Additive Manufacturing: A Comprehensive Review of 3D Printing Technologies, Pharmaceutical Applications and Regulatory Perspectives

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ABSTRACT

Background

The advent of 3-Dimensional printing technologies has significantly impacted pharmaceutical manufacturing, opening new avenues for personalized medicine, precise drug delivery systems, and on-demand production. Since the Food and Drug Administration approval of Spritam® in 2015, interest in additive manufacturing in the pharmaceutical sector has grown rapidly.

Main Body

This review highlights key advancements and techniques in 3-Dimensional printing for drug formulation, focusing on extrusion-based, inkjet-based, and laser-based systems. Among these, Fused Deposition Modeling (FDM), often combined with Hot-Melt Extrusion (HME), is widely used for its ability to fabricate complex dosage forms. Semi-Solid Extrusion (SSE) is particularly promising for incorporating heat-sensitive drugs and bioactives, such as plant extracts. Laser-based approaches, including Selective Laser Sintering (SLS) and Stereolithography (SLA), enable the production of highly precise oral dosage forms and microneedle systems. The integration of artificial intelligence, especially generative adversarial networks (GANs), further enhances formulation design and process optimization. Despite substantial progress, challenges remain in standardizing processes, achieving regulatory approval and scaling up for commercial manufacturing.

Conclusion

3-Dimensional printing holds significant potential to transform pharmaceutical development through the creation of polypills, pediatric and geriatric-specific formulations, implantable devices and transdermal systems paving the way for truly personalized drug therapy.

Keywords: 3D printing, Novel techniques, Drug delivery, Pharmaceutical applications and Regulatory aspects.

1. INTRODUCTION

Since the FDA approval for Spritam (levetiracetam), a 3D-printed medication, back in 2015, both scientists and drug manufacturers have become significantly more intrigued by 3D printing (3DP). Spritam's unique manufacturing process grants it exceptionally rapid disintegration, a characteristic difficult to achieve with traditional tablet production. The binder jetting technique creates tablets with high porosity, enabling the drug to dissolve quickly.(1) Consequently, researchers are now actively investigating other 3D printing methods to create specialized drug formulations previously unattainable. Moreover, the rise of personalized medicine makes 3D printing a highly attractive solution for producing small batches of customized medications with tailored dosages and release profiles**.**(2) The majority of medications, like capsules and tablets are formulated for adults and are not appropriate for children. Adult medications cannot always be given to children because developing medicines for childs requires specific protocols. Despite this, prescribing medications "off-label" (using them in ways not specifically approved) is still widespread in pediatric medicine. It impacts roughly 40% of drugs used in pediatric intensive care and as high as 80% in newborn care. This is concerning because a newborn's underdeveloped organs and body systems can change how their body absorb and process the active ingredients and other components in those medications. The demand for ceramic 3D printing is skyrocketing, both at home and abroad. This intense interest is fueling exciting breakthroughs in the technology itself, as well as its real-world uses. Ceramic 3D printing successfully applied in areas like medicine, artistic creations and even building design. The beauty of this technology lies in its ability to eliminate molds, dramatically cutting costs, speeding up production and allowing for designs that were previously impossible. Compared to traditional methods, it is no wonder industries are embracing ceramic 3D printing.(3) Current research is laser-focused on high-growth areas like healthcare, aerospace, and communications. Researchers are deeply invested in exploring and pushing the boundaries of this technology, with a keen eye on driving industrial growth. This analysis delves into the hurdles and technical limitations facing ceramic 3D printing in different sectors, highlighting opportunities for advancement in materials development, equipment manufacturing, and finding new applications. Ultimately, this exploration underscores the incredible potential of ceramic 3D printing to shape the future of manufacturing and innovation. Traditional pharmaceutical manufacturing focuses on producing large quantities of identical medications, a "one-size-fits-all" approach. However, advancements in genomics and diagnostics are making this less effective, as they highlight the need for personalized medicine.(4) 3D printing, officially called Additive Manufacturing (AM), is on the verge of dramatically changing how drugs are made, opening the door to personalized medicine. Currently, the AM market is worth $17 billion, and experts predict it will balloon to $44 billion by 2027, showcasing impressive annual growth of 27%. Driven by progress in AI and machine learning, AM is expected to become a cornerstone technology in the creation of many customized medical solutions.

