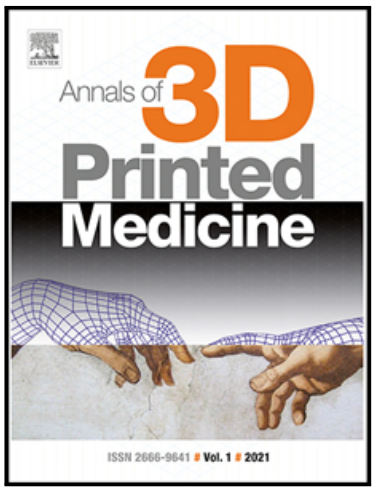

Integration of 3D Printing Technology in Pharmaceutical Compounding: Progress, Prospects, and Challenges

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Review

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Integration of 3D Printing Technology in Pharmaceutical Compounding: Progress, Prospects, and Challenges

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Abstract

A significant limitation of current medication development and usage is the reliance on the 'one-size-fits-all' approach. 3D printing technology is an innovative strategy for customizing medication design and preparation. In this review, we highlighted the potential of 3D printing of medications as an effective strategy to achieve personalized precision medicines. Particular attention was paid to possible integration of 3D printing technology in pharmaceutical compounding process to improve flexibility, efficiency, safety, quality, trust, and utility. Significant barriers to overcome include: (i) insufficient training on 3D printing compounding and regulation requirements, (ii) limited choices of 3D printers and approved excipients that are amenable to routine pharmacy operations, and (iii) lack of efficient medication verification techniques to ascertain that the intended medication qualities and characteristics are achieved through 3D printing customization.

KEYWORDS: 3D Printing Technology, Medicine, Pharmacy, 3D Printers, Drug Delivery.

1. Introduction

Three-dimensional (3D) printing technology is a medication and formulation development method that relies on computer-aided designs (CAD) and printing settings to build in adjustability of the medications that are subsequently printed. Meanwhile, traditional pharmaceutical compounding is the process of combining, mixing or altering ingredients to prepare medications in response to unique patient situations that warrant special dosage forms, drug strengths or excipients [1]. We are of the opinion that pharmaceutical compounding will continue to gain the lost ground in pharmacy practice with the pressing need for medication customization. Integration of 3D printing technology in pharmaceutical compounding will be a significant improvement of the current formulation and medication development systems that have few opportunities for customization (Figure 1). 3D printing technology has great potentials to revolutionize the personalized medicines field as we strive to break from the current status quo of "one size fits all." The main goal of personalized medicines is to tailor medications to patient needs while factoring in differences in genetic profiles, age, race, gender, epigenetic and environmental factors. We envision that timely integration of 3D printing technology to pharmacy practice operation is vital to making progress and improving health care for all patients. Meanwhile, not many health care professionals have the right background and knowledge about 3D printing technology. Thus, this review is an assessment of what it will take to fully integrate 3D printing technology into pharmacy practice settings while highlighting opportunities and challenges of adopting 3D printing as a compounding method in pharmacies.

3D Printing technology can offer many benefits to operations of pharmacy practice as enumerated below:

(i) 3D printing technology can promote the manufacture of personalized precision medicines, including the ability to choose optimal dose, appearance, flavor, dosage form, and release profile, while also reducing the number of doses for each patient by custom-designed multi-drug dosage forms with customized release profiles of each contained drug [2]. The adjustability of medication shape and design could help diverse groups of patients (Figure 1). For example, patients with vision impairment could have customized shapes or designs to identify medications [3], and pediatric patients could have effective personalized flavor masking and appearance of

medications to improve compliance [4, 5]. Additionally, opioids can be 3D printed with abuse deterring and alcohol resistant properties [6, 7].

(ii) 3D printing in compounding increases the flexibility to adjust drug contents and their release profiles for each patient [2]. For instance, 3D printed dietary supplements with controlled-release patterns may be of interest to dietary supplement users [8]. After additional studies exploring the printing of nutritional supplements, pharmacists could print dietary supplements in polypills combined with prescribed medications to increase such patients' interest and compliance while reducing pill fatigue and ensuring the safety and consistency of co-administered supplements. Pharmacists will need to familiarize themselves with potential dietary supplement interactions with prescriptions and personalize the dosage forms accordingly.

(iii) 3D printing technology makes it possible to use fewer excipients for on-demand medication printing than commercialized mass-produced versions [9], reducing the variety of pharmaceutical ingredients needed and saving pharmacies money while making medications safer for patients in special population groups.

(iv) With 3D printing technology, it is possible to consistently achieve high accuracy, precision, and drug uniformity throughout dosage forms. Drug formulation changes are controlled by altering the 3D model or ink deposition instructions compared to standard methods [10]. 3D printing technologies can be combined or used in sequence to increase the possible dosage forms and drug combinations by delegating substrate formation or drugs not well suited for a printing type to a more ideal automated process (Figure 2).

