



Advances and Innovations in 3D Printing Technologies for the Development of Customized Pharmaceutical Dosage Forms: A Comprehensive Review

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Abstract

Background: The pharmaceutical industry is experiencing a transformative shift toward personalized medicine, driven by advances in 3D printing technologies. Unlike traditional manufacturing, which relies on subtractive methods, 3D printing employs additive techniques to create complex drug formulations tailored to individual patient needs.

Methods: This review systematically examines various 3D printing technologies, such as binder jetting (BJ-3DP), fused deposition modeling (FDM), and selective laser sintering (SLS). A comprehensive literature search was conducted across multiple databases to analyze the current applications, benefits, and challenges of 3D printing in pharmaceuticals, focusing on its capacity for customized dosing and rapid production.

Results: Findings indicate that 3D printing enhances drug personalization, allowing for tailored dosages suitable for specific populations, such as children and the elderly. The technology facilitates precise control over drug release profiles and accelerates the production process, significantly reducing the time and costs associated with traditional methods. Notable advancements include the development of 3D-printed medications like Spritam®, which exemplify the potential for immediate-release formulations that meet diverse therapeutic needs.

Conclusion: This review highlights the significant impact of 3D printing on pharmaceutical manufacturing, emphasizing its role in advancing personalized medicine. As the technology matures, regulatory

frameworks will need to evolve to ensure safety and efficacy. The future of 3D-printed pharmaceuticals appears promising, with ongoing research poised to refine and expand its applications in tailored drug delivery.

Keywords: 3D Printing, Personalized Medicine, Pharmaceutical Technology, Drug Formulation, Additive Manufacturing

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1. Introduction

Unlike conventional "subtractive manufacturing" methods, 3D printing employs "additive manufacturing" technology, wherein a model is created using computer-aided design software, segmented, and sent to a printer, resulting in the 3D object being built incrementally through layered manufacturing principles [1,2]. As research and development in 3D printing technology progresses, several novel 3D printing techniques have arisen consecutively. The American Society for Testing and Materials categorizes 3D printing technologies into seven distinct classifications based on their technical principles: material extrusion, binder jetting, powder bed fusion, vat photopolymerization, material jetting, directed energy deposition, and sheet lamination, due to the diverse materials, deposition techniques, layering manufacturing mechanisms, and final product characteristics employed by each technology [3,4].

Three-dimensional printing technology is extensively used in the automobile, construction, aerospace, medical, and several other sectors. The pharmaceutical business is now seeing a worldwide surge in research on 3D printing technologies [5,6]. In contrast to conventional preparation technologies, 3D printing provides versatility in the design of intricate three-dimensional structures within pharmaceuticals, facilitates the modification of drug dosages and combinations, and allows for expedited manufacturing and prototyping. This technology enables meticulous regulation of drug release to address diverse clinical requirements, offers substantial flexibility and innovation for personalizing medications, and markedly decreases the time required for preparation development, thereby revolutionizing drug manufacturing technology and altering the methodologies of drug design, production, and application [7-9]. Three-dimensional printing methods have been used to produce many therapeutic items, including immediate-release tablets, controlled-release tablets, dispersible films, microneedles, implants, and transdermal patches [10]. The primary 3D printing methods used in pharmaceuticals are BJ-3DP, FDM, SSE, and MED in material extrusion, as well as SLA [11].

This review seeks to deliver a comprehensive analysis of various prevalent 3D printing technologies, elucidate their current applications and manufacturing principles in pharmaceuticals, and delineate the advantages and disadvantages of each technology along with the appropriate pharmaceutical dosage forms for production. Simultaneously, in conjunction with the literature, we analyze and evaluate the present state of 3D printing technology industrialization within the pharmaceutical sector, as well as the issues or hurdles it encounters.

2. The Benefits of 3D Printing Technology in Pharmaceuticals

The health and safety of medications for certain groups, including the elderly and children, has been a longstanding concern. Children experience growth and development, exhibiting heightened responsiveness and sensitivity to medications; conversely, the elderly have diminished absorption and metabolic capacity, sometimes complicated by the presence of various comorbidities and polypharmacy [12-14]. While current drug dosages are standardized, there is a scarcity of specialized medications for specific populations, and pediatric medications are frequently dosed by manually breaking tablets, which is not only imprecise but may also compromise the integrity of the formulation and lead to adverse reactions [15].

