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The Age of Digital Pharmaceuticals: Exploring 3D Printing – Present Realities and Future Outlook

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ABSTRACT

3D printing represents a cutting-edge approach for fabricating three-dimensional structures through the layer-by-layer deposition of materials guided by computer software. Its integration into the pharmaceutical field is driven by its transformative capacity to produce customized dosage forms tailored to individual patient requirements, as it allows for the fabrication of products in diverse sizes and geometries. A key benefit of personalized 3D-printed tablets lies in their ability to incorporate multiple active ingredients within a single dosage unit, thereby minimizing the number of daily medications, reducing dosing frequency, and enhancing treatment adherence. Moreover, this technology enables the manufacturing of limited or patient-specific batches, offering flexibility in drug production. However, several technical obstacles must be addressed before 3D printing can achieve broad implementation in pharmacy. Currently, five principal 3D printing methods are utilized in pharmaceutical research and development: powder bed printing, selective laser sintering, stereolithography, extrusion-based printing, and electrohydrodynamic 3D printing. This review explores the progress, research emphasis, and future potential of each of these technologies.

Keywords: Electrohydrodynamic 3D printing, Selective laser sintering, Powder-based printing, Extrusion moulding printing, Stereolithography

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Introduction

Three-dimensional (3D) printing is a modern manufacturing technique that constructs physical objects layer by layer under the guidance of specialized computer software. One of its defining characteristics is its ability to create intricate and geometrically complex structures. Because of this versatility, the technology has already become well established in engineering and is rapidly transforming medicine and pharmacy [1].

The expressions “three-dimensional printing,” “additive printing,” “additive manufacturing,” and “rapid prototyping” are often used interchangeably to describe this process. Unlike conventional “subtractive manufacturing,” which involves shaping an object by removing material from a solid block, additive manufacturing builds the desired structure through successive layering, giving rise to its descriptive name “3D printing” [2, 3].

In essence, the workflow of 3D printing begins with designing the desired object using Computer-Aided Design (CAD) software, which is then exported as a stereolithographic (STL) file. This file divides the digital model into a stack of two-dimensional slices that are sequentially printed to reconstruct the final 3D structure. Accordingly, the technology relies on three major components: (1) the hardware or printer itself, (2) the software that converts CAD images into printer-recognized STL files and manages printer operations, and (3) the materials used as printing substrates [3].

The adoption of 3D printing in pharmaceutical sciences is largely due to its transformative capacity to fabricate patient-specific dosage forms that align with individual therapeutic requirements [4]. The concept of personalized medicine originates from the biological complexity of the human body, where factors such as age, sex, genetic

expression, and health condition influence how drugs are absorbed, metabolized, and eliminated. Consequently, personalized dosing or formulations are often necessary but not always available [5]. This is particularly relevant in pediatric and geriatric populations, where dosage needs fluctuate significantly—children because of rapid developmental changes, and elderly patients because of gastrointestinal dysfunction, altered renal clearance, and frequent polypharmacy [6]. Despite advances in pharmaceutical technology that aim to individualize therapy, the full realization of patient-tailored medication based on genetic and physiological profiles remains incomplete [4]. Traditional strategies for dose personalization include the use of liquid formulations, which allow flexible dosing by adjusting the administered volume using a calibrated device, though this approach may introduce measurement inaccuracies. Similarly, dividing scored tablets is a common but imperfect method for dose adjustment. Other modern systems, such as multiparticulate pellet dispensers, Solid Dosage Pens, and cuttable oral films, have been explored for more precise dosing [6, 7].

Inkjet printing, regarded as a technological forerunner of 3D printing, offers another personalized dosing approach. It adapts digital inkjet principles—where images are printed by ejecting minute ink droplets—to pharmaceuticals by replacing ink with drug solutions and paper with edible substrates [6]. Dosing can be modulated by altering the number of printed layers or the surface area of the print, ensuring high precision and control over drug content and release. This makes inkjet printing particularly suitable for producing low-dose formulations in the microgram range [1, 6].

