REVIEW ARTICLE

Applications and Advancement of 3D Printing in Pharmaceutical Manufacturing and Drug Delivery

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Abstract: Three-dimensional (3D) printing is an innovative additive manufacturing technology that has tremendous potential to revolutionize various aspects of the pharmaceutical industry including drug development, product design, manufacturing and delivery. 3D printing enables precise fabrication of complex drug products with customized compositions and geometries that cannot be produced through conventional processes. It facilitates rapid prototyping thereby accelerating drug development process. 3D printed dosage forms with capability of controlled, delayed and triggered drug release have potential to enhance patient compliance and therapeutic outcomes. Further, 3D printed personalized medications tailored to individual patient needs hold promise to improve medication accessibility and efficacy. Though 3D printing in pharmaceuticals is still in its infancy, ongoing research efforts aim to address key challenges including regulatory compliance, process optimization, material characterization and scale-up. As the technology advances further, 3D printing is expected to significantly transform pharmaceutical manufacturing by making on-demand, decentralized production a reality

Keywords: 3D Printing; Additive manufacturing; Personalized medicines; Drug delivery systems; Pharmaceutical manufacturing; Rapid prototyping.

1. Introduction

Traditional manufacturing techniques have limitations in fabricating products with customized compositions and complex geometries. Three-dimensional (3D) printing offers an exciting new platform to address such challenges and has enormous potential to revolutionize various aspects of the pharmaceutical sector. 3D printing or additive manufacturing is a layer-by-layer process where a 3D digital model is translated into physical structures by selective deposition of material. Pharmaceutical applications of 3D printing were initiated in early 2000 with fabrication of drug-releasing implants and prosthetics using this technique. Since then, significant advancements have been made and 3D printing is now being actively explored for drug development, personalized drug products and novel drug delivery systems. One of the major drivers for the adoption of 3D printing in pharmaceuticals is the capability to design and produce complex drug delivery systems and dosage forms with customized compositions. Conventional manufacturing techniques provide limited control over spatial arrangements of multiple drugs and evolution of composition with time. In contrast, 3D printing allows incorporation of multiple drugs within a single dosage form with precise control over release kinetics and burst release. This facilitates development of personalized medicines tailored to individual patient needs and multi-drug regimens with enhanced efficacy. Further, 3D printed dosage forms such as tablets and capsules with patient-centric formulations hold potential to improve medication adherence.

Rapid prototyping is another key advantage offered by 3D printing which enables manufacturing of prototype drug products and devices in a timely and cost-effective manner. This significantly accelerates formulation development and optimization during early phases of drug discovery. Several studies have reported reductions in product development time from 18-24 months to just 3-6 months using 3D printing. The ability to rapidly modify design and composition supports iterative testing and screening of multiple prototypes thus facilitating nimbler innovation in dosage form design. 3D printing also enables scale-up and commercial manufacturing of approved drug products through automated, digital processes with minimal manual intervention and reduced requirement of tooling. Regulatory acceptance and safety concerns around 3D printed pharmaceuticals continue to be evaluated as the field advances. Research focus is ongoing to optimize materials and processes for regulatory compliance, develop efficient

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scale-up strategies and characterize mechanical properties and degradation behaviors of printed dosage forms. Standardization of 3D printing workflows, establishment of critical process parameters and implementation of quality by design principles also need attention to facilitate technology transfer.

The key advantages of 3D printing are:

- Precise and accurate dosage for potent medications.
- Production costs drop as a result of lesser wastage
- Higher medication loading when compared to standard dose formulations.
- 3D printers are less expensive and take up less room.
- Small-batch production is feasible.
- It enables multidosing, adjustable droplet size, complex drug release patterns, and dosage strength.

On the otherhand, the disadvantages of 3D printing include:

- High precision viscosity ink is the only kind that can be used in inkjet printers.
- Though it shouldn't attach to the printer's other components, ink formulation material should be self-binding.
- Ink binding with printer materials has an impact on the rate of medication release.
- It is impossible to print huge items.
- It can be used with only specific kinds of raw materials which may not be always compatible with active pharmaceutical ingredients

The main aim of this review is to comprehensively assess the impact of 3D printing technology in advancing various aspects of pharmaceutical R&D and manufacturing including drug development, product design, personalized medicines and novel drug delivery systems. It also aims to highlight the technology's significant potential as well as ongoing research areas that require further optimization to fully realize its transformative capabilities.