The three-dimensional printing technique is very versatile and may produce tailored medications by modifying model factors like as dimensions, configuration, or fill rate [16]. 3D printing technology can create low-dose personalized medications for pediatric patients, enhancing their appearance and taste to improve adherence. For elderly patients with swallowing difficulties, it can produce loose and porous

formulations, facilitating medication intake [17,18]. Additionally, for patients on polypharmacy, various medications can be partitioned and amalgamated into a single tablet to minimize errors and omissions, thereby enhancing safety and efficacy. Furthermore, uniquely shaped formulations or special symbols can be printed on the surface to assist visually impaired patients. The benefits of 3D printing technology for customized drug delivery facilitate the attainment of personalized medicine [19-22]. Several 3D-printed pharmaceutical companies, such as FabRx in the UK, are advancing towards this objective by producing tailored medications for children with maple syrup urine disease. Additionally, they have installed SSE printers in a pharmacy at a Spanish hospital and have conducted clinical trials on this topic [23].

3. Exact Regulation of Pharmaceutical Release

Tablets, the predominant solid oral dosage form, constitute 70% of total dosage form manufacturing [24]. Conventional manufacturing methods facilitate the production of tablets at reduced costs; nevertheless, they exhibit limited innovation in formulation development, characterized by prolonged development timelines and diminished capacity for on-demand tailored preparations. In contrast to traditional tablets, controlled-release formulations enable meticulous regulation of medication delivery, mitigating adverse effects and enhancing effectiveness. Nonetheless, conventional manufacturing methods provide significant obstacles in the development and production of controlled-release formulations owing to their constraints. Three-dimensional printing technology has significant versatility, making it ideal for the research and production of intricate formulations by integrating several pharmaceuticals, designing complicated models, and modifying printing settings [25].

Triastek's 3D-printed product, T19, which obtained IND approval from the FDA in January 2021, is a controlled-release formulation tailored for the circadian rhythm of rheumatoid arthritis. Patients administer it at bedtime, resulting in peak blood concentration in the morning when symptoms such as pain, joint stiffness, and dysfunction are most pronounced while sustaining daytime blood concentration for optimal therapeutic efficacy, thereby enhancing medication options for patients [26].

4. Accelerated Production Integration

In large-scale drug production, conventional pharmaceutical companies typically possess substantial production capacity to satisfy global demand for traditional medications. Their manufacturing equipment is generally extensive and predominantly uniform, resulting in a deficiency of requisite production flexibility to swiftly execute cleaning and alter the variety of drugs produced. Three-dimensional printing technology may facilitate quick manufacture via compact equipment, reduced production stages, automated and digital procedures, and the flexibility to alter the types of pharmaceuticals produced. SSE technology facilitates the direct substitution of disposable syringes with various medication formulations to accommodate the requirements of multiproduct manufacturing apparatus [27].

Moreover, during the drug development phase, 3D printing technology is particularly advantageous for small-scale drug production that necessitates customization and frequent design alterations, owing to its reduced costs for small-batch production and integrated manufacturing process, which can be crucial in situations with constrained time and resources. This has significant implications for drug development, as Merck employs 3D printing technology to expedite clinical trials, forecasting a 60% reduction in preparation development time and a 50% decrease in the active pharmaceutical ingredient required for medication preparation during clinical phases I-III [28].

