# 3D Printed Buccal Films for Personalized Drug Delivery

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**Abstract:** Advancements in pharmaceutical technologies have led to the personalization of therapies over the last decade. Three-dimensional printing (3DP) is an emerging technique in the manufacturing of pharmaceutical dosage forms because of its potential to create complex and customized dosage forms according to the patient's needs. Among the various 3DP techniques based on different functioning mechanisms, fused deposition modeling (FDM) 3D printing is a versatile and widely used method with advantages such as precision of quantity and the ability to incorporate different fill densities. This method is also economical and easily produces complex designs. Hot-melt extrusion (HME) is an established technique in pharmaceutical manufacturing that is utilized in the development of filaments which are used as "ink roll" or feedstock material in FDM 3D printing. This review discusses the various stages involved in FDM 3D printing, including feedstock filament preparation using HME, digital dosage form designs, filament characterization, and various novel applications, and future perspectives.

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## Introduction:

With the recent FDA-approved 3D printed drug product (Spritam®), research interest in 3D printing technology has been growing. 3D printing is believed to be the most effective way to attain patient-focused pharmaceutical product development. The application of 3D printing in the pharmaceutical field has been an emerging field of research because of its ability to customize therapy to meet the requirements of patients (Jamróz et al., 2018b). Owing to its flexibility and ease of adaptability, 3D printing technology is expanding from the early stage of development to the manufacture of end products with simplified design and production cycles (Zema et al., 2017). Because of its automated process and low operating cost, 3D printing is gaining popularity over traditional manufacturing processes in on-demand production (Norman et al., 2017)(Zhang et al., 2018).

3D printing is the process of creating objects three-dimensionally by depositing material in a layer-by-layer fashion from digital designs. The concept of 3D printing was first developed in the 1980s by Charles Hull for fabricating plastic devices from photopolymers (Pucci et al., 2017). It was later used in various other fields, including automotive, aerospace, robotics, and consumer goods industries for rapid prototyping purposes (Azad et al., 2020). After FDA approval of the first 3D printed pill, Spritam®, in 2015, the application of 3D printing has gained tremendous attention in the pharmaceutical field (Warsi et al., 2018). Although there are various 3D printing approaches such as stereolithography (SLA) and inkjet-powder bed, this review focuses mainly on fused deposition modeling (FDM) 3D printing.

The application of 3D printing techniques might facilitate the generation of precision medicine that aims to tailor therapeutic strategies to meet the unique physiological and lifestyle needs of individual patients (Afsana et al., 2019). Most of the pharmaceutical tablet dosage forms manufactured by the existing large-scale manufacturing processes are produced with one-size-fits-all approaches in which the dosage is based on Phase 3 clinical studies. The disadvantage of this approach is that the administered dose might fall outside the optimum dose for individual patients based on the patient's clinical requirements and may lead to toxicities, adverse events, or a lack of therapeutic activity (Goyanes et al., 2015b)(Wang et al., 2016). This is usually addressed by tablet splitting or compounded medications. However, tablet splitting can break the integrity of any coating material, which might alter the drug release and lead to ineffective drug administration. Compounded medicines often fail in dose accuracy and may become ineffective when

patients do not follow dosing instructions (Shah et al., 2010). Moreover, this will lead to a pill burden for patients. Orphan drugs for treating disease conditions affecting fewer than 200,000 people entail a small market in the pharmaceutical industry. As contemporarary manufacturing equipment are intended for large scale industrial manufacturing, 3D printing is highly adavntageous in development of suitable dosage forms. Recently Saydam et al., developed rufainamide tablets for Lennox-Gastaut Syndrome using FDM 3D printing, which is is a rare form of childhood epilepsy (Saydam and Takka., 2020). The 3D printing technique may offer solutions to all these problems because of its ability to selectively deposit and/or fuse (multiple) materials in a layer-wise manner, offering reproducibility in the creation of personalized pharmaceutical dosage forms by utilizing precise control of factors as well as active pharmaceutical ingredient (API) compartmentalization for combination of drugs (Curti et al., 2020).

The advantages of 3D printing over conventional tablet manufacturing methods include personalization, improved product complexity, and on-demand manufacturing (Norman et al., 2017). This technology offers tailoring of doses according to the patient's body mass index, metabolism, genetic variations, and other comorbid conditions, and also enables the production of drug products with tailored release profiles and designs (Trenfield et al., 2019)(Nukala et al., 2019b). It allows the combination of the patient's daily medications into a single multi-drug dose or polypill. This personalization could improve treatment adherence, especially for pediatric and geriatric patients. Furthermore, 3D printing may be applied in the manufacture of implants such as tracheal splints, bone grafts, and multi-drug implants for chemotherapy (Trenfield et al., 2019); it provides a simple and uniform drug that can easily achieve a targeted release profile. Printing in different shapes attracts the pediatric population where treatment adherence is a major problem. Another major advantage of 3D printing is on-demand manufacturing, which could be useful in time- and resource-constrained settings such as emergency rooms, military operations, and disaster areas, as drug products can be successfully printed according to requirements (Bandari et al., 2021).