1.1. Fundamentals of 3D Printing in Pharmaceuticals

The drug industry is increasingly adopting 3D printing to create personalized medications with complex structures. Techniques like FDM and SLA allow for very controlled drug delivery. Incorporating AI, particularly GANs, is speeding up the drug creation process by forecasting how well a formulation can be manufactured and imagining completely new compositions. Successful printing of AI-designed formulas suggests a future of automated drug development. While progress is promising, challenges remain, including regulatory approval and increasing production to meet demand. Future research should focus on improving AI algorithms, enhancing the physical properties of printed drugs, and ensuring consistent outcomes to further personalize medicine using 3D printing.(5) The advancements in 3D printing technology are transforming how drugs are made. This innovative method unlocks the ability to create medications in custom shapes and dimensions, going beyond the limitations of traditional manufacturing. A key application is the production of "polypills," which are single pills that combine multiple medications, offering a convenient solution for treating complex conditions.(6) The pharmaceutical industry is being transformed by 3D printing, paving the way for personalized medications designed to meet each patient's unique requirements. Moving beyond conventional manufacturing, this technology allows for the immediate production of tailored drug formulations and precise control over how these medications are released into the body. This method reduces waste and brings drug production closer to the point of care, even allowing for on-site creation within hospitals. Although challenges like regulatory approval, maintaining consistent quality, and scaling up production still exist, the potential for enhanced patient compliance and customized treatments is fueling advancements in the field. Clinical trials have already shown promising results for printed medications. However, widespread adoption hinges on overcoming obstacles such as the cost of equipment and the intricacies of validating the printing process.(7) The 3D printing process typically unfolds in two main stages. Initially, a design is created using computer software such as AutoCAD, 3D Slash, Sketch Up, Fusion 360, or Solidworks. Subsequently, this digital design is brought to life as a tangible object through the use of a 3D printer. Before printing, specialized slicing software like KISSlicer, Slic3r, OctoPrint, Simplify3D, or Cura is employed to ready the design. This software essentially translates the 3D design file, commonly in STL format, into G-code – a programming language that the 3D printer can interpret and execute.(8) The 3D printing process is made possible with the use of slicing software, which allows users to customize important printing options. These options include the number of layers, the infill density, and the starting height of the print head, layer thickness, printing speed, and total print duration. After these specifications are set, the G-code is sent to the 3D printer. Once the printer receives the command, it starts creating the object according to the predetermined size and shape.(9) The specific materials are applied during the 3D printing process depends on the specific printer being used. Popular methods include using inkjet technology, squeezing materials out through a nozzle (extrusion), or using lasers to fuse materials together.(10)