5. Fundamentals of BJ-3DP Technology and Its Applications in the Pharmaceutical Sector

BJ-3DP is the principal 3D printing method used in pharmaceutical manufacturing [29]. The printing principle is illustrated in Figure 1. Initially, the roller distributes a thin layer of powder on the platform, followed by the spraying of droplets from the removable printhead, which selectively adhere to the powder. Subsequently, the platform is lowered, the roller applies another layer of powder, and the printhead continues to dispense droplets, adhering to the layer-by-layer printing principle, and this process is repeated until completion. Finally, the preparations are extracted, the excess powder is eliminated, and post-processing is conducted [30]. Printing inks may consist just of the binder, while the powder bed

comprises the active pharmaceutical ingredient and other excipients. The API may be introduced into the powder bed either as a solution or as a suspension of nanoparticles [31]. The APIs applicable to BJ-3DP technology include those with favorable water solubility; nevertheless, for insoluble APIs, solubility enhancement may be achieved by pretreatment, although little research is available on the subject. Kozakiewicz-Latała et al. [32] used the hydrophobic active pharmaceutical ingredient clotrimazole as a model medication, formulating a solution with hydrophilic excipients PVP and lactose in a specific ratio, then using spray drying to enhance the wettability and printability of clotrimazole.

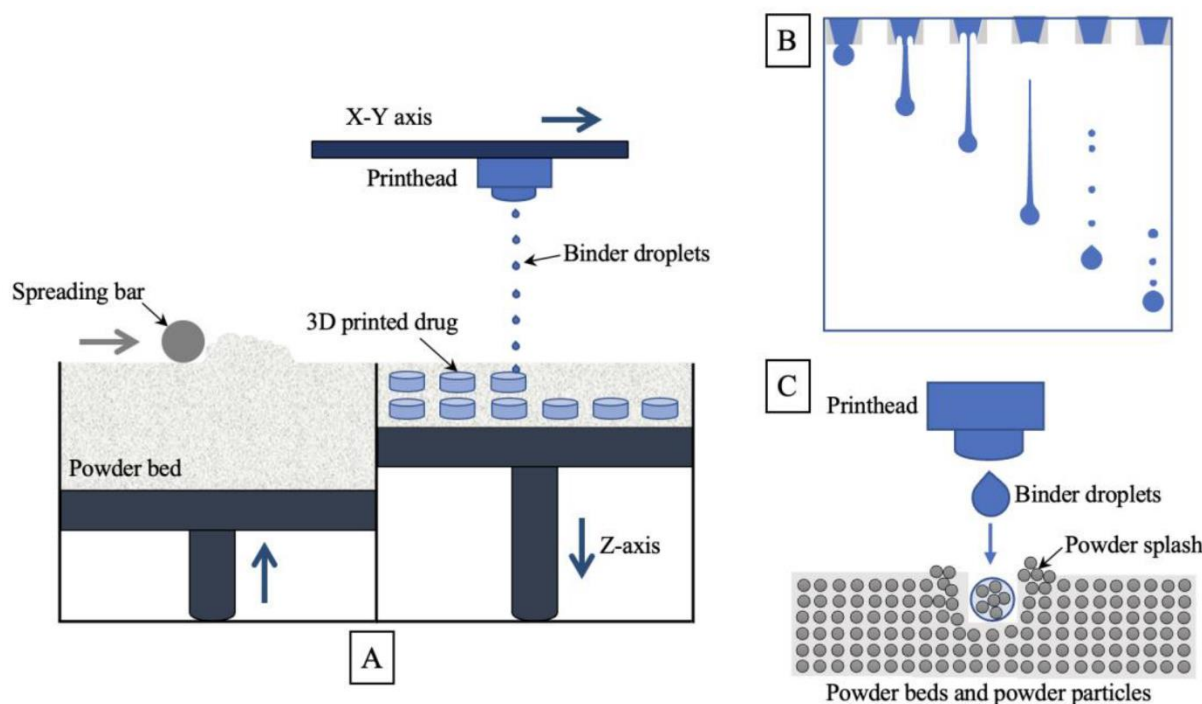


Figure 1. Schematic representation of the concept and method of tablet fabrication with BJ-3DP technology.