2. 3D Printing Techniques in Pharmaceutical Manufacturing

A variety of 3D printing techniques have been investigated for application in the pharmaceutical sector. Appropriate selection of the printing methodology depends on the material characteristics and structural complexity required for the drug product or device. Some of the commonly used techniques are discussed below: [6, 7]

2.1. Fused Deposition Modeling (FDM)

FDM, also known as Fused Filament Fabrication (FFF), is the most widely used 3D printing process in the industry. It involves extruding thermoplastic feedstock such as ABS, PLA or polycaprolactone through a movable extruder head which deposits the material layer by layer as per the digital design [1]. The simplicity, low cost and ability to print diverse functional polymers using FDM presents opportunities for rapid fabrication of pharmaceutical prototypes and customized dosage forms. Researchers have demonstrated FDM printing of oral thin films, tablets containing multiple drugs as well as complex implants [2-4]. However, issues pertaining to material residue in the printer head and difficulty in incorporating hydrophilic drugs limit the application of FDM in some cases.

2.2. Stereolithography (SLA)

SLA is based on photopolymerization where a liquid photocurable resin is selectively cured using a laser beam. Layer-by-layer solidification occurs as the laser traces the part cross-section pattern on the resin surface [5]. The high resolution and accuracy of SLA allows fabrication of structures with minimum feature size of about 100µm, making it well suited for cell scaffolds, medical models and complex topologies. Biofunctional resins are available that have been used to print cell-laden hydrogels, drug-eluting implants and microneedle arrays [6-8]. Post-printing processes like heat curing may be needed depending on the application. Nevertheless, limited choice of biocompatible resins and difficulties related to uncured resin removal restrict wider usage of SLA in pharma.

2.3. Selective Laser Sintering (SLS)

SLS fabricates parts by fusing powdered thermoplastic, ceramic or metallic materials on a build tray using an infrared laser [9]. This full melting mode enables fabrication of high strength parts and suits printing thermally sensitive materials like protein drugs. However, residual powder and requirement for support structures prove challenging for direct drug delivery applications. On the other hand, selective laser melting where complete melting occurs point-by-point has been utilized to print bioresorbable magnesium implants [10]. Overall, SLS is more suitable for medical device rather than drug product fabrication due to post-processing difficulties.

2.4. Inkjet Printing

Inkjet printing deposits photo-curable liquid pre-polymers, wax-based binders or pharmaceutical inks in a drop-on-demand manner to construct 3D structures [11]. This non-contact method avoids cross-contamination and enables inclusion of multiple components within a single print. Thermally stable as well as heat-labile drugs can be incorporated into soluble filaments, pre-polymers or edible inks for printing. researchers have printed various dosage forms including oral films, orodispersible tablets and transdermal patches using inkjet methodology [12-14]. Nevertheless, formulating stable and scalable inks/filaments remains a technical challenge

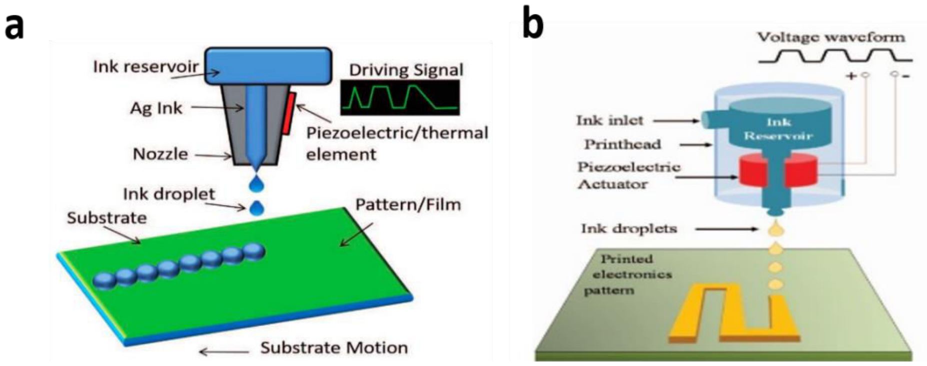

Figure 1. Process of a. Thermal inkjet printing b. Digital inkjet printing

2.5. Multi-photon Polymerization (MPP)

MPP employs near-infrared lasers to locally initiate polymerization via multi-photon absorption within a photoresist [15]. It facilitates fabrication at micro-nano resolution with minimal constraints on feature size. Thus, MPP enables structuring materials with exquisite control over pore size, shape and orientation. This allows manufacturing smart drug carriers, artificial tissues and cell scaffold mimics with close fidelity to native extracellular matrix [16]. However, limitations associated with lengthy process time and high equipment cost have prevented widespread use of MPP in pharmaceutical applications to date

