

FROM CONCEPT TO CLINIC: THE EVOLUTION OF 3D-PRINTED MEDICINES**Aditya Jaiswal, Sandip Prasad Tiwari*****Faculty of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh India (492101)***Corresponding Author's E mail: sandip.tiwari@kalingauniversity.ac.in

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ABSTRACT

Three-dimensional (3D) printing is transforming the field of pharmaceutical manufacturing by facilitating the development of individualized medications and sophisticated drug delivery mechanisms. This review explores the innovations, uses, and challenges associated with 3D-printed pharmaceuticals. Following the FDA's approval of Spritam® in 2015, research has broadened across different 3D printing methods, such as Fused Deposition Modeling (FDM), Stereolithography (SLA), Selective Laser Sintering (SLS), and Inkjet Printing. These techniques provide exact control over dosage forms, allowing for customized drug release profiles, intricate shapes, and formulations containing multiple drugs. The uses of 3D printing in the pharmaceutical sector encompass personalized dosages for children and elderly patients, modified-release systems featuring zero-order or pulsatile profiles, and polypills that combine several active ingredients to streamline medication schedules. Innovations including stimuli-responsive materials and bioprinting further improve therapeutic results by permitting active drug delivery mechanisms.

Keywords: Laser Sintering, Pharmaceutical, Stereolithography

1. Introduction

Three-dimensional (3D) printing, commonly known as additive manufacturing, has become a groundbreaking technology in numerous industries, particularly in healthcare and pharmaceuticals. Its use in drug production presents exceptional opportunities to tackle issues related to personalized medicine, intricate drug delivery systems, and efficiency in manufacturing. Katstra et al. (2000) were the first to utilize powder-based 3D printing technology for the production of oral dosage forms featuring precise geometric characteristics¹. Their research illustrated how 3D printing can influence both the microstructure and macrostructure of pharmaceutical goods, thereby allowing for customized drug release kinetics. In contrast to conventional manufacturing approaches that depend on compression or molding, 3D printing enables the design of complex internal geometries that enhance drug dissolution and bioavailability. This innovation served as a springboard for further investigation

into patient-specific formulations and cutting-edge drug delivery mechanisms, emphasizing 3D printing's potential to transform pharmaceutical manufacturing.

Expanding on this groundwork, Rowe et al. (2000) examined the practicality of creating oral dosage forms with various release mechanisms through 3D printing technology. Their findings revealed the capability to produce tablets that exhibit zero-order release kinetics by accurately laying down materials in specific patterns. This advancement showcased the potential to manufacture complex pharmaceutical products that provide drugs at a steady rate over time². The research also confirmed the feasibility of the ZipDose® technology, which was subsequently used by Aprelia Pharmaceuticals for Spritam®, marking it as the first FDA-approved drug produced through 3D printing. By addressing the challenges associated with traditional manufacturing strategies, such as the difficulty in achieving controlled release profiles, 3D printing facilitates the creation of advanced dosage forms that improve therapeutic effectiveness and patient adherence.

Beyond oral dosage forms, Wu et al. (2003) explored the use of solid free-form fabrication techniques to develop drug delivery devices with controlled designs and compositions. Their study assessed critical factors influencing print quality, drug loading efficiency, and dissolution behavior³. The findings indicated that 3D printing methods could effectively create intricate drug delivery devices with predictable dissolution patterns, providing enhanced control over pharmacokinetics compared to conventional matrix tablets or capsules. By allowing the precise adjustment of internal elements, such as channels or barriers within a device, 3D printing enables the creation of sophisticated drug delivery systems customized for specific therapeutic needs. This capability is especially important for overcoming challenges in sustained-release formulations or targeted delivery⁴.

The idea of personalized medicine has gained notable momentum recently, with 3D printing presented as a potential approach for customizing medications to meet individual patient requirements. Sandler et al. (2011) introduced inkjet printing technology as an innovative method for pharmaceutical manufacturing, demonstrating its capacity to accurately deposit specific amounts of active pharmaceutical ingredients on edible substrates. Their results showcased dosing accuracy within 5% of the target values across a broad range of doses, emphasizing the promise of this approach for producing personalized medicine⁵. This method is particularly beneficial for drugs with narrow therapeutic windows or those necessitating individualized dosing modifications based on patient-specific variables such as age, weight, or genetic factors. By facilitating on-demand production of tailored medications at

healthcare settings or pharmacies, 3D printing aids the shift from uniform treatment protocols to precision medicine that optimizes therapeutic results.