(v) There is lower equipment cost compared to other automated production technologies [9]. Free 3D modeling software is available online to anyone who wishes to use them, making 3D printing of medications accessible with the purchase or lease of a 3D printer (Table 1).

(vi) The ability to add Quick Response (QR) codes directly to dosage forms, known as Data-Enriched Edible pharmaceuticals (DEEP), can be used to convey information such as drug, dose, use, directions, side effects, pharmacy, patient, and date printed to ensure that once a drug is removed from packaging it still has the instructions, patient and pharmacy information needed to prevent misuse or counterfeit [9, 11]. QR codes are readable using a smartphone with a QR code reading application. A more complex QR code called a Uniform Resource Locator (URL) is suggested as an alternative to using QR codes because of the URL's ability to bring the patient to more detailed

information about the drug through a webpage [9]. A smartphone application URL scanner in existence can get a patient or designated caregiver to an Electronic Health Record webpage with a prerequisite of logging in before showing personally identifying information to allow the patient the confidence of access to detailed information about each prescribed drug, even when removed from packaging, as well as to facilitate clear, accurate communication about medications with the healthcare team.

2. Selecting Optimal 3D Printers for Pharmaceutical Compounding

Selection of the type of 3D printer for use in a pharmacy setting is a significant decision (Table 1). Generally, printers offer flexibility in setting ink usage to ensure an accurate blend of ink with the drug as needed for more predictable drug content. It is also important to note the type of formulation and materials because some 3D printers have restrictions regarding types of materials that are compatible with printing ink. Ideally, printers that can use current approved pharmaceutical ingredients are preferred to avoid the need to seek approval of new materials. (Table1) It is not conceivable that routine pharmaceutical compounding will seek approval of new excipients prior to 3D printing integration. Several preclinical studies have reported the use of new excipients toward creating gastro-retentive tablets as ultra-long lasting extended-release dosage forms that will need appropriate clinical studies and regulatory approvals for adoption in clinical settings [12-16]. It is also important to note that some 3D printers will expose drug formulations to high temperatures that are not suitable for thermolabile drug formulations.

If printers that are not designed for pharmaceutical processing are adapted in compounding, it is important to ensure that parts that will make close contact with formulation materials are made of acceptable materials such as stainless steel. In this regard, printers that do not allow direct contact between the machine and product ingredients are best for reducing contamination risk. It is important to note that 3D printers are often not designed for convenient cleaning of internal parts. As with any other compounding equipment, to meet USP 795 guidelines, pharmacies must develop suitable standard operating procedures for safely cleaning the printer and preventing product-to-product contamination.

3D printers vary significantly in price based on the method of printing, accuracy, and additional features that may increase the speed of printing or the number of formulation inks that may be used simultaneously. Some printers are offered only as industrial-size, which can present space and regulatory burdens to non-outsourcing compounding pharmacies. Further, some printers produce dosage forms that require post-processing drying time which may delay medication dispensing time with associated special handling and packaging methods.

3. Examples of Common Types of 3D Printers

Since there are different types of 3D printers, we present key features of the most common types that can be integrated with a pharmacy practice setting.

Binder Jetting (BJ) (Tables 1 and 2): This type of printer works by controlling the flow of liquid binding agents as droplet sprays from a nozzle onto a thin layer of powder drug formulation upon a build plate [17, 18]. An additional layer of powder is lowered by a powder reservoir, then rolled onto the drug product(s) in progress. Binding and layering steps are repeated until all required layers have been bound together as specified by the 3D model [17, 18]. Binder Jetting has demonstrated the capacity to print both immediate and extended-release dosage forms, with the ability to form a drug capsule of multiple compartments to separate active drugs components [17, 19]. Binder jetting has already created one FDA-approved medication, Spritam® [17]. Considerable challenges with Binder Jetting 3D printers include that they are large, expensive, difficult to find, and appear to be designed only for large-scale manufacturing. The resulting drug product must be cured to strengthen its form before separation from the unbound powder [17, 20].

Material Extrusion (ME) via Polymer Filaments (Tables 1 and 2): Material extrusion works by deposition of pliable drug formulations through one or more nozzles/orifices onto a stage in a layer-by-layer fashion to become 3D [20]. Material extrusion is accomplished via any of the following sub-classifications: Fused Deposition Modeling (FDM), Semisolid Extrusion (SSE), Direct FDM, or Embedded 3D Printing (e-3DP).

In the FDM process, solid thermoplastic polymer filaments loaded with active pharmaceutical ingredient(s), are first prepared by Hot Melt Extrusion (HME) **(Table 1 and 2)**. These are then fed into the printer via rollers (or narrow tubing through gears) while

exiting, through a heated printer nozzle, the filament is softened for extrusion and printing as directed in layers to replicate the shape of the 3D model [21, 22]. FDM is inexpensive, widely available, has been applied to print complex formulations such as gastro retentive floating tablets [15]. It is possible to modify the drug release of FDM-printed products through the infill percentage or drug/polymer ratio [23]. Some FDM printers can use multiple filaments at once by feeding them simultaneously into the heated nozzle [24] or having multiple heated nozzles -one for each filament- with independent settings [25]. The prerequisite process of HME produces filaments that sometimes enhance the dissolution and solubility of contained drugs, increasing the potential use of drugs that previously failed to reach adequate bioavailability [26].