**Methodology**

We performed a non-systematic literature review aiming to provide the most up-to-date information regarding three-dimensional printing technology in drug design and development, highlighting the feasibility, challenges, and potential applications of this technology. The review also focuses on the potential impact of the 3D printing of drugs on the pharmaceutical industry and personalized medicine. For the literature search, we used the databases Medline/PubMed, Google Scholar, and Science Direct using the search terms "3D printing", "three-dimensional printing", "3D bioprinting", "3D printed drugs", "additive manufacturing", and "drug delivery systems". We focused on journal articles published in the English language between the years 2000 and 2023. Theoretical treatments and experimental studies were covered, in general, with an interest in both from a drug development perspective.

**The History of 3D Printing**

It is important to mention that, during the invention of 3D printing in the industry, individuals pursued patents and pioneered innovations that led to the diverse applications of 3D-printing techniques known today. However, rapid prototyping was one of the earliest additive manufacturing techniques, enabling the rapid creation of prototypes to accelerate the testing of product viability before market introduction.

It is worth mentioning that, in 1859, a French "photosculptor" named François Willème demonstrated the world's first "3D scanning" technology by using 24 cameras to simultaneously photograph a subject from different angles. A few years later, in 1892, inventor Joseph E. Blanther was awarded a patent for a method of creating 3D topographical maps using a layering method, similar in concept to today's 3D printers.

Milestones in 3D-printing development from the early 1960s to the early 2000s in both the industry and medical systems [8]

The University of Battelle Memorial Institute in Ohio explored using photopolymers to create 3D-printed objects during the 1960s.

The invention of solid photography by the Dynell Electronics Corporation. This technology aimed to cut cross-sections based on a computer model, which represents one of the main 3D-printing-stage principles during the 1970s.

Hideo Kodoma from the Nagoya Municipal Industrial Research Institution in Japan published the principles for the automation of 3D models using photosensitive resin and rays. These were the first approaches toward stereolithography in 1980–1981.

Stereolithography (SLA) was invented in 1984. The first stereolithography patents by Alain Le Méhauté,

Olivier de Witte, Jean Claude André in France, and Charles 'Chuck' Hull existed in the USA

Dr. Hideo Kodoma patented the SLA invention in 1986.

The first commercial SLA printer in the world was produced by 3D Systems in 1988.

Scott and Lisa Camp founded "Stratasys" in 1989. They filed a patent for the formation of rapid prototyping, laying the groundwork for the first principles of fused deposition modeling (FDM).

Hans Langer formed the company electro-optical system (EOS) in late 1989, which made the fabrication of 3D parts directly from computer design models possible.

Carl Deckard developed the concept of the selective laser sintering process (SLS). The process consisted of a selective solidification of powder using a laser beam to fuse powdered materials layer by layer.

The 3D-printing industry split into two branches in the early 1990s: one focused on engineering complex parts, and the other on concept development and functional prototyping.

By the late 1990s, three companies remained in the 3D industry: Stratasys, 3D systems, and EOS.

The first production of SLS printers occurred in 1992.

Deckard founded "Sinterstation" in 2000 launching SLS technologies into the industry.

In the early 2000s, 3D printing gained interest and importance in the medical field. Oral fast-disintegration tablets, such as the FDA-cleared Spritam® (Levetiracetam), have been fabricated by SLA at Aprecia Pharmaceuticals, Blue Ash, Ohio, USA, while other ME techniques have been used for the fabrication of scaffolds and implants loaded with drugs intended for controlled release [9,10,11].

After 2010, advancements in bioprinting and drug-loaded implants occur. Cinnarizine is formulated by 3D-printing technology into a gastroretentive dosage form [12].

In 2003, Dr. Thomas Boland filed the first patent for a technique that involved the printing of viable cells.

In 2004, Gabor Forgacs patented a scaffold-free bioprinting technique that enabled the simultaneous printing of multiple cells.

In 2005, 3D-printed hydroxyapatite scaffold designs, based on anatomical information from individualized patient images, emerged.

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With the advancement of FDM technology by Stratasys in 2005, two open 3D-printer projects came to life: Fab@Home and the RepRap Movement. The goal of both projects was to make 3D-printer designs affordable to a wider audience.

In 2007, the first RepRap 3D printer, named "Darwin", was released, followed by the later versions of "Mendel", "Prusa Mendel", and "Huxley".

In 2009, Organovo was awarded the first NIH grant for bioprinting vessels.

Engineers at the University of Southampton in the U.K. designed the world's first unmanned 3D-printed aircraft. The total cost was less than USD 7000.