1.2. Basic Steps in 3D Printing (11,12)

Generally, the 3D printing process involves six steps, which are outlined below,

1. Concept Generation
2. 3D CAD Design
3. stl File Creation
4. G-code Conversion
5. 3D Printing
6. Processing/Evaluation

1.3. Novel 3D Printing Techniques (13)

Based on three fundamental principles, as mentioned below,

1. Inkjet-based system
2. Extrusion-based system
3. Laser-based system

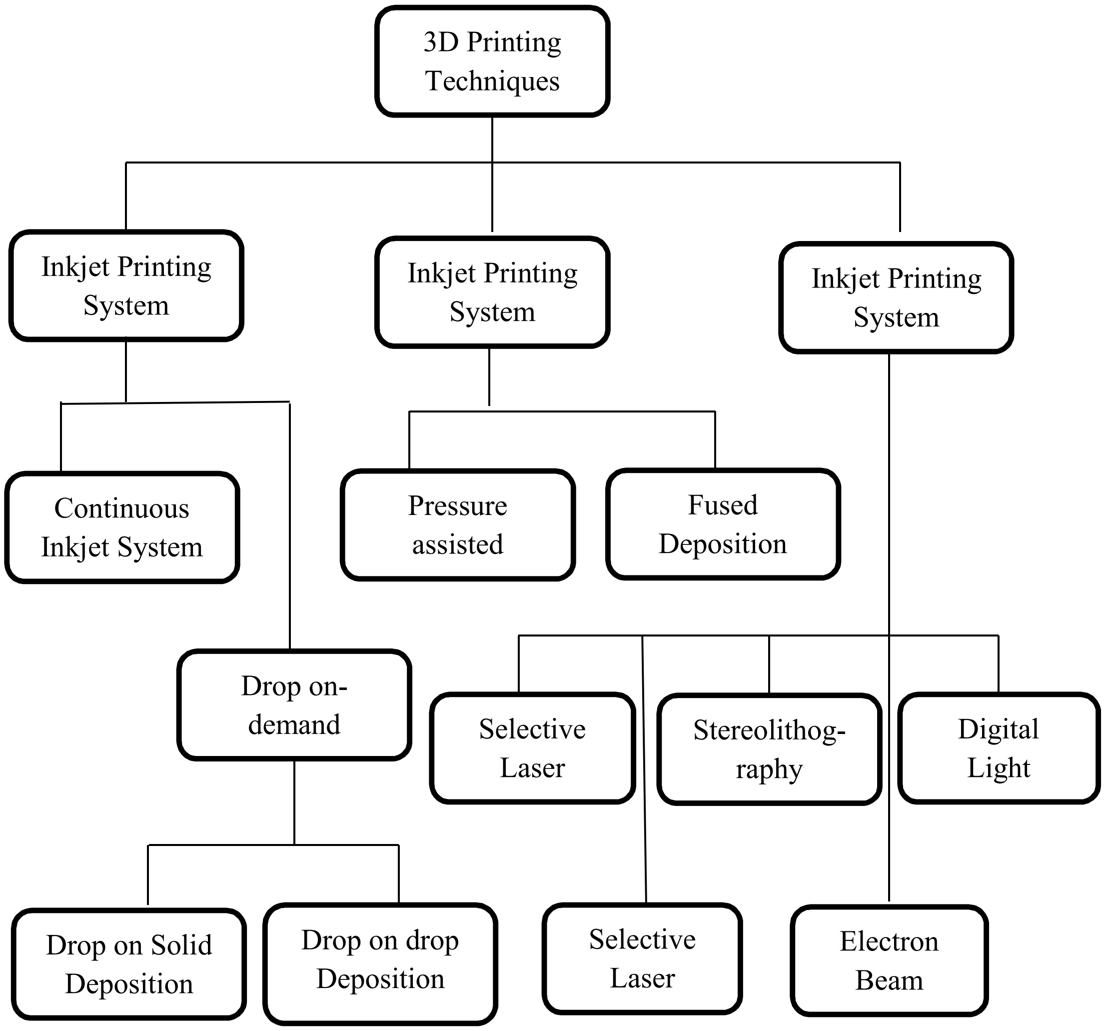

Figure: 1. 3D Printed Techniques in Pharmaceuticals (14),(15)

1.3.1. Inkjet-based system

Inkjet 3D printing is poised to revolutionize the pharmaceutical industry, proven by the FDA's green light for SPRITAM®, a medication manufactured using this innovative technology.(16) The honeycomb structure is considered perfect for creating tailored dosages because it allows for fine-tuning of the tablet's form, which directly impacts how the medication is released.(17) Inkjet 3D printing allows for the creation of intricate designs, but the ink formula is critical. It needs to be optimized to work well with the printer, especially ensuring the right thickness to avoid blocking the nozzles. On top of this, the amount of medication in the final product and the product's overall durability can sometimes be challenging to control.(18) The principle behind inkjet printing boils down to accurately shooting out minuscule drops of liquid in a way that's controlled by a computer. When it comes to 3D printing, inkjet technology splits into two main types: continuous inkjet (CIJ) and drop-on-demand (DOD). CIJ works by constantly spraying a stream of ink, diverting specific droplets onto the building platform. Though this is a faster process, it usually doesn't offer the same level of detail or accuracy as DOD. Conversely, DOD printers only release ink droplets precisely when and where they're needed, dictated by a computer. This provides superior resolution and precision but usually takes longer than CIJ.(19)

1.3.2. Extrusion-based system

When it comes to 3D printing medications, extrusion techniques are the dominant approach. For the past half-decade, over four-fifths of studies and scientific papers on 3D-printed drug delivery have focused on these methods. Extrusion can be further classified into sub-techniques such as Paste Extrusion (PAM) and Fused Deposition Modeling (FDM).(20) The pharmaceutical world is being transformed by 3D printing, which promises custom-made drug delivery perfectly suited to each patient. Yet, the potential of using natural, plant-derived ingredients in 3D-printed medications remains largely untapped. The delicate nature of these substances, often breaking down with heat, air, or specific solvents, presents a significant challenge to the 3D printing process.(21) Due to the limited research available, the use of 3D printing for plant-based medicines is still a relatively new field. However, because many beneficial compounds found in plant extracts are easily damaged by heat, a low-temperature 3D printing technique called semi-solid extrusion (SSE) is gaining popularity. SSE, which includes methods like micro-extrusion and pressure-assisted micro-syringe printing (PAM), allows for printing at room temperature, making it a potentially valuable tool for creating new and effective drug delivery systems.(22) Previous studies have shown that polyethylene oxide (PEO) gels are perfect for 3D printing using the Suspended Solid Extrusion (SSE) method. They've even been used to successfully print tiny capsules of eucalyptus extract. Furthermore, recent research has pinpointed and fine-tuned the critical settings needed to effectively use watery PEO gels in SSE 3D printing.(23) In the pharmaceutical industry, 3D-printed drug delivery systems (3DP-DDSs) utilizing powder-based and material extrusion techniques are widespread. Material extrusion relies primarily on fused deposition modeling (FDM) and direct ink writing (DIW). FDM is the more established and extensively studied of these two methods.(24)