Some of the FDM challenges are listed: (i) There are few thermoplastic polymers approved as pharmaceutical excipients [27, 28]. (ii) In the printing of drug-containing filaments, thermolabile drugs are not known to be well-suited for printing by FDM because most studies investigating FDM use thermoplastic polymers with high printability, and that require a printing temperature of 150–230°C [29]. However, FDM printing of drugs has been performed using temperatures as low as 90°C [29, 30]. The glass transition temperature, melting temperature, miscibility, and solubility differ with each formulation, while each contributes to the printability and dosage form properties [27, 31]. (iii) FDM printed solid tablets do not disintegrate well, often causing a slow or incomplete release of active(s) and instead rely on erosion and diffusion mechanisms for drug release, necessitating increased surface area in the design to facilitate faster release [27, 32].

Material Extrusion (ME) without Polymer Filaments (Tables 1 and 2): It is also possible to achieve material extrusion, without the use of filaments, through approaches such as direct powder extrusion printing or single process 3D printing [33] [9, 31, 34, 35]. In this process, a chamber or syringe of the printer is filled with powder or pellets, followed by melting or stable heating of the drug formulation materials by heating the chamber or nozzle until the formulation becomes a printable semisolid ink [31, 33, 34]. The formulation is selectively deposited onto packaging or previous layers by an assisting force via a screw, ram, or plunger within the chamber [31, 33-35]. This printing process is identical to FDM except that filaments are not needed [35]. Some of the challenges associated with direct powder extrusion are: (i) the printer uses a heated chamber to directly contain ink formulation, requiring cleaning and reusing of the chamber for each formulation or batch, (ii) this printer is not capable of printing with semisolids or liquids and is instead restricted to

loading with pellets and powders to be melted into semisolid form during printing, (iii) similar to FDM, this technique generally does not produce dosage forms with immediate release characteristics and will require channels in the dosage form design to cause faster drug release.

Material Extrusion (ME) without Application of Heat (Tables 1 and 2): It is possible to achieve material extrusion without the application of heat. This can be achieved through semisolid extrusion [36], also termed: 3D micro-extrusion [37], Pressure-assisted micro-syringe extrusion [16], Extrusion-based Bioprinting [38], and Melting Solidification Printing Process (MESO-PP) [16]. In this method, a syringe, cartridge, or chamber is filled with a paste, gel, or solid that melts at low temperatures (~49°C) [16] as drug formulation ink, then uses an assisting pressure with or without [38] heat to print that ink onto a heated or non-heated build plate and subsequently onto previous layers to create a 3D formulation [38]. The non-heated extrusion 3D printers are amenable to a wide variety of semisolid materials as ink. Some versions allow the use of disposable syringes for depositing drug formulation without allowing contact of the drug ink and printer to reduce sterility concerns for the printed product [38].

A significant challenge with non-heated extrusion is that the printed product will often require a long time to dry before direct handling to prevent damage to the dosage form. Current mitigation strategies include printing directly into a commercially available capsule [39], printing directly onto packaging to allow indirect handling during drying, and increasing drying time between printed layers to reduce overall drying time [40]. Semisolid ink formulations can change temperature and viscosity during printing, impacting the ink flow characteristics and decreasing each layer's consistency and repeatability over time [37]. Therefore, a heated jacket or other temperature control method can be necessary surrounding the syringe or cartridge body [16].

Embedded 3D Printing (e-3DP) (Tables 1 and 2): This method is a modification to combine FDM and semisolid extrusion printing technologies, allowing ease of swallowing extended-release formulations and customizability of flavoring or appearance without impacting drug release behavior [5]. A paste or gel drug formulation is extruded into the center of edible liquid gelatin- or jelly-based matrix while that matrix solidifies by cooling [5]. The gelatin- or jelly-coated dosage forms created by Embedded 3D printing are more manageable for elderly and pediatric patients to swallow [5]. The dosage forms created by

Embedded 3D printing do not require altering the formulation of the external matrix for each drug-containing core [5]. The design of appearance and flavor is separate from the drug-containing core design, enabling more creative exterior forms without impacting medication behavior [5]. This dosage form can easily allow multiple drugs to stay separated while still contained in the same dosage form [5].

A significant challenge is that the Embedded 3D printing method requires modifying a dual extrusion FDM printer to build, using novel 3D printed parts and gelatin molds [5]. The gelatin matrix must of a similar density and with low miscibility compared to the drug-loaded core materials. It must be thixotropic or cured after loading the drug core to allow solidification and subsequent handling [5].