The BJ-3DP technique operates via a complicated mechanism, with the printing process categorized into three primary steps: droplet creation, selective adhesion of droplets to powder, and drying or curing of the final result [33]. The process of droplet formation is intricate, encompassing the generation and elongation of filaments, their necking, rupture, and rebounding, as well as the creation and amalgamation of primary and satellite droplets, as illustrated in Figure 1. Key physical parameters influencing the characteristics of printing inks include viscosity, density, and surface tension, which impact the mechanisms of droplet formation, as well as droplet volume and velocity. Reis and Derby [34] employed computational fluid dynamics to simulate the free surface flow characteristics of droplet formation, grounded in Fromm's prediction of the dimensionless Z values indicative of ink printability for stable droplet formation [35]. They investigated the influence of fluid properties on droplet ejection, conducting parallel experiments to ascertain that Z values ought to range from 1 to 10. Jang et al. [36] examined the ejection dynamics of inks composed of ethanol, water, and glycol, resulting in a redefinition of the Z value range from 4 to 14. To achieve optimal droplet ejection quality, the droplets produced by the printer should ideally be monodisperse, meaning that only one droplet is formed every pulse cycle.

Droplet diffusion upon impacting a smooth, nonporous surface primarily relies on droplet volume and equilibrium contact angle [37,38]. The impact of droplets on powder beds is considerably more intricate, as illustrated in Figure 1. Yarin's research indicated that the initial impact phase was governed by kinematic behavior, primarily influenced by inertial forces, succeeded by droplet diffusion, recoil, and oscillation induced by the impact, with capillary forces ultimately prevailing and regulating the diffusion process [39]. Research has examined the influence of droplets on powder beds, with ongoing investigations into the

correlation between the dimensionless number of ejected droplets and the effects of droplet impingement on a powder bed [40,41].

The drying or curing procedure may significantly influence the quality of the finished product. Typically, drying occurs via the evaporation of the solvent, making the evaporation rate a crucial factor in solvent selection [42,43]. Utilizing polymer-API-solvent solutions as printing inks to create amorphous solid dispersions post-droplet evaporation offers an efficient method for formulating low-dose medications from insoluble APIs [44]. Moreover, binder concentration, nozzle diameter, droplet spacing, print speed, and the frequency and velocity of droplet formation are critical elements to consider throughout the printing process [45].

6. BJ-3DP Technology in the Pharmaceutical Sector

The inaugural paper on the application of BJ-3DP in pharmaceuticals was published in 1996 [46], illustrating the viability of employing 3D printing technology for medication production. Subsequently, research has been conducted utilizing BJ-3DP technology to formulate diverse dosage forms, including immediate release, slow and controlled release, as well as compounded and implant preparations [47,48].

Initial investigations on a novel method for the formulation of oral solid dosage forms concentrated on validating the feasibility of intricate preparations. The selective deposition of droplets onto the powder bed necessitates the complete substitution of the powder bed material for the creation of multilayer compounded formulations, owing to the uniform composition of the powder bed. The print head can accommodate inks of varying compositions, and characteristics like as droplet volume, velocity, ejection frequency, and deposition location may be modified to facilitate the creation of intricate formulations. Spritam®, the first 3D-printed formulation introduced in 2015, was produced using BJ-3DP technology and is a dispersible tablet characterized by a high drug-loading capacity and uncomplicated architecture [49]. This preparation process exemplifies the technological attributes of the BJ-3DP, which fabricates tablets only by the contact adhesion of powder and ink, resulting in a porous structure that disintegrates swiftly, in contrast to the mechanical forces used in traditional technology. As investigations into BJ-3DP technology advance, the formulations produced by this technique increasingly emphasize immediate-release preparations.

7. Advancements in the Commercialization of the 3D Printed Pharmaceutical Sector

The 3D-printed pharmaceutical sector has been evolving for almost twenty years. In 1996, the US firm Therics obtained a license for the Massachusetts Institute of Technology's PB 3D-printing technology and established the world's inaugural 3D-printed pharmaceutical company; however, due to significant developmental challenges, Therics ultimately failed to achieve industrialization. In 2003, Aprelia re-licensed the PB technique and, after a decade, created the ZipDose technology. In 2015, the first 3D-printed medicine, Spritam®, was made and authorized using this method, initiating a surge in 3D-printed drug research.