Compared to previous personalization techniques, 3D printing provides greater versatility by producing dosage forms in various shapes, sizes, and internal structures. Researchers are actively investigating how manipulating parameters such as tablet geometry, surface area, and infill density can regulate dosage strength—an approach especially valuable in pediatric care, where dose variability and swallowing difficulties are prevalent [1]. When combined with 3D scanning that captures a patient's anatomical dimensions, this technology could enable the creation of customized drug delivery systems [8, 9]. Examples include patient-specific nasal devices [8, 10], dental guards fabricated from polylactic acid and polyvinyl alcohol composites [9], and intrauterine implants [11, 12].

A crucial advantage of 3D-printed personalized tablets lies in the potential to combine multiple active pharmaceutical ingredients (APIs) into a single dosage unit, thereby decreasing the number of daily medications and improving adherence [13]. Several studies have demonstrated the feasibility of such combinations—for instance, tablets integrating chlorpheniramine maleate with diclofenac [14], rifampicin with isoniazid [15], and paracetamol with caffeine [16]. While fixed-dose combinations are well established in managing cardiovascular disorders, they often fail to account for individual patient variability. To address this, 3D printing enables the fabrication of complex dosage forms containing three (captopril, nifedipine, and glipizide) [13] or even five (hydrochlorothiazide, ramipril, acetylsalicylic acid, pravastatin, and atenolol) [17] APIs within one unit.

Beyond dosage customization, additive printing technologies allow broad control over drug release kinetics. For instance, powder-based techniques can produce tablets that disintegrate almost instantly—an innovation exemplified by the FDA-approved product Spritam, created with Aprecia's ZipDose technology. Conversely, fused deposition modeling (FDM) enables formulations with immediate [18, 19], extended [20, 21], or delayed [15, 22] release profiles.

Another notable benefit of 3D printing is its capability to produce limited or even single-patient batches. Compact printer designs and simplified software make in-pharmacy or hospital-based drug manufacturing feasible [1], enabling on-demand fulfillment of digital e-prescriptions [5]. Additionally, the capacity to fabricate small-scale batches of pharmaceuticals and medical devices can substantially lower research and development costs [23] **(Figure 1)**.

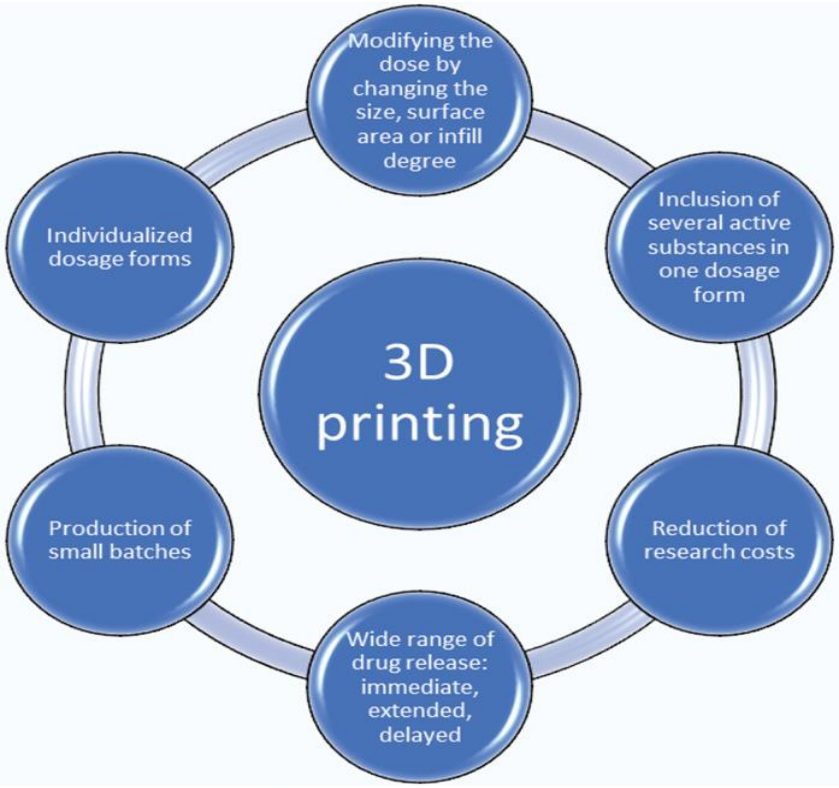

Figure 1. Advantages of 3D printing.