In 2015, the Swedish company Cellink released for sale the first commercial bio-ink. It is made from nanocellulose alginate, a material derived from seaweed, and can be used for printing tissue cartilage.

FDA approval of Spritam (the first 3D-printed drug) in 2018.

In 2018, a gastric floating system was developed with riboflavin, showing an excellent floating ability of up to 3 days. This was a new way of achieving optimum drug release and thus showed this by merging different 3D-printing techniques; new frontiers were established for generating sophisticated drug delivery systems (Fu et al., 2018) [13].

Emerging developments in bioprinting also led to the fabrication of tissue scaffolds able to deliver drugs right to the disease sites, with greater potential for effectiveness in applications within regenerative medicine [14,15,16].

Advances in drug-loaded implants and bioprinting in 2023.

To provide a concise overview of the key milestones in the development of 3D printing technology, a timeline summarizing the historical progression from the 1960s to the present has been included in

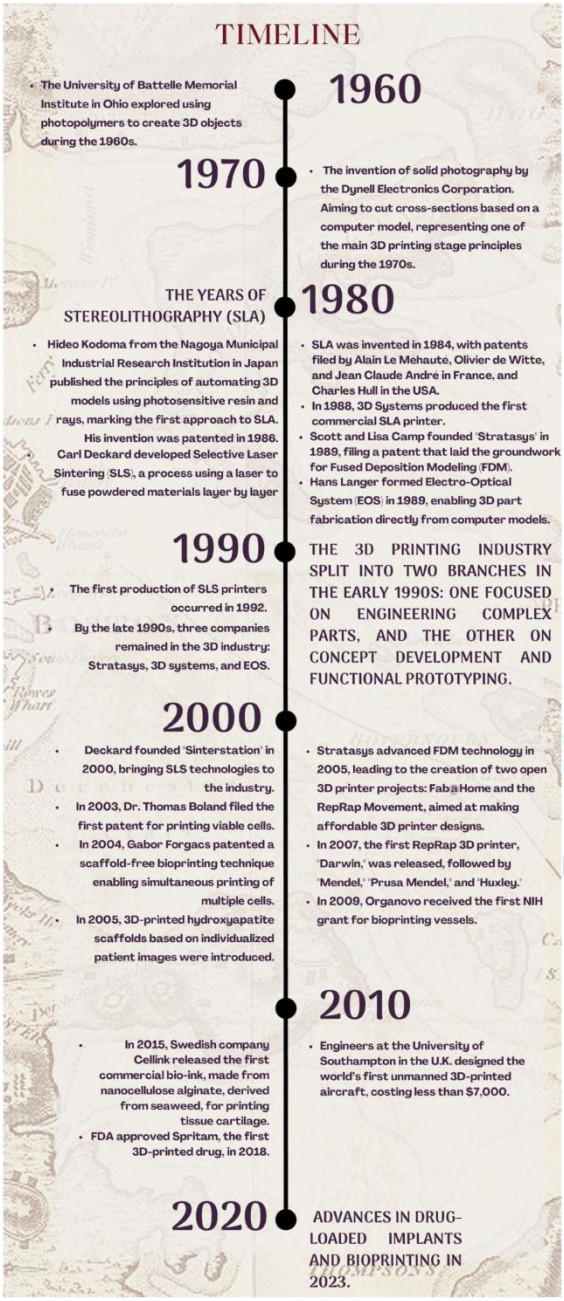


Figure 1. Brief historical overview of 3D printing.

Charles W. Hull—The Pioneer of the 3D-Printer Industry [17]

Charles W. Hull is a well-known inventor and engineer recognized for his innovations in the creation of 3D-printing technology. Hull is considered one of the pioneers of 3D printing for his major contribution to the field through the invention of stereolithography (SLA). Hull's work initially involved using UV light to harden tabletop coatings, which inspired his use of UV light in the SLA process. The first object he built using this technology was a small cup, 5 cm tall. In 1984, he co-founded 3D Systems, which gained popularity in the automobile and aerospace industries and was widely used in medical applications [8].

4. Basic Principles and Methods—The Traditional Methods of Drug Manufacturing

The future of medicine appears to be shifting toward personalized dosage regimens, tailored to individual metabolic profiles [1]. Advances in gene sequencing

offer promising avenues for enhancing drug delivery efficiency [16], highlighting the significant variability among individuals.

Among various technological innovations, additive manufacturing (AM), or 3D printing, is especially emerging in pharmaceutical applications, aiming to offer personalized solutions. This technique involves translating computer-aided design (CAD) models into physical objects through layer-by-layer construction. Its versatility has elevated its significance in drug delivery over the past decade [18].

Traditional drug delivery methods include oral drugs, scaffolds, transdermal patches, rectal or vaginal delivery, implants, and intravenous devices [18].