1.3.3. Laser-based system

3D printing uses lasers to create objects by hardening materials one layer at a time. In a process called Stereolithography (SLA), a laser solidifies liquid resin to build precise parts, like tiny needles or dental equipment. After each layer is hardened, the platform moves down, allowing the laser to create the next layer on top.(25) Selective Laser Sintering (SLS) is a 3D printing method that utilizes a laser beam to fuse together powdered plastic layer by layer. The laser precisely melts and solidifies the powder according to the desired shape, then a fresh layer of powder is spread on top and the process is repeated. The accuracy of the final product hinges on the laser's precision and power, as well as the fineness of the powder used. A key advantage of SLS is that it's a cleaner process compared to Stereolithography (SLA), as it doesn't require hazardous chemicals. Furthermore, SLS parts typically don't need any additional processing after printing.(26) This innovative 3D printing method, which uses lasers, is being investigated for its potential in tailored healthcare, specifically for producing "printlets" – customized oral tablets with precise medication amounts. These personalized tablets have already been tested in real-world medical situations. For instance, scientists have used Selective Laser Sintering (SLS) to enhance how well drugs like lopinavir (LPV) dissolve in the body. Tablets created using SLS showed a large amount of LPV in a non-crystalline state, which allowed them to dissolve more quickly. Research indicates that higher drug concentrations result in tablets with more pores, and the speed of the laser used during printing significantly affects the drug's crystalline structure.(27) Selective Laser Sintering (SLS) is an eco-friendly 3D printing method that uses powdered materials to build objects. The characteristics of these powders are critical to the success of the SLS process and the quality of the final product. Prior studies have emphasized the importance of powder properties, highlighting them as a key factor in determining whether a material is suitable for SLS. Specifically, the optimal average particle size for powders used in SLS 3D printing is generally considered to be between 45 and 90 micrometers.(28)

A. Fused Deposition Modelling (FDM)

Fused Deposition Modeling, is a widely used 3D printing method that's gaining popularity in research and industry. The process works by melting plastic filament and carefully layering it to build objects from the ground up. A heated nozzle precisely deposits the melted material, based on a digital design, creating the final 3D part, layer by layer.(29) Hot-melt extrusion is proving to be a highly effective method for producing filaments with specific characteristics, opening up possibilities for diverse uses. Our research focused on using a hot-melt extrusion process, combined with 3D printing via fused deposition modeling, to create tablets containing a drug (MS) within filaments, designed for a prolonged release of the medication.(30) Hot-melt extrusion, a sophisticated manufacturing method used in various industries, has been around since the 1930s. The process involves blending an active drug (API) with a carrier material, effectively dispersing the drug within the matrix as a single, unified composite.(31)