Although 3D printing offers numerous advantages, several technical barriers must still be addressed before it can achieve widespread implementation in the pharmaceutical field. In extrusion-based and powder-bed printing systems, for instance, material deposition relies on nozzles that can become clogged, which compromises process consistency and reproducibility [1, 2]. In powder-based and selective laser sintering techniques, the removal of residual unbound powder from the build platform poses an additional challenge, requiring that such printers be operated only in controlled laboratory or industrial environments rather than in open-access pharmacies [1]. Moreover, methods that employ solvents—such as semi-solid extrusion or powder-based printing—necessitate a supplementary drying phase, thereby extending production time. Both approaches can also result in mechanically weak dosage forms that fail to comply with pharmacopoeial standards for tablet friability [24]. Material selection further limits the process: stereolithography is restricted to photopolymerizable oligomers [25], while Fused Deposition Modeling (FDM) requires thermoplastic polymers as feedstock [5].

3D printing technologies in pharmaceutical applications

Currently, five primary 3D printing techniques are utilized in pharmaceutical manufacturing: powder-based (PB) printing, selective laser sintering (SLS), stereolithography (SLA), extrusion molding printing (EMP), and electrohydrodynamic (EHD) 3D printing [26] **(Figure 2)**.

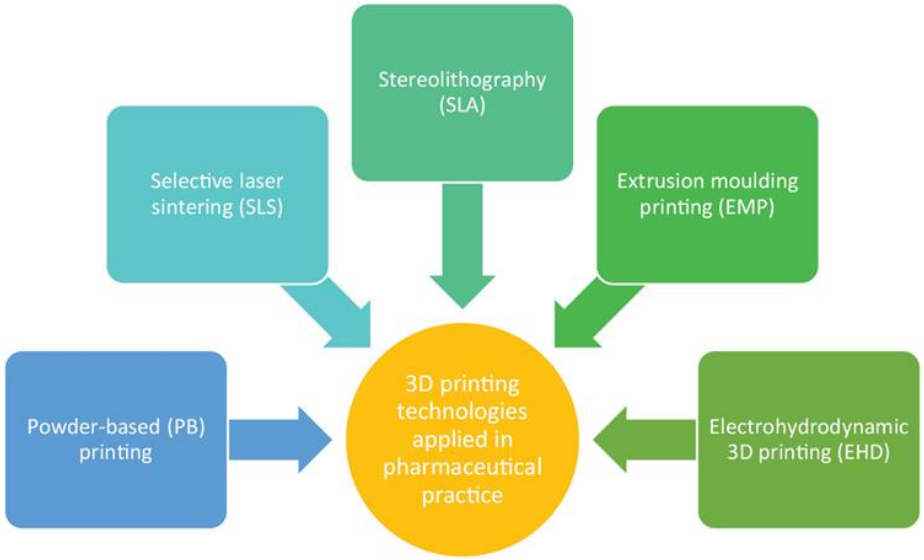

Figure 2. 3D printing technologies applied in pharmaceutical practice.

Powder-based 3D printing technology

The Powder-Based (PB) or Binder Jet 3D printing approach originated at the Massachusetts Institute of Technology and represents one of the earliest additive manufacturing methods. In this process, a thin film of powdered material is evenly laid down over the build surface, after which a printing head—typically inkjet or piezoelectric—precisely deposits binding liquid onto targeted areas, causing the particles in those regions to adhere and form the desired pattern layer by layer [14] **(Figure 3)**.