3. Materials for 3D Printing Pharmaceuticals

Selection of appropriate materials is a critical aspect in the development of 3D printed drug products and medical devices. The printing material should not only be compatible with the 3D printing process but also meet functional requirements like biocompatibility and mechanically stability after printing. Some of the commonly investigated materials for pharmaceutical applications are:

3.1. Polymers

Thermoplastic and photopolymers constitute the major class of materials used for 3D printing. Polylactic acid (PLA), polycaprolactone (PCL) and polyvinyl alcohol (PVA) are some favourable biodegradable and biocompatible thermoplastics that have been 3D printed into drug-loaded scaffolds, implants and tablets [1,2]. Acrylonitrile butadiene styrene (ABS), polyethylene terephthalate glycol (PETG) and nylon provide good mechanical properties suitable for durable devices [3]. Photopolymers like polyetheylene glycol diacrylate (PEG-DA) and GelMA offer excellent resolution for SLA printing of cell-laden constructs, while methacrylated gelatin supports printing temperature-sensitive cultures [4,5]. In addition, chitosan, alginate and heparin can be combined with thermoplastics or photopolymers to imbue antimicrobial or bioadhesive properties. Overall, functional polymers with customizable degradation and release profiles are highly desirable for 3D printed pharmaceuticals. [12-14]

3.2. Ceramics

Bioinert and osteoconductive ceramics like hydroxyapatite and titanium dioxide are preferred for fabricating bone grafts and dental implants using 3D printing [6]. Hydroxyapatite ceramics in particular have been fabricated as anatomically shaped scaffolds to promote tissue ingrowth owing to their chemical resemblance to the mineral component of bones and teeth. However, brittleness and difficulty in sintering porous architectures limit their application in load-bearing implants. On the other hand, bioglass 45S5 and glass ceramics exhibit superior bioactivity through formation of hydroxycarbonate apatite (HCA) upon interacting with body fluids. Ongoing research focuses on incorporating drug-releasing capacity and mechanical strength optimization in 3D printed ceramics for enhanced performance [11].

3.3. Hydrogels

Hydrogels made up of natural (collagen, gelatin, alginate, chitosan) or synthetic (PEG, PVA, PNIPAM) polymers have emerged as ideal biomaterials for pharmaceutical and tissue engineering applications due to their high water content, permeability and structural similarity to living tissues [7]. 3D printable hydrogels have tunable physical properties like stiffness, degradation and swelling behavior. Additionally, they can encapsulate both hydrophilic and hydrophobic drugs in a sustained manner. Thus, researchers are actively exploring hydrogel bioinks for printing customized cell-laden constructs, soft tissue implants and wound dressings with spatially controlled porosity using various 3D bioprinting methods [8].

3.4. Waxes and sugars

Phase change materials like waxes (paraffin, beeswax), polyvinyl alcohol and sugars (glucose, sucrose) offer advantages like low cost, printability at ambient temperature and safe degradation into non-toxic products. They have been utilized for 3D printing orally disintegrating tablets, porous tissue templates and rapidly dissolving microneedles using pharmaceutical printers [8-10]. The printed constructs made of sugars or waxes can incorporate labile drugs and cells, providing opportunities for advanced personalised therapies and regenerative medicine applications

4. Applications of 3D Printing in Pharmaceuticals

4.1. Drug Development and Product Design

3D printing offers numerous advantages for drug development by facilitating rapid prototyping of drug products and formulations. It enables manufacturing of complex internal architecture prototypes in days instead of the conventional weeks or months. This significantly reduces product development timelines and costs by allowing high-throughput screening of multiple design iterations. Researchers have 3D printed various prototypes like immediate-release tablets, multiparticulates with sustained release coatings, as well as complex core-shell structures to prove drug release concepts in the early development phases [1,2]. 3D printing also helps in developing bioprinted tissue and disease models for in vitro drug testing, reducing reliance on animal studies. Altogether, 3D printing supports more agile and effective product design within compressed drug development windows.