2. Fundamentals of 3D Printing Technology

2.1 Principles of 3D Printing (Additive Manufacturing)

3D printing, also known as additive manufacturing (AM), refers to a layer-by-layer fabrication process that constructs three-dimensional objects directly from digital models. Unlike traditional subtractive manufacturing, which involves cutting away material from a solid block, AM builds objects by depositing successive layers of materials such as polymers, ceramics, or biological substances. In the pharmaceutical domain, 3D printing enables the precise engineering of drug dosage forms with customized shapes, structures, and drug-release profiles, thereby offering a new frontier in personalized medicine. The process begins with the creation of a computer-aided design (CAD) file, followed by slicing into 2D layers, and subsequent layer-by-layer deposition using specialized printers⁶.

2.2 Types of 3D Printing Techniques Used in Medicine

Several 3D printing techniques have been adapted to pharmaceutical and biomedical applications, each offering distinct advantages depending on the formulation needs, material compatibility, and intended clinical application.

2.2.1 Fused Deposition Modelling (FDM)

Fused Deposition Modelling is one of the most widely used techniques in pharmaceutical 3D printing. It involves the extrusion of a thermoplastic filament (often drug-loaded) through a heated nozzle, which deposits the molten material layer by layer onto a build platform. After cooling and solidifying, these layers form the desired structure. FDM is cost-effective and user-friendly but limited to thermally stable drugs due to the high temperatures involved. It is particularly suitable for producing immediate and controlled-release dosage forms⁷.

2.2.2 Inkjet Printing

Inkjet printing is a non-contact technique that dispenses small droplets of ink-like formulations onto substrates with high precision. In pharmaceutical applications, it is often used to deposit active pharmaceutical ingredients (APIs) or excipients in a defined pattern. It supports both thermal and piezoelectric mechanisms for droplet generation. Inkjet printing is ideal for low-dose formulations and

combination therapies, allowing for personalized and rapid-dose adjustments. However, its limitations include difficulty in achieving higher drug loadings and the requirement for low-viscosity inks⁸.

2.2.3 Stereolithography (SLA)

Stereolithography utilizes a laser or UV light source to selectively cure and solidify photopolymer resins layer by layer. SLA provides extremely high resolution and is capable of fabricating intricate internal geometries, making it suitable for developing complex drug delivery devices and implants. However, its application in pharmaceutical printing is limited by the need for biocompatible, photo-curable resins, and the risk of residual photo initiators that may be toxic.

2.2.4 Selective Laser Sintering (SLS)

Selective Laser Sintering employs a high-powered laser to fuse powder particles (such as polymers or drug-polymer blends) together. It does not require support structures, allowing for the production of highly complex shapes. SLS can handle a wide range of materials and is suitable for both immediate- and sustained-release systems. Despite its advantages, the high temperatures and limited availability of pharmaceutically acceptable powders can be challenging⁹.

2.2.5 Semi-Solid Extrusion and Binder Jetting

Semi-solid extrusion involves the use of a syringe-based system to extrude pastes or gels containing APIs and excipients. This technique operates at room or body temperature, making it suitable for thermolabile drugs. Binder jetting, on the other hand, involves the deposition of a liquid binder onto a powder bed to selectively bind particles together. This method allows for high-speed printing and is used in the fabrication of fast-dissolving tablets, such as the FDA-approved product Spritam (levetiracetam). The main limitations include post-processing steps (e.g., drying) and the risk of poor mechanical strength.

3. Design and Engineering of Personalized Dosage Forms

The ability of 3D printing to create intricate structures with high spatial accuracy has revolutionized the design and engineering of pharmaceutical dosage forms. Unlike conventional drug manufacturing, which follows a “one-size-fits-all” approach, 3D printing enables the creation of patient-centric medicines tailored to individual physiological and therapeutic needs. Key design parameters such as dose strength, drug release profile, and tablet geometry can be digitally controlled, offering unprecedented flexibility in personalized therapy¹⁰.

3.1 Customization of Drug Dose, Release Profile, and Geometry

One of the core strengths of 3D printing in pharmaceuticals is its ability to customize drug dosage forms on-demand. Using CAD software, the drug dose can be precisely adjusted by modifying the volume or concentration of the active pharmaceutical ingredient (API) within the printed matrix. This is especially beneficial for patients requiring dose titration, such as those with renal impairment or paediatric patients. Moreover, by varying infill density, layer thickness, internal structure (e.g., honeycomb or hollow patterns), and surface area, the drug release profile can be engineered to meet therapeutic goals—ranging from immediate to sustained or pulsatile release. Additionally, altering tablet geometry (e.g., ring-shaped, multi-layered, or porous forms) allows for controlled disintegration, swallowing ease, or targeted delivery within the gastrointestinal tract¹¹.