Material extrusion, such as fused deposition modeling (FDM), stands out as one of the most cost-effective methods for printing drug delivery systems. It processes a wide range of materials, including thermoplastics, waxes, gels, pastes, and clay, allowing for versatile fabrication. FDM operates by heating an input filament to a molten state and depositing it layer by layer onto a printing platform using a moving nozzle. This method is applied for oral tablets, implants, scaffolds, iodine delivery, rectal/vaginal delivery, transdermal patches, meshes, and catheters [18].

Vat polymerization techniques, such as stereolithography (SLA) and digital light processing (DLP), offer high-resolution printing capabilities. SLA utilizes a UV-light source to solidify liquid resin layer by layer, while DLP uses visible light to achieve the same result. Although these techniques have fewer compatible polymers, they excel in producing drug delivery channels loaded with various drugs. SLA and DLP can be used for fabricating oral drugs, scaffolds, and transdermal patches [18].

Binder jetting/inkjet printing (IJ) deposits ink on a powdered bed, creating layers that bind together to fabricate oral tablets, orodispersible films (ODFs), and implants. Notably, this technique was used to produce the first FDA-approved 3D-printed drug with ZipDose® technology. ZipDose® technology is a platform that allows for the rapid disintegration of high-dose medications in a small volume of water. Its applications include oral tablets, orodispersible films (ODFs), and implants [18].

Table 1 provides a comprehensive comparison of the various 3D-printing techniques employed for the development of pharmaceuticals. Their applications include oral drugs, implants, scaffolds, and transdermal patches, and the special features of each process.

Direct energy deposition (DED) techniques, while limited by material availability and accuracy, still have potential for printing drug-loaded implants and scaffolds. DED involves locally melting a powdered or filament material using a laser or electron beam and then depositing it layer by layer onto a heated substrate [18].

Powder bed fusion encompasses techniques, like selective laser sintering (SLS) and selective laser melting (SLM), which fuse powdered materials layer by layer to create solid objects. These techniques are valued for their accuracy and strength, making them suitable for implants and scaffolds in drug delivery systems.

Material jetting (IJ) involves jetting droplets of material onto a substrate and solidifying them, typically using UV light. It offers a high-resolution and surface finish, making it suitable for fabricating oral tablets and transdermal patches.

Sheet lamination builds objects by stacking layers cut from sheets of material. While less commonly used for pharmaceutical manufacturing, it can be suitable for certain drug delivery applications where layer-by-layer construction is advantageous.

Ensuring regulatory compliance presents substantial challenges in the additive manufacturing of pharmaceuticals. In this respect, clear regulatory pathways are needed for the full integration of 3D printing into clinical settings to guarantee the quality and safety of 3D-printed medications. In this context, it is essential to address specific challenges in material selection, printability, and scalability, which are crucial for the wider adoption of these technologies [3]. Issues, such as drug degradation, improper loading percentages, and toxic reactions, necessitate rigorous in vivo testing for biocompatibility and suitability. Regulatory approval from bodies like the FDA is mandatory before commercialization. Draft guidelines issued by the FDA in 2016 provide a regulatory framework, emphasizing the importance of in vivo, in vitro, and clinical evaluations for printed drug forms [18].

The National AM Innovations Cluster (NAMIC) in Singapore and similar initiatives worldwide highlight the growing emphasis on regulating additive manufacturing in the pharmaceutical sector. Forecasts indicate significant revenue growth in additive manufacturing, underscoring the importance of addressing regulatory and legal challenges to ensure safe and effective drug delivery systems [18,31,32].

**Applications of 3D Printing for Pharmaceuticals**

The strategic integration of 3D-printing technology in pharmaceutical manufacturing promises extensive advancements, aligning medication formulations precisely with individual patient needs. The importance of 3D printing lies in its ability to revolutionize drug dosage forms and enhance therapeutic outcomes through tailored drug delivery mechanisms.

The integration of 3D printing in pharmaceuticals presents revolutionary steps in tailoring drug formulations to patients' needs, which can improve therapeutic outcomes through personalized drug delivery mechanisms. Various 3D-printing technologies, including powder-based, extrusion-based, inkjet-based, and laser-based methods, enable the precise creation of complex drug delivery systems and formulations. For example, 3D printing facilitates the development of child-friendly formulations, such as chewable tablets with specific dosages and flavors. It also improves compliance among pediatric patients. Additionally, integrating 3D printing with artificial intelligence can enhance quality control and customization, ushering in a new era of digital pharmacy [3].