4.2. Personalized Drug Products and Precision Medicine

3D printing is uniquely positioned to advance precision medicine through fabrication of customized drug formulations tailored to suit patients' individual conditions, physiology and medication history [3]. It allows incorporation of multiple active ingredients, with variations in dosage and release profiles, within a single printable composite. Researchers have demonstrated 3D printed tablets containing patient-specific combinations of drugs in pre-determined ratios [4]. 3D printed pellets and capsules containing stratified layers of different drugs offer another avenue for precision dosing [5]. Going forward, incorporation of real-time diagnostics and feedback loops have potential to enable truly personalized drugs on demand. This promises effective patient management while minimizing adverse effects associated with one-size-fits-all treatment approaches

4.3. Novel Drug Delivery Systems

3D printing facilitates fabrication of novel ingestible, implantable and transdermal drug delivery systems with intricate architectures not possible through traditional methods. Some examples explored include controlled release tablets with multiple release zones, capsules containing drug reservoirs separated by diffusion barriers, and customizable bioresorbable implants [6-8]. By enabling multi-material printing, complex constructs have been 3D printed layer-by-layer with drugs encapsulated in one material and released in a controlled manner upon exposure to another material [9]. 3D printed microneedle and dissolvable micromachined pill arrays constitute other innovative platforms for transdermal and sublingual delivery explored by researchers [10,11]. Overall, the geometric freedom offered through 3D printing holds promise to greatly augment the biopharmaceutical toolbox with unprecedented control over drug release profiles and targeting capabilities.

5. Advancements in 3D printed dosage forms

5.1. Tablets

Tablets remain the most widely researched 3D printed dosage form due to advantages like easy portability and functionality. Researchers have fabricated tablets containing multiple drugs in predetermined compositions using inkjet, powder bed fusion and extrusion techniques [1,2]. Novel structures like core-shell tablets with drug cores encapsulated in immediate/extended release polymer shells have shown promising release modulation [3]. Combining computing assisted 3D printing with real-time process monitoring allows production of personalized dose-on-demand tablets on an industrial scale [4]. Recent advances expanded the repertoire to orally disintegrating tablets, swallowable drug capsules and tableted medicinal pellets with intricate geometries tailored for pulsatile release [5,6]

5.2. Capsules

3D printed capsules serve as innovative alternatives to replace conventional hard/soft gelatin capsules. Liquid polymeric filaments have been extrusion printed to yield highly customizable capsular forms containing multiple drugs, cells or biologics [7,8]. Researchers have also fabricated complex capsular implants containing drug and cell patterns within a multipart structure using stereolithography [9]. Edible capsules printed from sugars/gelatin using inkjet have shown potential for pulsatile release with "on/off" switches [10]. Bioprinted capsular constructs hold promise as personalized organoid growth structures and implantable 3D tissue engineered constructs

5.3. Implants and injectables

3D printing enabled manufacturing of intricate, patient-matched craniofacial and orthopedic implants using biocompatible polymers like PEEK and titanium. Such implants showed mechanical properties matching native bone along with drug/growth factor incorporation abilities for regeneration [11,12]. Biodegradable magnesium and polyester implants have also been printed for controlled antibiotic elution at specific sites [13,14]. Microparticle-laden hydrogel bioinks supported extrusion bioprinting of cell-laden implants and injectable scaffolds/ constructs with promise in tissue engineering applications [15,16]. Nanorobotic 3D printing further facilitates production of targeted intracellular drug delivery vehicles with superior cellular uptake [17].

3D printing continues to revolutionize dosage form fabrication by unlocking new avenues to reimagine design, architecture, compositional versatility and performance of personalized drug products. Advancements from basic research tables/capsules to clinically translatable implants/injectables bring the technology ever closer to realizing its true potential in future healthcare systems. Success will depend on overcoming key issues including regulatory compliance, cost effectiveness, biomaterials optimization and clinical validation through well-designed studies. Continuous multi-stakeholder efforts can help accelerate 3D printing adoption across diverse pharmaceutical applications

6. Conclusion

3D printing has made substantial advances in transforming various aspects of the pharmaceutical landscape. Its unique abilities to fabricate intricately structured and customized dosage forms hold immense potential in facilitating individualized patient care. 3D printed drug products can address pressing needs around convenient dosing, controlled delivery and medication adherence. Meanwhile, its role in product design and prototyping supports more agile drug development paradigms. While technological and regulatory challenges persist, ongoing advancements provide optimism around 3D printing's capability as an industrial manufacturing platform. With continued improvements in materials science, modeling and quality management processes, 3D printing is anticipated to significantly impact the future of pharmaceutical manufacturing. Regulatory clarity and collaborative efforts across academia, industry and healthcare stakeholders will be instrumental in realizing 3D printing's transformative promise.

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