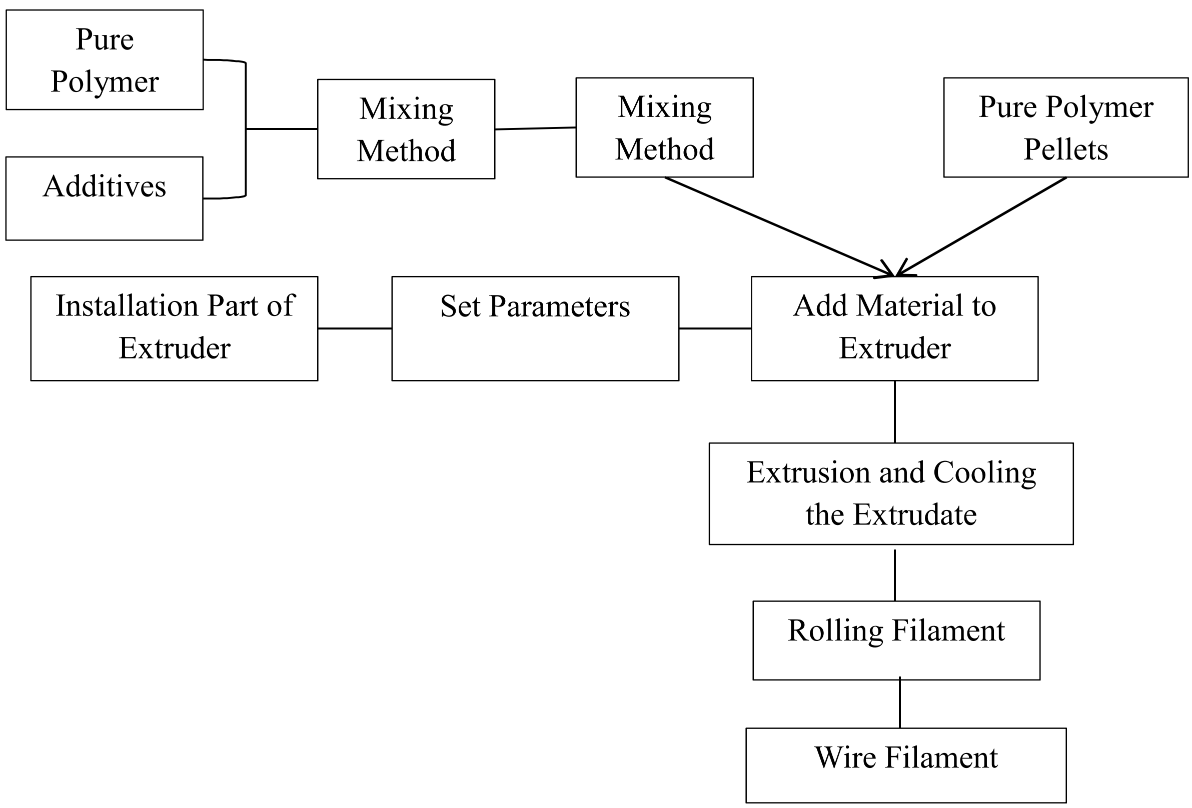

Figure 2. Workflow of Filament (32)

2. Pharmaceutical Applications of Fused Deposition Modeling

Numerous studies have explored the potential of Fused Deposition Modeling (FDM) in creating diverse pharmaceutical products. These studies have successfully produced tablets in different shapes and with varied release mechanisms, including bilayer tablets and more complex drug delivery systems that combine a tablet with a device. As an example, researchers have used FDM to create sustained-release, capsule-shaped tablets (caplets) containing theophylline. Furthermore, the technology has been employed to develop capsules and multi-compartment capsules for targeted drug delivery.(33) Recently, significant research has explored the application of Fused Deposition Modeling (FDM) in creating gastro-retentive drug delivery systems. This includes a wide range of forms, from conventional tablets and capsules to more complex designs like capsular devices and pulsatile release mechanisms. Furthermore, FDM has been utilized to produce oral fast-dissolving films and mucoadhesive buccal films.(34) FDM technology served as the foundation for creating platforms upon which drugs were applied via inkjet printing. Beyond this, its uses in the pharmaceutical field extend to manufacturing microneedles, orthodontic retainers infused with medication, therapeutic topical masks, and vaginal rings designed to release drugs.(35) Hot Melt Extrusion (HME) is a well-established, ongoing manufacturing method used in the drug industry to improve how well medications dissolve and to hide unpleasant tastes. Lately, HME has also become popular for creating filaments used in Fused Deposition Modeling (FDM) 3D printing.(36) Combining hot-melt extrusion (HME) with 3D printing (FDM) opens the door to creating bespoke and intricate medications, delivering multiple drugs in a single, personalized dose. Utilizing HME to create polymer filaments for FDM provides unprecedented flexibility in drug delivery design. This review showcases HME's significance and growing integration with 3D printing as a catalyst for groundbreaking pharmaceutical advancements.(37)

3. Application of 3DP technology to pharmaceutical dosage forms

Techniques like Inkjet, FDM, and SLS, all forms of 3D printing (3DP), are now being used to create effective pharmaceutical medications. This review highlights the areas where 3DP is showing the most promise in drug manufacturing, particularly for dosage forms that are well-suited for widespread 3DP application.(38)