For instance, powder-based methods, such as selective laser sintering, fuse powdered materials layer by layer to provide robust and accurate drug delivery devices. Inkjet printing of indomethacin-loaded transdermal films resulted in promising drug release and permeation properties, making it a suitable technique for personalized transdermal medication [33]. Extrusion-based methods, like fused deposition modeling, are associated with the use of heated filaments to build an object layer by layer and provide cost-effective and versatile solutions for drug fabrication. Furthermore, inkjet printing was successfully used for the preparation of amitriptyline hydrochloride tablets, showing promising drug release profiles combined with effective drug loading [34]. Selective laser sintering was also applied to manufacture paracetamol tablets that exhibited strong structures and pH-independent drug release, with no evidence of drug degradation during this process [35]. Further development using SLS technology resulted in orally disintegrating paracetamol tablets with enhanced drug release profiles, optimized through laser scanning speed for a rapid onset of action in patient care [36]. Additionally, stereolithography technology was used for the printing of drug-loaded hydrogels, including ibuprofen-loaded hydrogels. This resulted in higher drug release due to the high water content in the hydrogel, demonstrating its promising potential in personalized drug delivery systems (Martínez et al., 2017) [37]. In another study, SLA technology was used to fabricate hydrogels loaded with ascorbic acid. Hydrogel structures with geometric shapes demonstrated controlled release characteristics, with the highest release rates observed in honeycomb and coaxial annulus geometries, further demonstrating the use of SLA technology for drug delivery applications (Karakurt et al., 2020) [38]. Inkjet-based methods, such as binder jetting, involve depositing droplets of liquid onto substrates to create complex drug structures, as seen in the FDA-approved 3D-printed drug, Spritam (Levetiracetam). Laser-induced methods, which include stereolithography, use UV light for the solidification of liquid resins and allow for high-resolution printing of oral drugs and implants.

Different PBF techniques have been developed into various drug delivery devices of high accuracy, including, but not limited to, implants, for localized release. Inkjet printing of ketoprofen-loaded buccal films demonstrated excellent drug release and permeation, proving its potential in personalized drug delivery systems [39]. Additionally, orodispersible tablets offer advantages, such as fast drug disintegration and easy swallowing, which help pediatric and geriatric conditions. Research on ondansetron orodispersible printlets showed rapid disintegration in less than 15 s, with more than a 90% released within five minutes, demonstrating its quick therapeutic response [40]. Implants created using the PBF technique can be designed to deliver drugs at the disease site, offering localized treatment while limiting systemic exposure. Three-dimensional printing of paracetamol tablets achieved a zero-order release profile, which may provide more consistent in vivo drug release and enhance the therapeutic outcomes for chronic diseases [41]. This is particularly valuable for cancer treatment, where precision and minimal side effects are critical. Additionally, PBF enables the creation of complex geometries with internal channels that can house multiple drugs, allowing for controlled release over time, which is particularly needed for diseases requiring chronic treatment [21].

Several investigations have focused on bioprinting medication-loaded, patient-specific scaffolds for tissue regeneration. three-dimensional printing methods have also applied inkjet printing to several biologics. Inkjet printing of lysozyme onto buccal films was successfully performed without compromising mechanical or mucoadhesive properties, showing the effectiveness of inkjet

printing in making buccal films for the delivery of biologics [17]. Moreover, the inkjet printing technique has been applied to prepare the oromucosal dosage form. Lidocaine hydrochloride and piroxicam were printed successfully onto fibrous matrices and showed good drug entrapment and solidification. The printed drug closely matched the theoretical dose, demonstrating the accuracy of 3D-printing technologies in drug delivery systems [42]. Scaffolds can be designed to release numerous bioactive agents, such as growth factors and antibiotics, thereby enhancing tissue regeneration or preventing infection. Tissue engineering makes use of scaffolds to support cellular ingrowth, while bioprinting allows the deposition of materials with defined precision and, as such, builds matrices that are similar to the native ECM. A case in point is the use of scaffolds in bone regeneration, where 3D-printed scaffolds loaded with BMPs have shown considerable improvement in healing times and bone density. Moreover, bioprinting is being studied for its potential application in producing scaffolds with controlled drug release to support long-term tissue recovery [43].

Despite these innovations, the field faces considerable technical and regulatory challenges. Regulatory frameworks need to catch up to accommodate the specific characteristics of 3D-printed pharmaceuticals and ensure the safety and efficacy of these products through new guidelines. Scaling up introduces its own set of challenges, requiring development to bridge the gap between prototype innovation and mass production [14,18,22].

Fundamental to this innovation is a spectrum of materials selected for their biocompatibility, solubility, and mechanical properties. Materials, such as polylactic acid (PLA), polyvinyl alcohol (PVA), and hydroxypropyl methylcellulose (HPMC), emerge as frontrunners, facilitating the formulation of implants, scaffolds, and drug delivery systems with unparalleled precision and safety [2,25,26].