4.0. Challenges of 3D Printing Technology:

General Challenges with 3D printing:

- Even with computerized processes such as 3D printing, various unintended differences can be produced from the same 3D computer-aided design model, based upon factors including but not limited to: age or quality of ink materials, changed slicer program-based printer settings [24], changes to the stage level or angle, and wearing of parts. This issue presents a need for quick and convenient analytical tools to determine if the medication intended was successfully printed, including qualities of uniformity, release profile, and concentration of each drug contained [41, 42]. Some suggest using Artificial Intelligence or predictive models to get the job done [42, 43]. Others have suggested using a portable Near-Infrared Spectrometer with calibration models created by partial least squares (PLS) regression to confirm multiple drug dosages within polypills [41].
- The ideal 3D printer selected for use in a pharmacy setting should be easy to use, has minimal setup and training, saves time compared to traditional compounding, efficiently uses approved pharmaceutical ingredients [44], and can print a plethora of medications helpful to that pharmacy. Some printers seem close to reaching most of these goals, while others can better address one or more ideal qualities now or with further development.
- There are contamination concerns in the 3D printing of edible products [40]. All 3D drug printers must be easily cleaned where they contact edible printed products and their ingredients. Drug formulation materials reused from one 3D printing task to the subsequent present additional contamination concerns surrounding their possible

exposure to previously used drug formulation ink or processing conditions. Another contamination source can be the printer parts; for example, the FDM printers have brass nozzles containing lead as a default standard and must be upgraded to have stainless steel nozzles for medical applications.

- Most polymers currently used in the traditional compounding of pharmaceuticals do not print well, prompting the use of nonpharmaceutical grade polymers in many studies of thermoplastic polymer requiring printers, such as FDM [27]. Formulation change is often necessary for printing different drugs and can result in different release characteristics. Optimized formulas are needed for each 3D printer to produce a tremendous variety of medications while requiring the fewest necessary pharmaceutical ingredients and predicting drug release with altered excipients. Artificial Intelligence can help predict the effects of excipient changes on the final product's release pattern [43].
- There is a need to identify training requirements for pharmacists and technicians who will use 3D printers or counsel patients about medications produced by 3D printers for compliance with USP 795. Drafters are individuals experienced with 3D Computer-Aided Design building and printing models, with some gaining specialized experience in biomedical applications. These individuals typically require up to 2 years of training to become drafters for manufacturing industries, although some 3D modeling software are intuitive for individuals without formal training. The American Design Drafting Association (ADDA) offers general certification for the professional draftsman to prove competence in 3D modeling standards and certifications in several drafting specialties. Perhaps the ADDA could partner with pharmacy leaders to add pharmacy drafting as one of the certification specialties, establishing standard practices for 3D modeling and printing medications in pharmacy settings.
- The quality of a 3D printer chosen for printing medications is essential to consider regarding the size and drug concentration of desired printed drug products. Different printer models have different tolerance ranges, which can impact the accuracy of the printed drug product. For example, a printer's tolerance may be +/-0.1 mm, which will lead to the drug product dimensions being allowed to deviate by up to 0.1 mm shorter or longer than is defined by the 3D model. Printers generally increase in price with smaller tolerance ranges.

5.0. Our Perspectives and Conclusion:

The FDA and others cumulatively identify 3D printing as a process with the potential to inexpensively improve medication safety, strength, quality, precision, uniformity, and purity compared to those produced by traditional methods [42]. Integration in pharmaceutical compounding could help alleviate safety and quality concerns through increased automation, standardization, and communication methods.

As with other compounded medications, printed dosage forms require analysis to ensure the intended product characteristics have been successfully printed through established standard formulation procedures. The need to analyze each custom dosage formulation/medicine could delay the much-needed widespread implementation of on-demand 3D printing technology in pharmacy. Convenient analytical and predictive tools will need further development to fully enable customized medications with efficient timing relative to customized prescription receipt. Development of 3D printers and related programs specific to pharmaceutical compounding, including built-in predictive and analysis tools, will improve the quality of research in this area, improve the acceptability of 3D printed dosage forms, and promote any formulation changes required for printability to be accounted for in USP-NF preparation standards.

We believe that regulatory hurdles are minimal for 3D printers in non-sterile compounding operations. This is because 3D printing can fit into the standard processes of licensed non-outsourcing compounding pharmacies. Implementation of 3D printing technology in the compounding of non-sterile medications will facilitate the long-overdue upgrade of compounded processes for personalized precision medicines. As the health care professionals solely responsible for compounding, pharmacists must actively improve relevant skills and techniques toward optimal patient outcomes. The improvement of pharmaceutical compounding product quality and customization options will enhance the perceptions of pharmacists by also necessitating further integration of their pharmaceutical expertise within interprofessional teams toward improved medication therapy outcomes.

The different types of printers have shown to work well in synergy to reduce limitations and maximize benefits, including dosage forms currently exclusive to specific technologies. The ideal 3D printer for the future pharmacy may be a multi-printer modified to work with multiple technologies, allowing the most extraordinary possibilities of dosage forms and their release profiles. For now, the lack of diverse multi-printer options and studies using them forces pharmacists to choose their 3D printing technology primarily based on

their 503A pharmacy's budget, most clinically needed medication-specific dosage forms and release profiles, and capacity to contribute to the technology with compounding research.

