefore, the first 3D printer was based on stereolithography, after which a selective laser sintering technique was developed. The field of 3D printing did not become popular until the last two decades. In 2000, the first research article on oral dosage forms fabricated by 3D printing was published in the *Journal of Controlled Release.* Katstra and her team applied powder-based 3D printing to produce oral tablet dosage forms. Various types of binders, such as Eudragit E100, were added in different amounts to the PVP powder bed layer. Chlorpheniramine maleate was selected as the model drug, and the drug release profile was assessed to reveal the effect of binder type and amount on drug release behavior [19]. After that, in 2009, a biotechnology company called Organovo developed the first commercially available 3D bioprinter that could produce functional human tissues and organs [20]. This achievement represented a significant step forward in the evolution of 3D printing in the biopharmaceutical industry.

In 2015, the Food and Drug Administration (FDA) granted approval for the first 3D-printed drug, which was a seizure medication called Spritam® (levetiracetam) [21]. Spritam® is available in orodispersible tablet (ODT) dosage form. It was produced using the powder bed technique of 3D printing by adding liquid binder layer by layer. Spritam disintegrates extremely rapidly in comparison to other ODTs due to the absence of compressive force during tablet preparation. This was a significant milestone in the approval process of 3D-printed pharmaceutical products. The FDA also approved the first-ever 3D-printed medical device, which was a tracheal splint intended to treat an extremely uncommon respiratory condition in newborns [22][23]. In 2016, the world's first 3D-printed cranial implant, a titanium cranial implant used to repair skull defects, was approved by the FDA [24]. In 2017, the FDA initiated a pilot program to investigate the viability of employing 3D printing in the production of medical goods [25]. In 2018, the FDA approved the first drug-eluting stent produced using 3D printing technology [26]. Recently, the first once-a-day single inhaler triple therapy, a device used to deliver medication to the lungs, for treating both asthma and chronic obstructive pulmonary disease (COPD), received approval from the FDA in 2020 [27].

A significant amount of research and development has since been conducted in this area, and many pharmaceutical companies have started to explore the use of 3D printing for a variety of applications, including drug dosage forms, drug delivery devices, and medical devices and implants [28]. The following is a timeline highlighting several significant turning points in the evolution of 3D printing in the pharmaceutical industry. Thus, this technology will continue to evolve and be used in new and innovative ways in the coming years.

3. Pharmaceutical Application of 3D Printing in Hospitals and Pharmacies

3.1. Personalized Medicine

A major benefit of 3D-printing medicines is the potential to adjust the individual dose. Therefore, this technology is advantageous for treating patients with complex diseases who need personalized medication. Warfarin is one drug where the dose needs to be adjusted due to its narrow therapeutic index [29]. Dose titration of the drug is achieved by monitoring the international normalized ratio. Even though the strength of a commercial warfarin tablet varies from 2 to 10 mg, tablet splitting is still common a practice in hospital wards to adjust the dose for each patient [30]. The use of 3D printing to tailor the warfarin dose was reported for oral films and tablets [31][32][33][34]. Orally disintegrating tablets of warfarin were prepared using binder jet printing [33]. The tablets had an accurate drug content, acceptable mechanical strength, and a rapid disintegration time. As powder bed fusion was used to develop the first commercial 3D printing tablet, the application of this in the pharmaceutical industry is indisputable. However, the administration of powder bed fusion technology in healthcare units is not easily accessible. The expensive processing tools and difficulty in relocating the processing unit have become crucial obstacles to using this technology in hospitals and pharmacies.

Other technologies that have been reported for the dosing adjustment of warfarin rely on extrusion-based systems. Fused deposition modeling (FDM), which is simpler and more cost-effective [35], was used to prepare various doses of warfarin tablets [34]. The 3D-printed tablets had a range of dose accuracy between 91.5% and 102.4%, with a high correlation between the target and achieved dose, even at very low doses of 500 µg. Due to the drug-loading method, warfarin dispersed in the methacrylic polymer matrix is in an amorphous form. Thus, the pharmacokinetic behavior of warfarin in the animal model was altered for sustained drug release to enable a lower C_{max} and longer T_{max} in comparison with that of the warfarin solution.

Orodispersible films containing various doses of warfarin intended for use in pediatric and geriatric patients were successfully developed using semi-solid extrusion printing (SSE) [31][32]. Warfarin was dispersed in a matrix of hydroxypropyl cellulose, and the dose was controlled by an adjustment of the film size. The accuracy of the dose was found to be superior in comparison with that of unit dose sachets prepared by manual compounding [31]. Furthermore, a QR code containing dosage information can be incorporated into the 3D-printed films to avoid medication errors.

The first clinical study on the application of a 3D-printed dosage form in a hospital was reported in 2019 [36]. Chewable 3D-printed tablets, so-called printlets, prepared by SSE 3D printing, were used to treat pediatric patients (aged 3–16 years) with maple syrup urine disease, where supplementation of valine and isoleucine must be strictly controlled throughout life [37]. The isoleucine-loaded printlets were produced in the hospital with various doses and flavors. The drug content, in vitro dissolution, and stability of the printlets were investigated to ensure the efficacy of the dosage form. Isoleucine blood levels were evaluated using the dried blood spot method, and the acceptability of the 3D-printed formulation was evaluated in comparison with that of isoleucine capsules prepared by manual compounding. Isoleucine blood levels from both capsules and printlets were within the target range. However, the printlets were found to be more appropriate and acceptable for pediatric patients due to their candy-like characteristics.