The advantages of 3D printing expand beyond material selection. Its fundamental ability to customize dosage forms, intricate geometries, and drug-release profiles marks a new era of patient-centric healthcare. For instance, the fabrication of polypills tailored to individual medication regimens exemplifies 3D printing's potential to streamline treatment protocols and enhance patient adherence [10]. Specific examples include the design of a multi-layered polypill containing six drugs using a novel stereolithographic method, which allows for better control of the drug release from the polymeric matrices and improves patient compliance through the consolidation of several medications into one dosage form [30]. Another example is the five-in-one combination polypill with defined immediate and sustained release profiles, demonstrating that 3D printing can be used to create complex tablets containing multiple drugs to treat different conditions with varying kinetic requirements simultaneously [9].

Moreover, 3D printing catalyzes breakthroughs in the development of medical devices, particularly focusing on implantable drug delivery systems. One significant example is the development of 3D-printed biodegradable stents for cardiovascular applications. Such stents can locally deliver drugs to the site of implantation with controlled release and reduced systemic side effects, as seen with antibiotics for treating osteomyelitis, where structural support is combined with localized delivery.

It has also enabled microneedle production in pain-free drug delivery. One notable example is the delivery of cisplatin using 3D-printed microneedles. In this study, microneedle arrays were fabricated, demonstrating good release rates and effective anti-cancer activity, proving the potential of microneedles in targeted chemotherapy delivery [44]. These microneedles are designed to dissolve and release the drug directly into the bloodstream after penetrating the skin. By combining drug therapy with patient-specific implants created through 3D printing, this approach offers optimized treatment efficacy, comfort, and safety for patients [18,19,20].

However, the promise of 3D printing is met by regulatory and technical challenges. The regulatory framework is always behind technological development, and it needs comprehensive guidelines to set up the quality and safety measures for 3D-printed pharmaceuticals. For example, the FDA has published guidance for 3D-printed medical devices, but it has not yet fully addressed pharmaceuticals leaving a gap in regulatory oversight that is clouding the approval process for new 3D-printed drugs. Additionally, guidelines are currently being formulated by the European Medicines Agency and other international regulatory bodies, but comprehensive standards have not yet been implemented. Moreover, 3D-printing technologies evolve so rapidly that existing regulations quickly become outdated, requiring continuous updates to regulatory frameworks to keep pace with technological advancements. Additionally, large-scale production presents another obstacle; several steps must be taken to bridge the gap between innovation and mass production [1,6,18].

**Feasibility—The Effectiveness of Printed Drugs**

We now explore the effectiveness of printed drugs, looking at their efficacy, safety, bioavailability, long-term outcomes, and cost-effectiveness. It enhances efficiency and cost-effectiveness in pharmaceutical manufacturing. By allowing on-demand production and reducing wastage, it reduces time and costs incurred in production, hence forming a sustainable alternative to traditional techniques [45]. Based on various clinical trials and studies, we gain insights into the therapeutic outcomes and impact of 3D-printing technology on pharmaceutical development.

Starting with efficacy and therapeutic outcomes, one example is the FDA's approval of Spritam (Levetiracetam) in 2018 [11]. Ongoing research emphasizes the potential for tailored medication formulations, especially for pediatric and geriatric patients, ensuring optimized therapeutic impact through dimension-specific product designs [11].

Clinical trials of 3D-printed pharmaceuticals have presented promising results. A pediatric patient trial showed the efficacy of orodispersible film, which was printed using binder jetting technology, in improving adherence [2]. Another trial that tested drug-loaded implants for localized cancer treatment showed improved targeting of drugs with reduced side effects [14]. A clinical trial in gastroretentive floating tablets further demonstrated the capability for zero-order drug release and, hence, more precise and regular chronic medication. Three-dimensional printing was used to manufacture floating tablets in this trial, presenting a significant increase in bioavailability with improved compliance in patients [28]. Another approach is the polypill, whose stereolithography-manufactured, multi-layer, 3D-printed system contained six drugs, evidencing its potential in the consolidation of complex medication regimens. This has improved patient compliance, especially among the elderly, as fewer doses are taken per day [30]. Three-dimensional printing influences drug release kinetics, since some studies revealed that binder volume affects drying time and residual solvent release, while powder and ink properties and porosity variations influence product quality attributes. Also, observations of drug dissolution profiles designate the impact of layer height and scale count on release kinetics [11].

It is crucial to acknowledge the advantages and limitations of 3D-printing technology in terms of the assessment of the safety profile and tolerability of printed drugs. Regulatory oversight is essential to ensure the safety and effectiveness of medication production, given the variables affecting the efficiency and health of computationally engineered dosage forms [11].

Regarding bioavailability and pharmacokinetics, the SLA method allows for flexibility in object geometry and porosity, resulting in fast-disintegrating dosage forms without the need for binding agents. The approach of SLS, on the other hand, offers advantages for strong dosage formulations [11].