Since 2015, the 3D-printed pharmaceutical business has seen accelerated growth, resulting in the emergence of several specialized 3D-printed medicine firms. The advancement of 3D-printed pharmaceuticals necessitates expertise not only in mechanical engineering and pharmaceutical research but also in materials science, software, and information engineering, alongside adherence to stringent legal regulations within the pharmaceutical sector; thereby elevating the overall complexity. The worldwide 3D-printed medicine sector is still nascent, with several pharmaceutical firms hastening the research and introduction of 3D-printed medications.

Large-scale production employs the conventional drug manufacturing model, commencing with the development of pharmaceutical products, followed by their declaration and registration. Subsequently, the approved drugs are produced en masse by pharmaceutical companies and distributed globally. Aprelia was founded in 2003 with the objective of large-scale production, and in 2011, it commenced operations of a GMP-compliant 3D-printed medication production line capable of manufacturing 100,000 tablets daily. Despite the introduction of Spritam® in 2015 catalyzed a surge in 3D printed drug research, the product's

commercial performance was lackluster, prompting Aprecia to pivot into a technology-driven enterprise, collaborating with pharmaceutical and biotechnology firms to create or manufacture medications. In 2017, Aprecia collaborated with the orphan drug business Cycle Pharmaceuticals to enhance the availability of medications for people with rare disorders. By the conclusion of 2020, a sustained strategic alliance with Oak Ridge National Laboratory in the United States is anticipated to enhance the ZipDose 3D printing facility, therefore broadening the use of the technology in the domain of 3D-printed pharmaceuticals.

In 2018, Triastek introduced its continuous and intelligent MED 3D-printed drug production line, which integrates material mixing and tablet formation in a single step while enabling real-time quality control via process analysis technology. The MED technology has been industrialized, achieving an annual production capacity of 50 million tablets. Currently, four 3D-printed medicines have undergone registration filings; apart from Spritam®, the other three are from Triastek, two of which have previously obtained INDs from the FDA in the United States. Triastek's business plan includes partnerships with other firms in the development of medicinal goods. In March 2022, Triastek formed a relationship with Siemens to provide global pharmaceutical firms solutions for the digital development and production of medications, and in July 2022, it collaborated with Eli Lilly to enhance drug bioavailability in the gut via precision targeting and programmed drug release.

8. Customized Pharmaceutical Administration

Beyond large-scale manufacturing, 3D-printed pharmaceutical technology is particularly advantageous for the formulation of individualized medications tailored to individuals with varying illness conditions and ages. This model's primary use is in hospital pharmacies, providing a rapid and automated medication solution for patients with individualized pharmaceutical requirements. Figure 2 illustrates that research in this area is now more vigorous in Europe, with prominent entities such as specialized 3D printed pharmaceutical firms FabRx, Multiply Labs, and DiHeSys, the independent research organization TNO, and the multinational pharmaceutical corporation AstraZeneca.