Another study that applied 3D printing in a hospital setting was reported in 2020 [38]. Commercial spinorolactone tablets were ground and blended with other excipients before being printed into subdivided tablets using an extrusion-based 3D printer. The printer was located in a hospital pharmacy within an ISO5-level environment and was operated by well-trained operators. The 3D-printed tablets were qualified by a pharmacist before being dispensed predissolved in water to pediatric inpatients.

3.2. Multiple Medications

Multiple medications or polypharmacy are commonly defined as the regular use of at least five medications in an individual patient [39]. This situation is frequently found in elderly or young patients with specific conditions. In addition to causing confusion and noncompliance problems, patients also face the risk of adverse medical outcomes. To solve the polypharmacy problem, several studies have combined various active pharmaceutical ingredients into one tablet [40][41]. Multiple drugs, dosages, and drug-release profiles can be combined into one dosage unit of a "polypill" fabricated using 3D printing technology [41][42]. Sangnim and her colleagues developed an assembled polypill prepared from a 3D-printed mold inspired by Lego bricks. This polypill was composed of three commonly used hypertension drugs (amlodipine, hydrochlorothiazide, and valsartan). This innovation could potentially increase patient compliance, particularly among the elderly [43]. Mark and his team explored the perceptions and preferences of polypharmacy patients regarding 3D-printed medicine, including their acceptance of patient-designed medication. The patients were asked about their perceptions and preferences regarding 3D-printed solid dosage forms and were shown various shapes, colors, embossing patterns, and polypills. The findings revealed that the patients' perspectives and preferences regarding 3D-printed medicine varied. Appealing, swallowing, handling, comprehension, and psychological factors affect a patient's perspective [44]. However, no clinical studies on the administration of polypills in patients have been conducted to date. Knowledge of and trust in 3D printing technology are suggested as important factors in determining whether geriatric patients accept or reject this technology [44]. Therefore, the advice from pharmacists at the point of care plays an important role in the success or failure of bringing the personalized 3D-printed dosage form to reality.

3.3. Drug-Loaded Medical Devices

The advent of 3D printing has changed the development of medical devices, particularly drug delivery systems. Many drug-loaded medical devices, such as implants [45][46][47], inhalers [48][49], transdermal patches [50][51][52], and orthodontic retainers [53], have been made via 3D printing. For implantable drug delivery systems, the use of 3D printing for drug-eluting implants combines the benefits of targeted local drug therapy over longer periods of time at the precise location of the disease with a manufacturing technique that allows easy modification of the implant shape to meet the individual needs of each patient. Until recently, research has concentrated on a variety of features of this topic, such as 3D printing using various materials or printing procedures, to create implants with distinct forms, mechanical properties, and release profiles. For example, Sarah and colleagues developed a biodegradable subcutaneous implant for prolonged drug delivery using 3D printing. Five implant designs were created. It was found that the release rate varied based on the implant design and drug characteristics. In addition, a rate-controlling membrane was constructed, which further delayed the release from the manufactured implants, indicating its potential utility for chronic illnesses [54].

Apart from the implantable drug delivery system of the dosage form, Suwanpitak and his team developed an add-on device for dry powder inhalers (Accuhaler) prepared via 3D printing. This add-on device could improve drug administration efficiency in patients with limited inspiratory capacity, including young children, the elderly, and those with COPD. The add-on device consisted of a motor and fan that could be attached to the Accuhaler. The use of the add-on device in conjunction with a sufficient inhalation flow rate led to an increase in the DPI-emitted drug dose for patients with low inspiratory rates, thereby facilitating the administration of adequate drug doses for improved treatment outcomes [55].

For advanced transdermal medication delivery applications, 2D and 3D printing is used. The applicability of several printing technologies has been researched for the direct or indirect printing of microneedle arrays or for the modification of their surface through drug-containing coatings [52]. Using a digital light processing 3D printer, Lim and coworkers created a splint with microneedles for the treatment of trigger fingers. Using the device to puncture the skin prior to the topical administration of diclofenac gel, they successfully increased the drug amount that permeated the skin demonstrating that 3D printed patient-specific microneedle devices can be effective in systems designed using the 'poke-and-patch' strategy [56]. Personalized orthodontic retainers containing clonidine hydrochloride have been fabricated using a 3D printing process involving hot–melt extrusion. This invention addresses the unanticipated side effects caused by the in vivo burst release of clonidine hydrochloride [53]. Another innovative 3D-printed medical device for drug delivery systems is a customizable design mouthguard. The study showed the first-in-human use of the 3D-printed mouthguard and demonstrated the immense potential of 3D printing as a platform for the development and translation of next-generation drug delivery devices for personalized therapy [57].