Concerning the long-term outcomes and approval status, Spritam stands as a pioneer in commercially available pharmaceutical drugs authorized by the US FDA [9] and represents a significant milestone in the integration of 3D printing into pharmacotherapy. While legislative decisions are increasingly focused on advancing science and technology, 3D printing remains a key approach in pharmaceutical development [11].

In terms of cost-effectiveness and healthcare economics, 3D printing demonstrates sustainable advantages over conventional manufacturing methods, revolutionizing drug production and distribution. With the global 3D-printing market projected to have a substantial economic impact by 2025, pharmaceutical companies can adopt this technology to enhance efficiency and accessibility [11]. The effectiveness of printed drugs encompasses a complex evaluation spanning efficacy, safety, bioavailability, long-term outcomes, and economic considerations.

**Challenges of 3D Printing Drugs**

Despite the promising opportunities presented by this technology, various technical and regulatory difficulties obstruct its widespread implementation in the pharmaceutical and healthcare sectors [46].

One significant challenge lies in the selection of suitable materials for the 3D printing of drugs. Factors, such as biocompatibility, stability, and regulatory approval, must be carefully considered to ensure the safety and efficacy of the printed formulations. In addition, issues related to printability, including nozzle clogging, layer adhesion, and print accuracy, pose significant obstacles that can affect the quality and consistency of printed drugs.

Another remarkable challenge is to achieve uniform drug dosage within printed formulations. Enhancing dose consistency and accuracy is essential to meet regulatory requirements. Scalability, particularly in the mass production of drugs, remains a concern. Addressing issues such as production time, cost-effectiveness, and regulatory compliance on a larger scale is essential for the widespread adoption of 3D printing in pharmaceutical manufacturing.

Regulatory barriers further hinder the approval of 3D-printed drugs. The lack of specific regulatory guidance for drug production using 3D-printing technology poses a problem to its implementation in the healthcare system. While the FDA has issued regulations for the use of 3D printing in medical devices and prosthetics, drug production remains unexamined [46].

Intellectual property issues also present challenges in the 3D printing of drugs, including patent infringement, technology licensing, and protection of proprietary formulations. These legal considerations add complexity to the development and commercialization of 3D-printed pharmaceuticals.

Technological factors, such as the use of heat, solvents, and light in 3D printing processes, may affect the stability and quality of printed drugs [45].

In post-printing products, essential steps to overcome are the challenges of quality control and developing reliable evaluation methods. Non-destructive techniques, such as NIR and Raman spectroscopy, offer promising solutions for the real-time evaluation of drug product quality at production sites, such as clinics and hospital pharmacies [46].

While various types of 3D printers have been explored for pharmaceutical dosage form production, ensuring compliance with good manufacturing practice (GMP) standards remains a challenge. Efforts are being made to develop compact printers that meet GMP requirements, with companies like FabRx taking the initiative [46].

8. Issues/Limitations of 3D Printing and Future Potential Applications

Currently, 3D printing encounters several limitations that shape its present applications. Particularly, while the technology enables the creation of pill molds and direct printing using drug powders as raw materials, it battles with challenges inherent in different printing technologies, like FDM, SLA, and SLS [14].

Despite its current limitations, the future holds promise for 3D printing, particularly in pharmaceuticals. Three-dimensional printing in personalized medicine envisions the customization of nutritional products, organs, and drugs. It is expected that this tendency will spread throughout pharmacy settings, potentially altering the production and delivery of pharmaceuticals. With the advent of on-demand drug printing, pharmacies can receive medication formulations via email, leading to cost-effectiveness and increased patient-centric healthcare solutions [47].

Another noteworthy advancement to mention in 3D-printing technology is the bioprinting of complex organs. Progress in printing vascular networks bodes well for the potential fabrication of viable organs. Some breakthroughs include the successful fabrication of complex tissues, such as liver and kidney tissues, opening the door for live implants and tissue models for drug discovery. In the future, stem cells taken from deciduous teeth can be used as a source of stem cells to develop new tissues and organs [47].

Innovative trends, like in situ printing and implants printed within the human body during surgeries, hold promise for precise lesion repair. Utilizing 3D bioprinting enables the deposition of cells, growth factors, and biomaterial scaffolds to repair internal and external organs. Advances in portable 3D printers and robotic bioprinters for in situ tissue repair signal a combination of precision and efficiency to redefine the future of medical intervention [47].

**Ethical Considerations**

Integrating 3D-printing technology into pharmaceutical drug development raises many questions and pitfalls that need to be addressed.

Ethical challenges in personalized medicine are significant. The primary concerns involve the secure storage and management of patient data used to personalize drugs [7]. Lee (2005) highlights the ethical and social challenges surrounding pharmacogenomics and personalized medicine, emphasizing the critical importance of securing patient data due to their sensitivity and implications for patient privacy and consent [16]. Other issues include the equitable distribution of 3D-printing technologies, ensuring they do not exacerbate existing healthcare disparities among underserved populations [32].