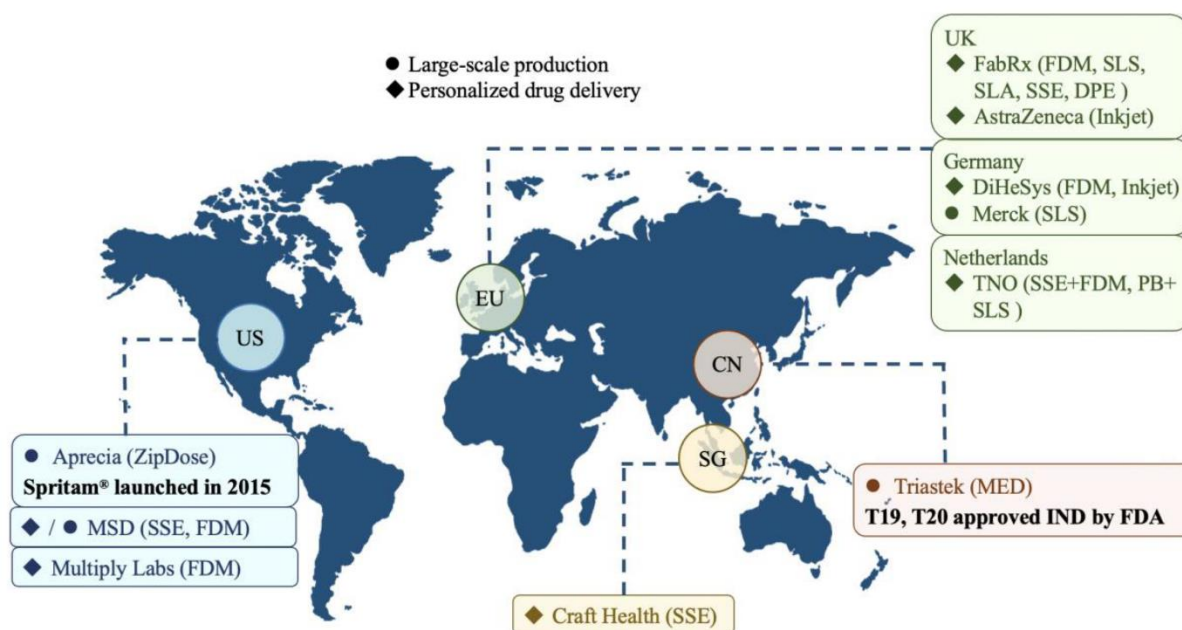


Figure 2. Global advancements in the sector of 3D printed pharmaceuticals.

Founded in 2014, the UK company FabRx is a prominent entity in the realm of 3D-printed pharmaceuticals. The company has investigated various 3D printing technologies, including FDM, SLS, SLA, SSE, and DPE. With a strong focus on personalized drug delivery, FabRx introduced the innovative M3DIMAKER™ 3D printer in 2020, which integrates FDM, SSE, and DPE technologies. This allows users to select the appropriate print head based on their requirements, facilitating the rapid and adaptable production of 3D-printed medications tailored to diverse principles and materials suitable for personalized pharmaceutical

applications. In 2021, the business is partnering with the French cancer center Gustave Roussy to provide tailored medications for early-stage breast cancer therapy.

Multiply Labs, established in 2016 in South San Francisco, USA, creates robotic manufacturing systems to assist pharmaceutical businesses in the production of biological medicines. It also formulates tailored medications using a two-step methodology, first with the fabrication of capsules of varying thicknesses and compartments using FDM technology, followed by the infusion of diverse pharmaceuticals or nutrients into the capsule chambers to provide multi-drug combinations. In 2021, the company partnered with the global life sciences firm Cytiva and researchers from the University of California, San Francisco, to create an advanced robotic control system aimed at automating cellular therapies and enhancing the efficiency of cellular therapy drug production.

9. Policies and Regulations Concerning 3D Printed Pharmaceuticals

3D printing, as an innovative technology in the pharmaceutical sector, offers numerous advantages, and the 3D-printed drug industry is progressing towards contemporary personalized medicines, directly linked to the initiatives of leading companies and the proactive support of governmental bodies, such as the Drug Review Centre.

Spritam®, the first 3D-printed formulation, obtained IND clearance from the FDA in 2013. In 2014, the FDA created the ETT to promote and streamline the approval of emerging technology products in the pharmaceutical sector, which directly contributed to the successful approval of Spritam® in 2015. In January 2017, the FDA released a review concerning a novel chapter in pharmaceutical manufacturing: 3D-printed drug products, asserting that 3D printing represents an emerging technology for the future. In July of the same year, the FDA provided industry guidance on the progression of emerging technology applications for pharmaceutical innovation and modernization, emphasizing that 3D printing technology and continuous manufacturing are critical strategic directions. In 2019, the China CDE issued an assessment acknowledging its understanding and apprehension about the 3D-printed medication sector, anticipating that 3D printing will expedite the advent of individualized and intelligent drug administration.

In 2020, Triastek's MED 3D printing technology was included in the FDA's Emerging Technology Program and received approval, signifying its recognition at the regulatory level. In January 2021, T19, the world's second 3D printing apparatus, obtained FDA IND clearance. In the same year, Triastek participated in the Q13: Continuous Manufacturing conference held by CDE in China, contributing to the advancement of pharmaceutical technology innovation. In 2021, the National Academies of Sciences, Engineering, and Medicine, at the behest of the Center for Drug Evaluation and Research, published a report on advancements in drug manufacturing, concluding that 3D-printing technology represents a novel manufacturing method distinct from traditional drug production techniques and is poised to supplant them.