Although pediatric, elderly, allergy restricted, or genetically distinct drug metabolism patients may benefit most directly from decreased excipients, improved flavor, and appearance, or with more adjustable dose and release characteristics: well, implemented, the ability of more readily available high-quality personalized medications to result in increased compliance could improve medication therapy outcomes for all patients struggling with compliance unrelated to insurance coverage.

Professional development of pharmacists must include training with 3D printers for compounding medicines. To facilitate this, the Accreditation Council for Pharmacy Education should supplement standard curriculum requirements of PharmD programs with training in 3D printed medication compounding.

Further research is needed to establish efficient, effective medication verification techniques to realize the full spectrum of opportunities presented by 3D printing in a timely fashion. Pharmacy schools must research efficient medication verification techniques to improve current compounding safety and allow techniques to stay up to date with anticipated dosage form options.

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Table 1: Examples of Common 3D Printers for Potential Integration in Pharmaceutical Compounding

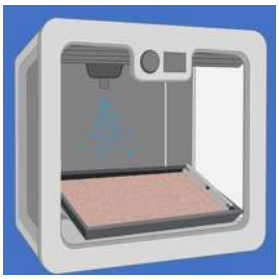
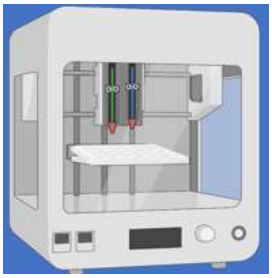
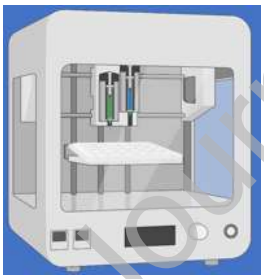
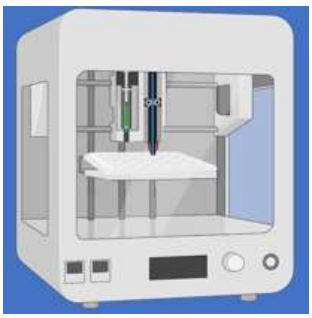
3D Printer	Pros	Cons
 **BINDER JETTING**	-Minimal ink preparation. -Avoids contact between printer and drug formulation. -Minimal or avoidance of heat in processing. -Suitability in current FDA-approved 3D printed medicines.	-Potential high cost. -Limited supply for pharmacy compounding application. -Requirement for post-printing drying.
 **FUSED DEPOSITION MODELING**	-Very affordable. -Most commonly available. -Suitability for formulations with novel drug release designs. -Requires minimal post-printing processing.	-Limited approved excipients. -May expose drugs to high temperatures. -Requirement for accessory equipment.
 **SEMI-SOLID EXTRUSION**	-Enhances formulation sterility and ease of cleaning. -Can avoid use of heat.	-Difficult to maintain viscosity and dispersal of ingredients. -requires a long post-printing time.
 **EMBEDDED**	-Combines benefits of FDM and semisolid extrusion. -Enhances ease of swallowing core FDM dosage form.	-Expensive. -Limited availability. -May require custom design.

Table 2: Representative List of 3D Printing Technology Applications in Drug Delivery

Drug Name	Type of Dosage Form	3D Printing Type	Reference
4-Aminosalicylic acid	Tablet (IR)	Fused Deposition Modeling (FDM)	[29]
Acetaminophen	Tablets shaped as disk, donut, cuboid, oval or grid in 3 sizes each	3D-Screen printing	[45]
Acetaminophen	Capsules filled with multi-drug flexible films with ibuprofen	Electrohydrodynamic (EHD)	[46]
Acetaminophen	Chewable Polypill with Ibuprofen made with gelatin and shaped as Lego™-like bricks	Embedded (e-3DP)	[5]
Acetaminophen	Single-layered Orodispersible Films, or Multi-layered Orodispersible Films with Taste-Masking Layers Separated from Drug Layer	Fused Deposition Modeling (FDM)	[21]
Acetaminophen	Orodispersible Film	Hot-Melt Ram Extrusion	[33]
Acetaminophen	Polypill of various shapes with Caffeine, Naproxen, Chloramphenicol, Prednisolone, and Acetylsalicylic Acid	Modified Stereolithography (SLA)	[47]
Acetaminophen	Polypill Tabet (Miniprintlet of 1 or 2mm diameter) Controlled Release with Ibuprofen; Tablet (ER) (Miniprintlet of 1 or 2mm diameter) Without ibuprofen	Selective Laser Sintering (SLS)	[48]