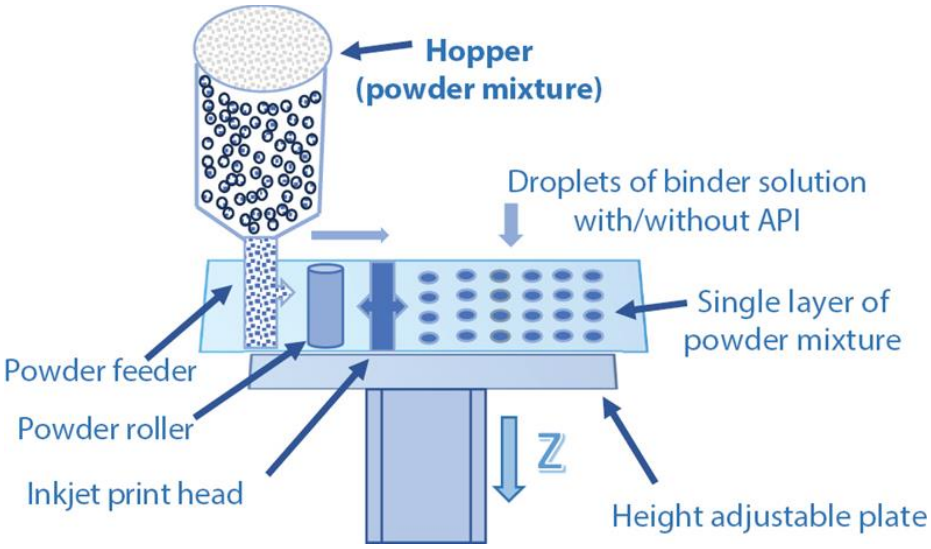

Figure 3. Powder-Based 3D printing.

This technology has been utilized across various fields, including implant fabrication [27], bone scaffold construction [28], production of solid oral dosage forms [14], cosmetic applications [29], and plastic surgery [30]. Powder bed (PB) 3D printing has enabled the creation of tablets with sophisticated drug release profiles, such as extended-release, dual-pulsatile, and first-order kinetics [1]. A notable recent application is the production of rapidly disintegrating tablets like Spritam (levetiracetam), the first FDA-approved 3D-printed drug product. These tablets consist of loosely packed particles that rapidly disintegrate in the mouth with minimal liquid, classifying them as orodispersible, and are available in doses ranging from 250 to 1000 mg, which would be challenging to achieve with traditional methods [4].

PB 3D printing relies on both a powder blend and a binder solution, and the characteristics of these components strongly influence the final product's properties, including mechanical strength, surface smoothness, and

disintegration rate. Critical powder attributes include particle size distribution [31–36], flow behavior [35, 37], packing density [28, 31, 33, 38–43], and interactions between the powder and binder [28, 44–47].
While PB printing offers advantages such as rapid-dissolving formulations, accurate drug dosing, customizable medications, and scalability, it also faces limitations, including a lack of formal regulatory guidance and the need for process optimization.

Selective laser sintering (SLS)
Selective laser sintering, introduced by C.R. Dechard at the University of Texas in 1989 and patented in 1990 [48, 49], is conceptually similar to PB 3D printing but fuses powder particles using a laser beam. The fused particles form the object, while unfused powder serves as a temporary support structure that must be removed [4]. SLS is widely used for metals but can also process polymers such as polyamides, polystyrenes, and polycarbonates [1] and has applications in tissue engineering and other scientific areas [50]. Its solvent-free process makes it particularly attractive for pharmaceutical applications [4]. Current research emphasizes material innovation, process refinement, and expanding SLS applications. The process is highly sensitive to laser power and scanning speed, which directly influence sintering quality [51–53]. Additionally, polymer properties often require enhancement through additives, expanding the method's utility in medical devices, tissue engineering, and implants [54–59].
High-speed sintering (HSS), a related technique patented by Professor Neil Hopkinson in 2003 [60], employs nylon and some elastomers [61, 62]. HSS deposits a radiation-absorbing material on the powder surface and uses infrared lamps instead of a laser, reducing equipment cost and enabling faster production by heating larger areas simultaneously.

Stereolithography (SLA)
SLA constructs 3D objects through laser-induced photopolymerization of resin. A laser traces the desired pattern at a specific depth in a resin-filled tank, forming the first layer. The tank then shifts, and subsequent layers are built sequentially, gradually forming the final object **(Figure 4)**.