These matters primarily concern the ethical implications of patient data privacy and public access to 3D-drug-printing methods, which could lead to misuse. The customization of drugs through 3D printing relies heavily on detailed patient information, including genetic data, medical history, and specific health needs. Personal health data are essential for creating personalized medications that meet individual requirements. The collection, storage, and use of such information raises concerns about privacy and data security. Protecting patient data from unauthorized access or breaches is crucial. In the event of a personal data breach, skepticism and negativity toward the medical community could give rise to new conspiracy theories, potentially undermining public trust in healthcare institutions. One of the main questions that also arises is the

ownership of the data. Guidelines on patient data ownership are essential to ensure that patients retain control over their personal health information, used solely for their benefit unless agreed otherwise. For the medical community, a prime target would be ensuring that the benefits of 3D printing are distributed at an affordable cost, to make the technology accessible to a great part of the world's population. The industry should aim to make 3D-printed drugs affordable. The potential for misuse of 3D-printing technology in non-pharmaceutical industries is also concerning. The ability to print narcotics on demand opens the door to the unauthorized production of dangerous substances. This could lead to serious public health risks, as individuals might access harmful drugs without proper regulation, potentially creating a black market for 3D-printed narcotics. Establishing regulatory frameworks to prevent the misuse of 3D-printing technology without stifling innovation is vital.

**Discussion**

Three-dimensional printing can introduce breakthrough developments in pharmaceutical drug design. Key advantages of by 3D printing, for which many benefits can be derived by patients, are personalizing the formulation of drugs and customizing dosages. Each of these opportunities is tempered by various technical, regulatory, and ethical challenges if 3D printing is to achieve mainstream use. The effective integration of 3D printing in pharmaceutical manufacturing, on the other hand, depends on technological advancement, clear-cut regulatory frameworks, and ethical concern resolutions.

The FDA's approval of Spritam (Levetiracetam) in 2018 created a new opportunity for personalized medication, particularly for pediatric and geriatric patients, through the use of 3D-printing techniques. Another important aspect is that 3D printing can affect the kinetic properties of drug release. Key factors of 3D printing, such as binder volume, powder properties, and porosity, determine the quality and functionality of drugs.

These AM 3D-printing technologies have revolutionized drug design by making personalized formulation possible targeting patient's specific needs. Manufacturing techniques, such as SLA and FDM, allow the creation of elaborate dosage forms, like polypills and extended-release profiles. Such innovations are imperative in the management of chronic conditions where the precision of dosage and timing is crucial for optimized therapeutic outcomes. Bioprinting technologies offer drug creation upon demand in rare diseases as well [10,22].

Even with these developments, technical challenges are still present. Material selection, printability issues, and quality control are major problems. Homogeneity of drug dosage in the printed formulations is very important for regulatory compliance and a desired therapeutic outcome. Moreover, issues concerning scalability, mainly related to mass production, should be tackled if 3D printing is going to be applied in pharmaceutical manufacturing.

Currently, considering regulatory barriers, very few 3D-printed pharmaceuticals have been approved. While the FDA has issued guidelines on 3D-printed medical devices, there is a lack of good regulatory surveillance for pharmaceuticals, which engenders problems in the approval process for new 3D-printed pharmaceutical drugs. While the EMA, and other international regulatory bodies, have guidelines in various stages of development, no comprehensive standards have been adopted to date.

The impact of 3D printing on healthcare systems and patient outcomes is very promising. It has the potential to revolutionize drug production, distribution, and patient care, from facilitating personalized medicine and optimizing drug delivery mechanisms to increasing the effectiveness of treatments. However, a collaborative platform among the stakeholders to achieve full potential of 3D printing in healthcare is necessary.

Emphasis on establishing regulatory frameworks should be made to make sure that the 3D-printed pharmaceuticals are safe and effective. Encouraging innovation through investment in research is another essential factor. In particular, the ethical concerns related to the use of personal patient data and issues of consent will need consideration regarding the adoption of 3D-printing technology in healthcare.

**Future Directions**

We anticipate further progress of 3D-printing technology, parallel to the changes in regulations and healthcare requirements. Bioprinting and in situ printing are emerging technologies that can expand the use of 3D printing in pharmaceuticals. Consistent regulatory updates, such as refining guidelines for 3D-printed pharmaceuticals, will be vital in shaping the field's direction. We still need to overcome scalability issues and promote interdisciplinary collaboration to maximize the benefits of 3D printing in healthcare.

**Conclusions**

Current technologies in additive manufacturing (3D printing) drive the revolution in drug design and development. For the first time, there are new opportunities to consider each patient's needs individually, which is the case for chronic and complex diseases requiring specific treatments. As the regulation frameworks continue to improve and overcome technical barriers, 3D printing in design and manufacturing will continue to play an increasingly important role in personalized medication.

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