3.2 Multidrug Printing (Polypills)

Multidrug printing, or polypill technology, is a transformative application of 3D printing where multiple APIs with different release kinetics are incorporated into a single dosage form. Each compartment of a polypill can be engineered to release its content at different rates or times, enabling complex therapeutic regimens to be simplified into a single administration. This approach is particularly beneficial in managing chronic diseases such as diabetes, hypertension, and cardiovascular disorders, where polypharmacy is common. Reducing the pill burden improves patient compliance and decreases the risk of medication errors. 3D printing enables spatial separation of incompatible drugs and allows the customization of drug combinations for individual patients, making polypills a promising step toward precision medicine¹².

3.3 Paediatric and Geriatric Applications

Children and elderly patients often face difficulties with standard dosage forms due to swallowing challenges, taste aversion, or physiological differences in metabolism. 3D printing addresses these concerns by allowing the fabrication of patient-specific formulations in terms of dose, size, shape, color, and flavour.

For paediatric use, chewable or rapidly dissolving tablets with cartoon shapes or flavours can improve acceptance. For geriatric patients, tablets can be printed with higher porosity for easier swallowing or modified-release profiles to match slowed metabolism or polypharmacy requirements. The ability to

rapidly produce small-batch, customized formulations makes 3D printing particularly well-suited to these age groups¹³.

3.4 Complex Release Kinetics (Immediate, Sustained, Delayed)

Traditional drug formulations often rely on chemical excipients or coatings to control release, but 3D printing introduces spatial control over drug placement and matrix composition. This enables the precise engineering of complex release kinetics within a single dosage form. Immediate-release zones can be constructed with porous structures or water-soluble polymers for rapid disintegration. Sustained-release segments can incorporate denser matrices or hydrophobic excipients to slow drug diffusion. Delayed-release features can be achieved by printing enteric coatings or creating physical barriers that dissolve at specific pH levels or time points¹⁴.

4. Preclinical and Clinical Development

The translation of 3D-printed medicines from concept to clinical use requires rigorous preclinical and clinical evaluation to ensure safety, efficacy, and therapeutic equivalence to conventional formulations.

4.1 In Vitro Drug Release Testing

In vitro testing is a critical first step in evaluating 3D-printed dosage forms. These tests assess drug release kinetics, stability, mechanical strength, and dissolution profiles under simulated physiological conditions. The complexity of 3D-printed structures demands customized testing protocols, especially when dealing with multi-compartment systems or variable geometry. Modified USP apparatus and advanced imaging techniques (e.g., micro-CT, Raman mapping) are increasingly used to analyze spatial distribution and drug release behaviour¹⁵.

4.2 Animal Models for Bioavailability and Efficacy

Animal studies provide essential insights into the bioavailability, biocompatibility, and therapeutic performance of 3D-printed formulations. Rodent and porcine models are commonly used to evaluate oral dosage forms, while implantable 3D-printed drug devices are tested for site-specific release and tissue interaction. These studies help establish pharmacokinetic parameters such as absorption, metabolism, and elimination before transitioning to human trials¹⁶.

4.3 Clinical Trials of 3D-Printed Drugs

Clinical trials validate the safety and efficacy of 3D-printed drugs in human populations. The most notable example is Spritam® (levetiracetam), the first FDA-approved 3D-printed oral tablet, which

demonstrated bioequivalence to its conventional counterpart while offering rapid disintegration. Ongoing clinical investigations are exploring 3D-printed drugs for individualized therapy in oncology, infectious diseases, and paediatric care. Adaptive trial designs may be employed to evaluate personalized formulations¹⁷.

4.4 Pharmacokinetic and Pharmacodynamic Considerations

3D-printed formulations can significantly influence pharmacokinetic (PK) and pharmacodynamic (PD) profiles through controlled drug release and site-specific delivery. Key PK parameters like C_{max} , T_{max} , and AUC must be carefully monitored to ensure therapeutic consistency. Personalized dose customization also necessitates individual-level PK/PD modelling, especially in populations with altered metabolism or polypharmacy.

5. Regulatory and Quality Considerations

5.1 Regulatory Challenges (FDA, EMA, etc.)

Regulatory frameworks are still evolving to accommodate 3D-printed pharmaceuticals. Agencies like the U.S. FDA, European Medicines Agency (EMA), and MHRA face challenges in defining 3D-printed dosage forms under existing drug categories. Current regulations require equivalence in safety, efficacy, and quality to conventional formulations, but lack detailed guidance on process validation, software control, and digital models used in printing¹⁸.