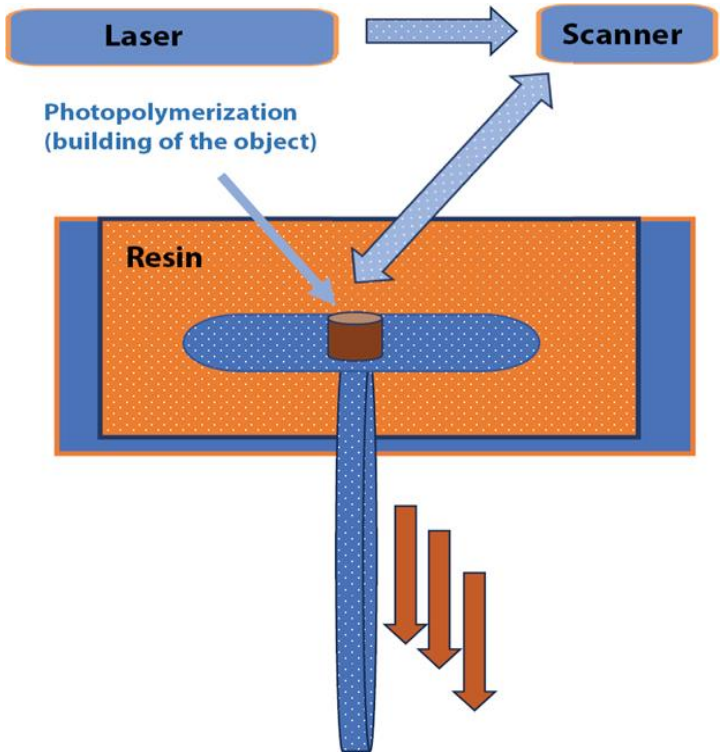

Figure 4. 3D Printing by Photopolymerization (SLA).

A straightforward approach to incorporating an active ingredient involves dissolving or dispersing it directly into the resin [4]. In stereolithography (SLA), both solid and powdered materials are typically thermoplastic polymers, including polyamide (PA), polylactic acid (PLA), and acrylonitrile butadiene styrene (ABS). SLA is infrequently

employed for producing oral dosage forms because most photopolymerizable materials are highly toxic, brittle, or sensitive to light. However, recent advances in material science are gradually mitigating these limitations. For instance, a study demonstrated the use of SLA to embed acetylsalicylic acid into polyethylene glycol diacrylate (PEGDA) medical devices, achieving complete drug release within three hours. A key advantage of PEGDA is that it allows for the direct printing of hydrogels [63].

Extrusion-based methods

Extrusion 3D printing encompasses processes in which material is forced through an opening to form fine, semi-solid filaments that solidify to construct a three-dimensional structure. Depending on whether the starting material is semi-solid or a rigid thermoplastic filament, the technique is classified as semi-solid extrusion or fused deposition modeling (FDM) [1, 5].

In semi-solid extrusion, the feedstock is a gel or paste with suitable viscosity, loaded into a syringe-like printer module. The material is deposited layer by layer according to the software-defined model. A distinctive feature of this approach is the necessity for a subsequent drying step [13, 64]. Its feasibility in pharmaceutical applications was first validated through the production of bilayer guaifenesin tablets, which exhibited release profiles comparable to the commercial equivalent containing the same drug [64]. To date, up to five different substances have been incorporated into a single 3D-printed dosage form, each in separate compartments with independently controlled release profiles [17].

A clear benefit of semi-solid extrusion is the low processing temperature, making it suitable for thermolabile compounds. Conversely, the use of solvents can compromise dosage form stability, and drying often causes shrinkage and deformation. Additional drawbacks include limited printing resolution and the mechanical fragility of the printed tablets, which may not conform to pharmacopoeial standards [1].

Fused Deposition Modeling (FDM; also known as Fused Filament Fabrication, FFF) was patented by Scott Crump and his wife in 1989 [5] **(Figure 5)**.