3.1 Tablets

Oral medications are the most common way people take pharmaceuticals. Tablets and capsules are familiar examples of solid oral medications. Tablets, in particular, have been thoroughly studied to see if 3D printing can be used to manufacture them. Generally, 3D-printed tablets can be divided into two types: those containing a single active ingredient and those containing multiple active ingredients. Examples of each type will be discussed in the following sections.(39) In children with HIV who need extra nutrition or rely on feeding tubes (EFTs) to take their medication, this study explores a new solution. It's the first time researchers used a special 3D printing technique called selective laser sintering (SLS) to create quickly dissolving "printlets" containing efavirenz (EFZ). These printlets are designed to be easily administered through EFTs. Using water-loving materials, the researchers made printlets in two sizes (containing 500 mg and 1000 mg total mass, each with 200 mg of EFZ). The resulting printlets packed a lot of medicine (20-40% of their weight was EFZ), turned the drug into a more readily absorbed form, and disintegrated quickly – in under 230 seconds. The larger printlets, however, didn't fully break apart. The results suggest that SLS 3D printing could be a valuable way to create EFZ medications specifically for children with HIV who use feeding tubes.(40) This research investigates the creation of child-sized, 3D-printed tinidazole tablets using a combined process of hot melt extrusion (HME) and fused deposition modeling (FDM), employing Kollidon®25 as a key excipient. Kollidon®25 was chosen for its ability to improve tinidazole dissolvability, a characteristic validated through solubility and interaction studies. Both placebo and drug-containing filaments were successfully manufactured and used to produce tablets that met acceptable quality standards in terms of weight, hardness, and friability. Advanced analytical techniques (DSC and PXRD) confirmed that the drug transitioned to an amorphous form within the tablet structure. Scanning electron microscopy (SEM) revealed surface characteristics that enhance the penetration of fluids and promote rapid drug dissolution. Importantly, these tablets achieved complete (100%) release of tinidazole within two hours, demonstrating the potential of 3D printing for creating personalized, pediatric-friendly tinidazole dosage forms.(41) This research introduces a new method for manufacturing long-lasting Metoprolol succinate tablets. It combines hot-melt extrusion (HME) and fused deposition modeling (FDM) 3D printing. By mixing Soluplus® and HPMCAS polymers with citric acid (a softening agent), they created strong, easily extrudable filaments. These filaments were structurally sound and uniform, confirmed by FTIR, XRD, and μCT analysis. The resulting 3D-printed tablets released the drug in a controlled manner, with 70% of the drug released over a six-hour period in a pH 6.8 buffer solution. This approach presents a valuable foundation for producing customized medications with specifically designed release patterns.(33)

3.2 Medical Device

To ensure the success of 3D-printed medical devices, close attention must be paid to the manufacturing process to catch and correct any problems that arise. Strong regulatory guidelines are essential for effectively managing these complexities. The growing trend of customized healthcare has highlighted the potential of 3D printing to create adaptable, patient-tailored medications. By refining these 3D printing procedures, we can enhance treatment results and minimize the reliance on extensive testing after production. Consequently, developing well-defined regulations and industry best practices is crucial for ensuring the safe and reliable use of 3D printing in the pharmaceutical field.

Polyether ether ketone (PEEK), a strong and heat-resistant plastic, is commonly used in medicine for things like dental and bone implants. This research explores how the settings on material extrusion 3D printers influence the strength when pulled, the smoothness, and the biological compatibility of PEEK parts. We used a statistical method called Taguchi analysis to find the best settings for factors like nozzle temperature, printing speed, layer thickness, and build plate temperature. Tests on cells and microscope images confirmed that the printed parts were biologically compatible and had good internal structure. This study created a helpful model connecting 3D printing settings to the strength and biological performance of PEEK, making it easier to create high-quality, biocompatible PEEK parts.(42)

3.3 Microneedles

Microneedles are becoming increasingly popular as a gentle and less invasive method for delivering medication. This research introduces a new type of hollow microneedle array, inspired by the lip-like structure of certain biological organisms, created using a specialized 3D printing technique. Made from a biocompatible resin, these microneedles are designed to deliver the antibiotic ceftriaxone sodium through the skin. The needles boast a precise design, robust strength, and require minimal force to pierce the skin. Testing confirmed their consistent structure, durability, and completes drug delivery through pig skin within 18 hours. Animal studies further revealed improved drug absorption, suggesting these microneedles hold great potential for personalized medication delivery via the skin.(43)