3.4. Customized Design

One benefit of 3D printing technology is its ability to construct various shapes of dosage units to suit patient anatomy and preferences. A standard FDM printer, inspired by Starmix® gummy sweets structures, was used in the production of taste-masked chewable tablets for pediatric patients [58]. In addition to drug-infused gummy candies, a variety of pediatric pharmaceutical dosage forms have been created and manufactured utilizing various 3D printing processes. Januskaite and colleagues evaluated the preference of children for 3D-printed tablets (Printlets™) made using four distinct 3D printing procedures, namely digital light processing, selective laser sintering, semi-solid extrusion, and fused deposition modeling. The digital light processing printlets were determined to be the most visually appealing to the children. Digital light processing provides an appropriate visual appearance (color and shape) for printlets, which is crucial for a child's first impression. However, pleasant flavor and chewing texture are two essential aspects that must be considered when developing formulations for children [59]. Another actual case study that used 3D-printed dosage forms in a trial was the study by Goyanes and his colleagues. They used a semi-solid extrusion 3D printer to prepare a small batch of isoleucine in the form of a chewable formulation at the point of dispensing (in a hospital setting) to treat a rare metabolic disease in children [36].

In geriatric patients, the most typical criterium is a reasonable dosage form size that is easy to swallow, which is relatively comparable to the requirements for pediatric dosage forms. Therefore, fast-dissolving tablets and films have been invented for elderly patients [60][61][62][63]. Several 3D printing techniques have been utilized to manufacture pharmaceutical dose forms with rapid dissolution or disintegration. Sorato and his team, for instance, employed the 3D printing process of fused deposition modeling to create fast-dissolving oral dose forms. Typically, fused deposition modeling 3D printing technology can only produce solid objects, which might result in cracking, chipping, and difficulty dissolving [64]. This is due to the fact that the printing materials used for fused deposition modeling are primarily thermoplastic polymers with insoluble or slow-dissolving characteristics. Thus, the authors added sugar alcohol to a formulation of poly (vinyl alcohol) filaments, resulting in a faster drug release [65]. In addition to the rapid dissolution formulation property, the concept of drug identification by color or shape connected to pharmacological categories is favored for geriatric patients. The embossing designs, which indicated the time for administration for an individual person, are also suggested to be useful for patients with cognitive impairments and health assistants who have to provide medication to these patients [66]. Moreover, 3D-printed tablets with embossing designs were developed for patients with visual impairment and blindness. Tablets embossed with Braille and Moon patterns were prepared using a desktop SLS printer. In addition to helping patients identify their medications and decreasing the risk of medical errors, patient compliance may be improved [67].

Lastly, 3D printing can be applied to scaffold applications. The 3D printing technique has several advantages over traditional scaffold preparation. For example, 3D printing allows for the fabrication of polymeric cellular materials with empty spaces in a well-defined periodic structure. Moreover, it can create scaffold tissues of precise and individualized size and shape for each individual patient. And recent 3D printing technology demonstrates the possibility of industrial scaffold production [68]. Tammaro and his team produced thermoplastic polymeric (polylactic acid (PLA)) foams with solubilized physical expanding agents using a continuous 3D printing process. In terms of morphology, the resultant foamed strands and hierarchical structures are novel and exhibit controlled local porosity and superior mechanical properties that are suitable for scaffold structures [68].

3.5. Telepharmacy

The delivery of pharmacy services at a distance can be accomplished using telecommunication and information technologies, such as videoconferencing and electronic health records. This practice is known as “telepharmacy” [69]. Telepharmacy refers to the remote provision of pharmacy services, often in underserved areas where access to healthcare facilities is limited. Telepharmacy benefits patients by enabling remote pharmacies to overcome logistical challenges and improve patient care. Three-dimensional printing technology may have the potential to be utilized in telepharmacy in various approaches. Three-dimensional printing can be used to prepare personalized medication for patients who are located at a distance from one another. Adjustments to the dosage of the medication can be made in accordance with the clinical results, such as changes in the patient’s heart rate, blood pressure, and blood sugar level. These clinical outcomes can be remotely monitored by wearable devices, such as sensors or patches [70][71]. Patients with chronic disease conditions that are stable and under their control can greatly benefit from this concept. This can give patients the convenience to reduce their travel, which also helps to limit the number of people in the hospital [72]. In the event of a natural disaster or other emergency that disrupts supply chains, 3D printers can be used to produce essential medications and medical supplies on-site, ensuring continued access to healthcare.

In addition, 3D printing can help telepharmacy facilities provide important medical devices. With the use of 3D printers, customized medical devices and aids, such as pill organizers, inhaler spacers, prosthetic components, and orthopedic supports, can be manufactured. These devices can be adapted to the specific requirements of each patient, thereby enhancing patient comfort and adherence to treatment plans. Telepharmacy facilities can collaborate with remote healthcare professionals using 3D printing technology. Experts can provide guidance, evaluate prescriptions, and guarantee the quality and safety of 3D-printed medications and medical devices by sharing their digital designs. This collaboration improves patient outcomes by facilitating access to specialized knowledge and expertise.

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