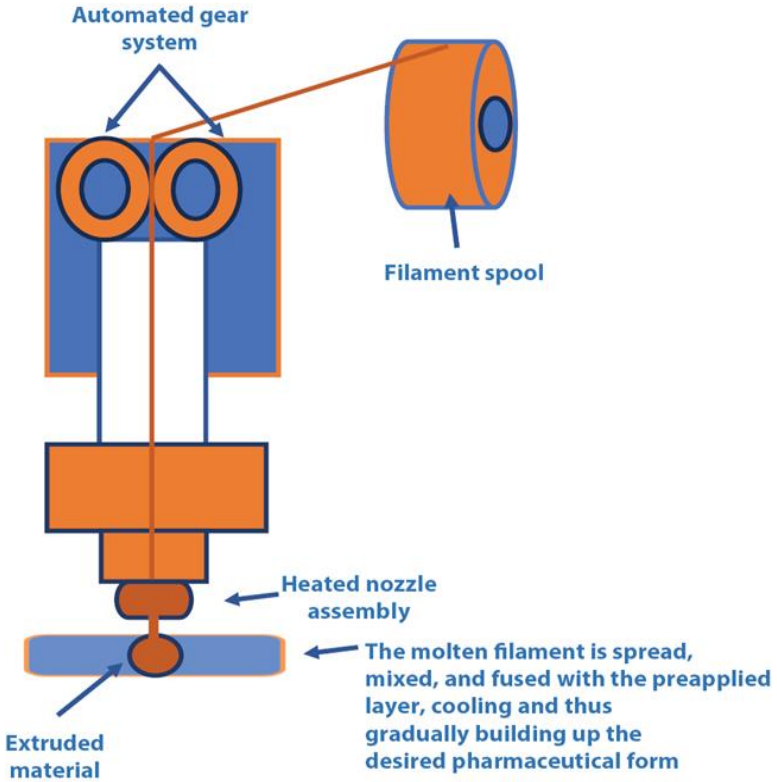

Figure 5. 3D printing by extrusion (FDM).

In this technique, the starting material is a thermoplastic polymer, which is either softened or melted within the print head nozzle. The nozzle deposits the material layer by layer onto the build platform, moving precisely along the x, y, and z axes. The platform temperature is regulated by the polymer itself, allowing the material to solidify rapidly. Once the first layer is completed, some printers lower the build platform along the z-axis, while others

raise the print head, enabling successive layer deposition until the object conforms to the designed digital model [4]. Among 3D printing technologies, this method is the most commonly utilized and will be explored in detail in this review.

Fused deposition modeling (FDM) is particularly versatile, allowing the production of virtually any solid dosage form with tailored drug release profiles [5, 65]. Medications produced via FDM benefit from the precise spatial distribution of both the active ingredient and excipients, which is challenging to achieve using conventional pharmaceutical methods [16]. Using FDM, solid dosage forms with immediate [18, 19], sustained [20, 21], and delayed [15, 22] drug release, as well as drug-eluting medical devices, can be fabricated [8, 9]. The availability of polymers soluble in physiological media with varying pH, such as methacrylic acid derivatives, further enables the development of targeted drug delivery systems [21].

Initial pilot studies applying FDM in pharmaceutical manufacturing emerged in 2014, highlighting how printer settings impact drug release profiles. A key process parameter (CPP) is the tablet's infill percentage; lower infill tablets generally release the drug more rapidly due to the differing swelling behavior of the polymer at varying densities [66]. Notably, low-density tablets may float on water, a "floating effect" that could theoretically extend gastric residence time and support sustained-release formulations [67]. However, this is debated, as lower infill tablets are often associated with rapid or unchanged release, whereas higher infill typically prolongs release. A more practical use of floating tablets may be to improve bioavailability of weakly basic drugs in acidic gastric conditions. When testing dissolution with the paddle method, modifications such as using sinkers to keep tablets submerged are recommended [5].

Another approach to accelerate dissolution from 3D-printed tablets involves incorporating channels or internal cavities to increase surface area, promoting rapid fragmentation and drug release without disintegrants [18, 68]. Controlling dissolution can also be achieved by printing mesh-like tablets with varying densities, a complexity difficult to accomplish with traditional techniques [69].

The mass-to-surface area ratio of FDM matrix tablets is another critical factor influencing drug release. Smaller tablets possess a proportionally higher surface area, resulting in faster dissolution [70]. Altering tablet geometry further modulates release; experiments with cube, pyramid, cylinder, sphere, and torus-shaped tablets demonstrated that a smaller surface area relative to mass corresponds to slower drug release [20].

Tablet shape and color, while sometimes underestimated, are vital for patient adherence and treatment effectiveness. An open-label randomized study showed toroidal tablets were most preferred, while diamond and spherical shapes were least favored. Capsules of size 2 or 3 were most acceptable regarding size. However, FDM has limitations in color variety compared to powder-based technologies [71]. The adaptability of FDM is particularly advantageous in preclinical and clinical research, allowing precise dosing for any animal model, such as printing size 9 caplets for rats. Moreover, 3D printing reduces the need for large batch production, minimizing costs in early study phases [23].