3.4 Hydrogels

The use of caprine esophageal tissue in the development of decellularized smooth muscle matrix (dSMM) hydrogels is explored in this study. A key aspect is the detergent-free decellularization process, which relies on alternating low and high salt concentrations. This method leads to efficient cell removal, leaving behind a matrix with significantly reduced DNA content and excellent preservation of essential extracellular matrix components like collagen and sulfated glycosaminoglycans.(44) Compared to traditional detergent-based methods, this approach better preserves the tissue's bioactivity. The dSMM hydrogel supported the differentiation of adipose-derived stem cells into smooth muscle cells, indicating its regenerative potential. Additionally, the dSMM was successfully optimized as a bioink for 3D bioprinting of muscle tissue constructs, showing promise for personalized esophageal tissue engineering.(45) The current main use of bioprinted tissues is testing drugs and cosmetics. However, the long-term ambition is to create fully functioning, human-sized organs for transplantation. To achieve this, scientists need to perfectly recreate the complex 3D structure and intricacies of real tissues. Decellularized extracellular matrix (dECM) bioinks are popular because they work well with living tissues. However, standard methods for removing cells and turning the material into a gel can weaken the material and make it difficult to print. This research presents a new approach using two types of crosslinking: first, a light-activated surface hardening, followed by a thermal gelation process. This improves the shape retention and supports cell function. This improved method successfully bioprinted complex shapes resembling anatomical structures, indicating promising advancements in tissue engineering.(46)

3.5 Oromucosal Drug Delivery

This research explores the creation of innovative, sticky patches made from chitosan oligosaccharide to deliver drugs through the lining of the mouth. The patches were created using a solvent casting method, both with and without the addition of alginate. They were then tested to see how much they swell, how well they absorb water, their potential to fight cancer, and how effectively they release drugs. Patches containing alginate swelled less and were less water-absorbent than those made solely from chitosan. Interestingly, both types of patches, even without drugs, showed anti-cancer properties. When loaded with drugs, the patches released them in a controlled manner, both in lab tests and in living organisms, with detectable levels of the drug appearing in the bloodstream. The results indicate that these chitosan oligosaccharide patches are promising candidates for delivering drugs systemically through the oral lining and could potentially be used in clinical settings..(47)

3.6 Bone Regeneration

This research details the creation of adaptable scaffolds designed for bone repair, utilizing 3D printing with a combination of polylactide-co-trimethylene carbonate (PLMC) and polydopamine nanoparticles (PDA). These scaffolds react to near-infrared (NIR) light, quickly and controllably changing shape within half a minute, allowing for minimally invasive implantation into oddly shaped bone injuries. Lab tests showed that the PLMC-PDA mixture significantly boosted bone cell activity, leading to increased production of alkaline phosphatase and bone mineralization compared to PLMC alone. Live animal testing using rabbit skull defects demonstrated effective adaptation of the scaffolds and almost complete bone regrowth within three months. These findings suggest that PLMC-PDA scaffolds hold promise for clinical application in the treatment of challenging bone defects.(48)

4. Challenges and Future Prospects

3D printing, a method of building objects one layer at a time from digital blueprints, presents advantages such as tailored designs, minimal waste, and affordable production. While the technology has been around since the '60s, its use in the pharmaceutical industry is a relatively new development. Various 3D printing approaches, including inkjet, extrusion, and beam-based techniques, employ a wide variety of materials, from common substances like lactose and HPMC to specialized bioinks like chitosan and hyaluronic acid. Fused Deposition Modeling (FDM) stands out for its adaptability in creating drug products using both biodegradable and non-biodegradable materials.(49) 3D printing offers exciting possibilities for crafting intricate medications, advanced drug delivery methods, and tailored medical tools. However, its widespread use is hindered by issues like difficulty with heat-sensitive drugs, problems scaling up production, and a lack of clear regulations. Further research is crucial to address these limitations and unlock the full benefits of 3D printing in creating new pharmaceuticals.(50) While traditional manufacturing methods are tried and true, particularly for mass production, 3D printing offers a unique advantage. It allows for highly accurate and customizable creation of objects from diverse materials, effectively filling gaps where conventional techniques fall short. Therefore, 3D printing and traditional manufacturing processes can work together to achieve optimal results. The rise of 3D printing is opening up exciting possibilities in the pharmaceutical world, offering innovative ways to research drugs. This technology allows for tailor-made medication and more intricate and accurate drug formulations. While there are hurdles regarding technology and regulations to overcome, progress is being made. The future looks bright, with 3D printing poised to transform how medicines are developed, leading to customized and smarter drug delivery methods.(51) Future advancements in 3D printing for pharmaceuticals and medicine need to prioritize the creation of cutting-edge materials. These materials must be safe for the body, able to break down naturally, and allow for highly accurate control over how medications are released, remain stable, and function mechanically. Ensuring patient comfort and acceptance is also critical. Better 3D printing methods, offering dependable and consistent accuracy, are essential for creating combinations of multiple drugs, tailoring release rates to individual needs, and incorporating sensors that can monitor treatment progress. Ultimately, these improvements will lead to more effective therapies and treatments customized for each patient. To successfully validate, approve, and sell 3D-printed medications, it's crucial to have well-defined regulations, understandable instructions, and consistent quality checks in place.(52) The future of medicine is looking incredibly personal, thanks to automated 3D printing. Imagine treatments and medical devices, like tiny needle patches or implants that react to your body, perfectly customized for you. The real trick is making this technology affordable and easy to produce on a large scale. If we can do that, personalized medicine can become a reality for everyone, leading to better health and a more efficient healthcare system.(53)