Acetaminophen	Chewable Chocolate-Based Tablets in Various Cartoon-Themed Shapes	Semisolid Extrusion (SSE)	[4]
Acetaminophen	Polypill Tablet (ER) with Acetylsalicylic acid (ER) with 28 doses created in one batch	Stereolithography (SLA)	[49]
Acetylsalicylic acid	Polypill Tablet of Various Shapes with Acetaminophen, Caffeine, Naproxen, Chloramphenicol, and Prednisolone	Modified Stereolithography (SLA)	[47]
Acetylsalicylic acid	Tablet (IR, ER) with Multiple Layers of Varying Thicknesses Using 2 Gel Drug Formulations	Semisolid Extrusion (SSE) into a Capsule	[39]
Albendazole Sulfate	Gastro-Retentive Tablet (ER for 6 Hours)	Melting Solidification Printing Process (MESO-PP) (Modified From SSE)	[16]
Amitriptyline	Tablet (IR) with Low Drug Loading	Binder Jetting	[17]
Amlodipine	Polypill tablet with Indapamide, Lisinopril, Rosuvastatin	Fused Deposition Modeling (FDM)	[30]
Amlodipine	Polyprintlets with Lisinopril as Orodispersible Films or Cylindrical Tablets	Selective Laser Sintering (SLS)	[41]
Aripiprazole	Orodispersible Film with QR Code	Hot-Melt Pneumatic (HMP) Extrusion	[9]
Ascorbic Acid (Vitamin C)	Tablets of multiple sizes and geometries including cylinder, honeycomb with 1, 4, or 7 holes through the center	Stereolithography (SLA)	[50]

Atenolol	Tablet	Semisolid Extrusion (SSE)	[51]
Benzydamine	Orodispersible Film with Multiple Layers	Semisolid Extrusion (Modified from FDM Printer)	[40]
Bicalutamide	Tablets with Immediate, Controlled, and Combined Release Profiles	Modified Fused Deposition Modeling	[24]
Caffeine	Tablet (IR)	Direct Powder (DPP) Extrusion	[34]
Caffeine	Capsules with Modular Internal Compartments	Fused Deposition Modeling (FDM) of hollow capsule shells, followed by manual filling with the drug by micro spatula	[8]
Caffeine	Polypill of various shapes with Acetaminophen, Naproxen, Chloramphenicol, Prednisolone, and Acetylsalicylic Acid	Modified Stereolithography (SLA)	[47]
Cannabidiol (CBD)	Orodispersible Film (IR) with delta-9-tetrahydrocannabinol (THC) and QR coded surface	Piezoelectric Inkjet printing of drug-containing ink/code pattern upon manually prepared substrate	[11]
Carbamazepine	Orodispersible Tablet	Semisolid Extrusion (SSE)	[36]
Carvedilol	Gastro-Retentive Extended-Release Tablet (24 hours)	Fused Deposition Modeling (FDM)	[12]
Carvedilol	Tablet in the form of Ring, Mesh, Cylinder; Orodispersible Film	UV Inkjet (Drop on Demand with UV Curing)	[52]

Catechin	Buccal Films (Delayed-Release) shaped as rectangle, oval, dog bone, and dried either by air or freeze-drying	Semisolid Extrusion (SSE)	[53]
Chloramphenicol	Polypill of various shapes with Acetaminophen, Caffeine, Naproxen, Prednisolone, and Acetylsalicylic Acid	Modified Stereolithography (SLA)	[47]
Cinnarizine	Gastro-Retentive Tablet with Controlled Release for 6-12 hours	Fused Deposition Modeling (FDM)	[15]
Cinnarizine	Tablets with Controlled Release for 8 hours	Fused Deposition Modeling (FDM)	[54]
Ciprofloxacin	Tablet	Fused Deposition Modeling (FDM)	[55]
Dapivirine	Vaginal Rings	Arburg Plastic Freeforming (APF) – a proprietary Droplet Deposition Modelling (DDM) process with Piezoelectric shut-off nozzle	[56]
Delta-9-tetrahydrocannabinol (THC)	Orodispersible Film (IR) with Cannabidiol (CBD) and QR coded surface	Piezoelectric Inkjet printing of drug-containing ink/code pattern upon manually prepared substrate	[11]
Diclofenac	Buccal Film of unidirectional drug release	Fused Deposition Modeling (FDM)	[57]
Diclofenac	Orodispersible Tablets	Selective Laser Sintering (SLS)	[58]
Diclofenac	Tablet (ER) of Reservoir Design in the form of a Heart, Cylinder, or Star	Semisolid Extrusion (SSE)	[59]