FDM, like other 3D printing methods, enables the inclusion of multiple active ingredients within a single dosage form. "Dual" FDM printers, equipped with two nozzles, can deposit different filaments to produce multilayer or bilayer tablets. In multilayer tablets, release depends on the properties of each polymer layer, whereas in bilayer tablets, the solubility of the outer layer primarily controls release [16]. Another strategy involves loading chemically incompatible drugs into multi-compartment 3D-printed capsules. With compartments printed from different materials or varying wall thickness, each drug can release at distinct times [72, 73].

One of the primary technological hurdles in FDM 3D printing is incorporating active pharmaceutical ingredients (APIs) into the filament. Currently, there are two widely explored strategies. The first involves immersing commercially available filaments in a concentrated organic solution containing the drug, allowing the active ingredient to diffuse into the polymer matrix. The second strategy introduces the drug directly during the filament extrusion process [5]. A less commonly reported method involves shaping short filaments in silicone molds [74]. Early experiments using the immersion technique demonstrated that drug release could be controlled by adjusting the tablet infill, as shown by Goyanes *et al*., who used polyvinyl alcohol filaments loaded with fluorescein as a model compound [66]. Follow-up studies confirmed that this approach could produce dosage forms with tailored release profiles [70, 75]. Despite these successes, this method is limited by the high temperatures required during printing and relatively low drug-loading efficiency [5].

The second method, hot melt extrusion (HME), is a well-established pharmaceutical process used to create solid dispersions and improve the solubility of poorly water-soluble drugs [76]. The process begins by precisely weighing and homogenizing the active ingredients with excipients. The mixture is then fed into an extruder, where

it undergoes high temperature and pressure, causing it to melt. Rotating screws push the molten blend through a nozzle to form continuous filaments, which are subsequently cooled and sealed to prevent moisture absorption [5]. Initial HME filaments were produced by reprocessing ground commercial filaments [20], followed by the development of laboratory-scale extruders capable of fabricating filaments from pharmaceutical-grade polymers [11, 21, 77]. Recently, industrial-scale extrusion systems have enabled continuous production of filaments suitable for 3D printing, with Korte and Quodbach providing a systematic framework for large-scale filament manufacturing [78, 79].

Electrohydrodynamic (EHD) 3D printing

Electrohydrodynamic (EHD) printing is a rapidly emerging 3D printing approach that uses an applied electric field to drive ink ejection through a conductive nozzle onto a substrate [80, 81]. A key advantage of this method is its ability to generate micrometer-scale fibers. EHD printing has been applied in diverse tissue engineering contexts, including scaffolds for general tissue regeneration [82, 83], tendon repair [84, 85], vascular structures [86], bone scaffolds [87], corneal stroma [88], and tumor modeling [89]. Despite its versatility, the technique has notable limitations: scaffold thickness is generally restricted to less than 7 mm [90], and the selection of compatible materials is limited, with polycaprolactone (PCL) being most commonly used. PCL is prone to plastic deformation even under low strain, which has led to the development of modified PCL-based materials tailored for EHD printing [85]. While overcoming these challenges requires considerable effort, EHD 3D printing is poised to become an important tool in tissue engineering applications.

Conclusion

This paper presents a concise overview of 3D printing technology, a cutting-edge method for creating three-dimensional structures by depositing successive layers of material under computer control. In pharmaceutical applications, five main techniques are currently utilized: powder-based printing, selective laser sintering, stereolithography, extrusion-based printing, and electrohydrodynamic 3D printing. The article examined the development, current research trends, and future prospects of each method. 3D printing is gaining traction in pharmacy primarily because of its transformative ability to produce personalized dosage forms tailored to individual patient needs, offering objects in a wide variety of sizes and geometries. This capability has driven research into optimizing dosage by adjusting tablet size, surface area, or infill density. A key feature of personalized 3D-printed tablets is the potential to incorporate multiple active ingredients within a single dosage form, thereby reducing the number of daily medications, lowering administration frequency, and enhancing patient adherence. Additionally, 3D printing allows the production of small batches—or even single units—of medication customized for individual patients.

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