So far, no regulatory authority has provided guidance for 3D-printed formulations, highlighting an urgent need to create regulatory standards for these products. It is anticipated that as technology advances and researchers investigate more, 3D-printing technology may construct a comprehensive framework of scientific standards within the pharmaceutical sector, including theory, practice, manufacturing, and regulation.

10. Conclusions

This paper examines the pertinent literature on various 3D-printing technologies prevalent in the pharmaceutical sector, clarifying the principles and attributes of each technology, the appropriate dosage forms, and the developmental trajectory; it also discusses the commercialization strategies of notable companies or institutions involved in 3D-printed pharmaceuticals, their historical progress, and the significant breakthroughs attained, thereby propelling the innovation of drug development paradigms. The registration and filing process for 3D-printed preparations is distinctive, since intellectual property rights, drug laws, and other rules are continually evolving. This research seeks to elucidate the present development state, industrial features, and overarching trends in the advancement of 3D-printed pharmaceuticals. We anticipate that this evaluation will serve as a significant reference for anyone involved

in relevant research. The future of the 3D-printed medicine business is anticipated to be bright, driven by ongoing research that will enhance intelligent and tailored medication manufacturing technologies.

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التطورات والابتكارات في تقنيات الطباعة ثلاثية الأبعاد لتطوير أشكال دوائية مخصصة: مراجعة شاملة

الملخص

الخلفية: يشهد قطاع صناعة الأدوية تحولاً كبيراً نحو الطب الشخصي، مدفوعاً بالتقدم في تقنيات الطباعة ثلاثية الأبعاد. وعلى عكس طرق التصنيع التقليدية التي تعتمد على أساليب الطرح، تعتمد الطباعة ثلاثية الأبعاد على تقنيات الإضافة لإنشاء تركيبات دوائية معقدة تُخصص لتلبية احتياجات المرضى الفردية.

المنهجيات: تفحص هذه المراجعة منهجياً تقنيات الطباعة ثلاثية الأبعاد المختلفة، مثل تقنية الربط بالنفث (BJ-3DP)، ونمذجة الترسيب المنصهر (FDM)، والتلييد بالليزر الانتقائي (SLS). تم إجراء بحث شامل في قواعد بيانات متعددة لتحليل التطبيقات الحالية والفوائد والتحديات المرتبطة بالطباعة ثلاثية الأبعاد في مجال الأدوية، مع التركيز على قدرتها على تخصيص الجرعات وتسريع الإنتاج.

النتائج: تشير النتائج إلى أن الطباعة ثلاثية الأبعاد تعزز تخصيص الأدوية، مما يتيح تصميم جرعات مخصصة لفئات محددة من السكان، مثل الأطفال وكبار السن. تسهم التقنية في التحكم الدقيق بملامح إطلاق الدواء وتسرع عمليات الإنتاج، مما يقلل بشكل كبير من الوقت والتكاليف المرتبطة بالطرق التقليدية. تشمل التطورات البارزة تطوير أدوية مطبوعة ثلاثية الأبعاد مثل Spritam®، التي تُظهر إمكانات عالية لتلبية الاحتياجات العلاجية المختلفة بتركيبات فورية الإطلاق.

الخلاصة: تسلط هذه المراجعة الضوء على التأثير الكبير للطباعة ثلاثية الأبعاد في تصنيع الأدوية، مع التركيز على دورها في تعزيز الطب الشخصي. ومع نضوج هذه التقنية، سيكون من الضروري تطوير الأطر التنظيمية لضمان السلامة والفعالية. يبدو مستقبل الأدوية المطبوعة ثلاثية الأبعاد واعداً، حيث تُجرى أبحاث مستمرة لتحسين تطبيقاتها وتوسيع نطاقها في تقديم الأدوية المخصصة.

الكلمات المفتاحية: الطباعة ثلاثية الأبعاد، الطب الشخصي، تكنولوجيا الأدوية، تركيب الدواء، التصنيع الإضافي.