5.2 GMP Compliance in 3D Printing

Good Manufacturing Practice (GMP) compliance remains a major hurdle due to the decentralized and highly customizable nature of 3D printing. Establishing controlled environments, validating printer hardware/software, and ensuring material traceability are crucial. GMP protocols must cover aspects such as printer calibration, operator training, and environmental control for sterility and reproducibility.

5.3 Quality Control and Assurance Protocols

Traditional quality control (QC) measures must be adapted to the unique attributes of 3D-printed dosage forms. Critical quality attributes (CQAs) like drug content uniformity, mechanical strength, porosity, and dissolution rate must be validated using advanced analytical tools. Inline and real-time QC using spectroscopic and imaging technologies are being integrated to monitor print consistency¹⁹.

5.4 Standardization and Reproducibility

The lack of standardization in printer hardware, software, and material specifications hampers reproducibility across different production sites. Regulatory bodies and industry stakeholders are working to develop consensus standards (e.g., ISO/ASTM) to ensure batch-to-batch consistency and inter-laboratory reliability. Harmonized guidelines for digital file management and process documentation are also necessary²⁰.

6. Manufacturing and Scale-Up Challenges

6.1 Scalability of 3D Printing in Pharma

While 3D printing excels in small-batch and personalized medicine, scaling it up for commercial manufacturing presents technical and logistical challenges. Limitations in printing speed, batch size, and material throughput hinder large-scale production. Multinozzle printers, continuous-printing systems, and parallelization are being explored to improve scalability²¹.

6.2 Automation and Software Integration

Automation is key to integrating 3D printing into pharmaceutical workflows. Robotic handling, real-time process monitoring, and software-controlled batch management can reduce human error and enhance throughput. Seamless integration of CAD/CAM software with quality assurance systems ensures consistency and regulatory compliance²².

6.3 Cost-Effectiveness and Production Time

The cost of 3D printing remains a barrier due to specialized equipment, high-grade materials, and regulatory overhead. However, it may prove cost-effective in niche areas such as orphan drugs, individualized therapies, and point-of-care manufacturing. Reduction in development time and inventory burden offers long-term economic benefits.

6.4 Integration into Existing Manufacturing Pipelines

To achieve clinical viability, 3D printing must complement, not replace, traditional manufacturing. Hybrid approaches—where 3D printing is used for specialized dosage forms while conventional techniques handle bulk production—are being considered. This demands adaptable infrastructure, workforce training, and revised supply chain logistics²³.

7. Conclusion

Three-dimensional (3D) printing has emerged as a groundbreaking technology in pharmaceutical production, presenting unique opportunities to tackle challenges in personalized medicine, intricate

drug delivery systems, and efficient manufacturing processes. This review emphasizes the progress, uses, and hurdles of 3D-printed medications, concentrating on the potential of this technology to transform drug development and enhance patient care. The capacity of 3D printing to create dosage forms with accurate shapes, customized release profiles, and individualized drug combinations has unlocked new avenues for personalized medicine. Techniques such as Fused Deposition Modelling (FDM), Stereo lithography (SLA), and Selective Laser Sintering (SLS) facilitate the creation of medications tailored to patients' specific needs based on factors like age, weight, metabolism, and health conditions. Applications encompass polypills for managing multiple medications, modified-release systems for controlled drug administration, and stimuli-responsive formulations that adjust to particular physiological states. Moreover, combining nanotechnology with 3D printing has allowed for the creation of sophisticated solid dosage forms aimed at targeted therapies. However, the broad implementation of 3D printing in the pharmaceutical sector encounters several obstacles. These include issues with material compatibility, limitations in scalability, regulatory ambiguities, and the necessity for strong quality control measures. Present regulatory frameworks need to be updated to address the distinctive features of additive manufacturing, such as validation of digital designs and monitoring of processes in real time. Furthermore, incorporating 3D printing into healthcare systems necessitates the development of infrastructure and the education of professionals. In the future, innovations in material science, computational modelling, machine learning-driven quality assurance, and the integration with digital health platforms are expected to propel the advancement of 3D-printed pharmaceuticals. By surmounting existing challenges, this technology holds the promise to reshape pharmaceutical manufacturing and enhance therapeutic outcomes through patient-centered solutions that revolutionize contemporary healthcare practices.

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