Diclofenac	Buccal Film (Sugar Sheet Based)	Thermal Inkjet (TIJ)	[60]
Diltiazem	Tablet (ER, IR, delayed-, and pulsatile-release profiles)	Fused Deposition Modeling (FDM)	[61]
Diphenhydramine	Polypill Tablet with Phenylephrine and Customizable Release via Internal Geometries, Created by 3d Printed Molds	Fused Deposition Modeling (FDM) Printed Molds	[2]
Dipyridamole	Liquid Filled Capsule (IR, ER)	Fused Deposition Modeling (FDM) of Capsule Shell with Automated Liquid Dispensing Syringe Modification	[22]
Dipyridamole	Gastro-floating (ER >8 hours) Tablet with Fine Lattice Internal Structure	Semisolid Extrusion (SSE)	[13]
Enalapril	Polypill Tablet with Hydrochlorothiazide (IR)	Fused Deposition Modeling (FDM) with 2 Thermal Nozzles	[25]
Enalapril	Orodispersible Film with Hydrochlorothiazide	Piezoelectric Inkjet	[62]
Fluorescein Sodium	Orodispersible Tablet with 5-Aminosalicylic acid	Fused Deposition Modeling (FDM)	[63]
Glimepiride	Polypill Tablet of Glimepiride (IR) with Metformin (ER)	Fused Deposition Modeling (FDM)	[64]
Glipizide	Tablet in the form of a Cylinder with Internal Grid Structure	Semisolid Extrusion (SSE)	[65]
Haloperidol	Tablet (Rapid Release)	Fused Deposition Modeling (FDM)	[27]

Hydrochlorothiazide	Polypill Tablet with Enalapril (IR)	Fused Deposition Modeling (FDM) with 2 Thermal Nozzles	[25]
Hydrochlorothiazide	Orodispersible Film with Enalapril	Piezoelectric Inkjet	[62]
Ibuprofen	Capsules filled with Multidrug Flexible Films with Acetaminophen	Electrohydrodynamic (EHD)	[46]
Ibuprofen	Chewable Polypill with Acetaminophen made with gelatin and shaped as Lego™-like bricks	Embedded (e-3DP)	[5]
Ibuprofen	Single-Layered Orodispersible Films, or Multi-layered Orodispersible Films with Taste-Masking Layers Separated From Drug Layer	Fused Deposition Modeling (FDM)	[21]
Ibuprofen	Tablet with gel center	Piezoelectric Inkjet-printed gel contents of preformed tablet shells that were made by direct compression	[66]
Ibuprofen	Polypill Tablet (Miniprintlet of 1 or 2mm diameter) Controlled Release with Acetaminophen	Selective Laser Sintering (SLS)	[48]
Ibuprofen	Chewable Chocolate-Based Tablets in Various Cartoon-Themed Shapes	Semisolid Extrusion (SSE)	[4]
Indapamide	Polypill Tablet with Amlodipine, Lisinopril, Rosuvastatin	Fused Deposition Modeling (FDM)	[30]
Indomethacin	Tablet (IR)	Binder Jetting	[18]

Indomethacin	Tablet	Electromagnetic (Valvejet) Ink-jet (Type of Drop on Demand Inkjet Material Jetting)	[67]
Indomethacin	Tablet (IR) in the form of a Lion, Heart, Bear, Ring, Bottle, with Effective Sweetening for Taste Masking, determined by human taste testers	Fused Deposition Modeling (FDM)	[68]
Isoleucine	Chewable Tablet	Semisolid Extrusion (SSE)	[69]
Itraconazole	Tablets	Direct Powder Printing (DPP)	[35]
Ketoprofen	Buccal Film with Lidocaine	Fused Deposition Modeling (FDM) of Ketoprofen Buccal Film, Followed by Thermal Inkjet Material Jetting of Lidocaine onto the Film	[70]
Levetiracetam	Tablets (IR) in the shape of a cylinder, torus, or oval. Torus shape has the most complete and rapid release profile	Semisolid Extrusion (SSE)	[10]
Lidocaine	Buccal Film of unidirectional drug release with Ketoprofen	Fused Deposition Modeling (FDM) of Ketoprofen Buccal Film, Followed by Thermal Inkjet Material Jetting of Lidocaine onto the Film	[70]
Lisinopril	Polypill Tablet with Spironolactone in Multi-Compartment Design	Binder Jetting printed blank tablets with dual compartments and subsequent Piezoelectric Material Jetting to load the tablets with drugs	[19]

Lisinopril	Polypill Tablet with Amlodipine, Indapamide, Rosuvastatin	Fused Deposition Modeling (FDM)	[30]
Lisinopril	Polyprintlets with Amlodipine as Orodispersible Films or Cylindrical Tablets	Selective Laser Sintering (SLS)	[41]
Loperamide	Tablets (IR) of Multi-dose Abuse-Deterrent Formulation in egg shape	Fused Deposition Modeling (FDM)	[6]
Lopinavir	Tablet (IR)	Selective Laser Sintering (SLS)	[71]
Metformin	Polypill Tablet of Metformin (ER) with glimepiride (IR)	Fused Deposition Modeling (FDM)	[64]
Metoprolol Tartrate	Tablet (ER)	Fused Deposition Modeling (FDM)	[23]
Minoxidil	Tablets (Rapid Release) in a disc shape	Fused Deposition Modeling (FDM) printed tablet scaffolds, loaded manually by applying liquid minoxidil formulation	[72]
Naproxen	Polypill of various shapes with Acetaminophen, Caffeine, Chloramphenicol, Prednisolone and Acetylsalicylic Acid	Modified Stereolithography (SLA)	[47]
Naproxen	Tablet with Customizable Release Rate and gel center	Piezoelectric Inkjet-printed gel contents of preformed tablet shells that were made by direct compression	[66]
Naptopidil	Tablet	Semisolid Extrusion (SSE)	[73]