5. Regulatory Aspects

Since the time of origin, 3D printing has captivated researchers and healthcare professionals alike. While the technology is undeniably promising, achieving the desired results requires meticulous planning and careful material selection. Furthermore, manufacturers currently face uncertainty regarding the specific regulations and guidelines they must adhere to in order to gain approval for their 3D-printed products..(54) The increasing significance of 3D printing has made it crucial to identify appropriate applications and prevent its unethical or harmful use. The FDA has already approved over 100 3D-printed medical devices, spanning orthopedic and cranial implants, and dental solutions like crowns, external prosthetics, and surgical tools. Furthermore, they've approved SPRITAM (levetiracetam), a 3D-printed medication utilizing the Zip Dose technique to treat epilepsy. (55) Because regulations for drug manufacturing, distribution, and compounding vary significantly from country to country, they must be carefully examined when implementing on-demand or industrial 3D printing for pharmaceuticals.(56) Once, the idea of using 3D printers to create our medications seemed like a futuristic fantasy. But now, it's rapidly becoming a tangible reality, and its use will undoubtedly continue to expand.(57) This section will explore the existing rules and regulations surrounding the large-scale production of 3D printed products. It will also highlight the areas where current regulations are insufficient or unclear, creating obstacles for the progress of advanced pharmaceutical manufacturing techniques.(58) The way 3D printing is used in medicine is generally governed by the same rules as conventional medical equipment in many places, even under the scrutiny of the FDA in the United States. However, because it's new and allows for tailored solutions, 3D printing creates specific technological, legal, and moral questions that current regulations need to address and evolve to handle.(59) To tackle the growing use of 3D-printed medical devices, the FDA issued guidelines in 2017. These guidelines covered the necessary considerations for design, production, and testing. However, the FDA's guidance did not include bioprinting technologies.(60) This document provides extra information to help manufacturers meet current rules for medical devices, focusing on things like how they're made, quality control, and what paperwork needs to be submitted. The FDA understands that this advice might change over time as technology improves, especially with new developments like using biological materials and making devices right where patients are treated. (61) The European Medicines Agency, much like the FDA in the US, is a major influence on how 3D printing is used in healthcare. Although there aren't specific rules yet for 3D-printed medications, companies still need to follow the Machinery Directive 2006/42/EC, which involves carefully evaluating potential risks. The EU's laws are designed to be adaptable to new technologies, offering companies the freedom to find different ways to meet safety and design standards. This allows them to select the most appropriate technological solutions to satisfy the necessary regulations.(62)

6. CONCLUSION

This review highlights the significant potential of 3D printing technologies in advancing pharmaceutical drug delivery systems through the fabrication of personalized, complex, and multifunctional dosage forms. Techniques such as fused deposition modeling, hot-melt extrusion, semi-solid extrusion, inkjet printing, selective laser sintering and stereolithography have demonstrated utility in formulating controlled-release, gastro-retentive, mucoadhesive and multi-drug systems with enhanced precision and therapeutic efficacy. FDM and HME, in particular, have shown superior applicability due to their compatibility with thermoplastic polymers and scalability for sustained-release dosage forms. SSE offers advantages for thermolabile drugs, while inkjet and laser-based approaches allow for high-resolution and on-demand drug deposition. These technologies support the incorporation of poorly water-soluble drugs, improve bioavailability, and enable real-time dose personalization. Despite these advances, challenges remain related to material limitations, process standardization, regulatory frameworks, and industrial-scale production. Further research is warranted to optimize formulations, develop biocompatible and regulatory-compliant excipients, and validate clinical efficacy. In conclusion, 3D printing represents a transformative approach in pharmaceutics, offering innovative solutions for precision medicine, personalized therapy, and enhanced patient compliance, thereby marking a progressive shift toward next-generation drug delivery systems.

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8. DECLARATIONS

8.1. Authors' contributions

All authors contributed equally to the preparation of this review study.

8.2. Ethics approval and consent to participate

Not applicable

8.3. Consent for publication

Not applicable

8.4. Availability of data and material

Not applicable

8.5. Competing interests

The authors declare that they have no competing interests.

8.6. Funding

Not applicable

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