Nifedipine	Tablet (ER)	Fused Deposition Modeling (FDM)	[28]
Octreotide	Poly-Capsules with Tylenol Designed to Break During Physiologic Pressures (Delayed-Release 1-2H)	Fused Deposition Modeling (FDM)	[74]
Olanzapine	Orodispersible Film	Hot-Melt Pneumatic Extrusion (HMPE)	[31]
Ondansetron	Orodispersible tablet with similar characteristics to the commercially available version	Selective Laser Sintering (SLS)	[75]
Phenylephrine	Polypill Tablet with Diphenhydramine and Customizable Release via Internal Geometries, Created by 3d Printed Molds	Fused Deposition Modeling (FDM) Printed Molds	[2]
Pramipexole	Tablet (IR)	Fused Deposition Modeling (FDM) Fused Deposition Modeling (FDM)	[76]
Prednisolone	Polypill Tablet of various shapes with Acetaminophen, Caffeine, Chloramphenicol, Naproxen, and Acetylsalicylic Acid	Modified Stereolithography (SLA)	[47]
Pregabalin	Gastro-Retentive (ER) Tablet in the Shape of a Cylinder	Fused Deposition Modeling (FDM)	[14]
Probiotic (*Streptococcus salivarius)*	Orodispersible Film (ODF)	Modified Thermal Inkjet (TIJ) with Two-Cartridges	[77]

Progesterone	Vaginal Ring (ER for 7+ days) with Diffusion Controlled Release in the form of letters "O," "Y," or "M"	Fused Deposition Modeling (FDM)	[78]
Ramipril	Tablet (IR)	Fused Deposition Modeling (FDM)	[29]
Ranitidine	Chewable Medicated Gummy Tablets ("Drugmies") in the shape of discs, hearts, and gummy bears with faster or slower release profiles	Semisolid Extrusion (SSE)	[79]
Ritonavir	Amorphous Solid Dispersion (ASD) for solubility and bioavailability improvement	Selective Laser Sintering (SLS)	[80]
Rosuvastatin	Polypill Tablet with Amlodipine, Indapamide, Lisinopril	Fused Deposition Modeling (FDM)	[30]
Rufinamide	Tablet with higher dissolution at therapeutic dose versus commercially available version	Fused Deposition Modeling (FDM)	[26]
Sodium Cromoglicate	Capsules (Delayed-Release) with hard gelatin shells	Fused Deposition Modeling (FDM)	[81]
Spironolactone	Polypill Tablet (ER for 24 Hours) with Lisinopril in Multi-Compartment Design	Binder Jetting printed blank tablets with dual compartments and subsequent Piezoelectric Material Jetting to load the tablets with multiple drugs	[19]
Tacrolimus	Suppositories	Semisolid Extrusion (SSE)	[82]

Theophylline	Tablet with Modifiable Release, made with various polymers	Fused Deposition Modeling (FDM)	[23]
Theophylline	Tablets (IR)	Semisolid Extrusion (SSE) with Low Heating (60-100°C)	[44]
Thyroxine (T_4)	Orodispersible Film with Triiodothyronine (T_3)	Modified Thermal Inkjet (TIJ) with Two-Cartridges	[83]
Triiodothyronine (T_3)	Orodispersible Film with Thyroxine (T_4)	Modified Thermal Inkjet (TIJ) with Two-Cartridges	[83]
Warfarin	Orodispersible Tablet	Binder Jetting	[84]
Warfarin	Orodispersible Film	Modified Thermal Inkjet (TIJ) with paper rolling mechanism replaced by a stationary stage.	[85]
Warfarin	Orodispersible Films with QR Code	Piezoelectric Inkjet	[86]
Tramadol	Tablets (Modified Release) with Alcohol-Resistant and Abuse-Deterrent Properties	Direct Powder Printing	[7]
Warfarin	Orodispersible Films with QR Code	Semisolid Extrusion (SSE) Printing with Piezoelectric Inkjet-Printed QR Code	[86]

Figure Legends

Figure -1: **Images of some 3-D printed medicines.** Images of 3D printed medicines showcasing the opportunity for flexibility in formulation type, shape and color with 3D printing technology.

Figure-2: **Illustration of potential workflow to integrate 3D printing in pharmaceutical compounding.** The major steps include **(A)** Review of

prescription to be compounded. **(B)** Select of 3D model and dosage form characteristics. This will include calculation, measurement and combination of dosage forms materials with inks. **(C)** Load the printer with dosage form materials and print directly into the packaging. **(D)** Conduct post-3D printing processing such as cooling, drying and removal of excess materials. This will be followed by medication verification. **(E)** Complete medication packaging, labelling and present medicines to patients.

Figure 1

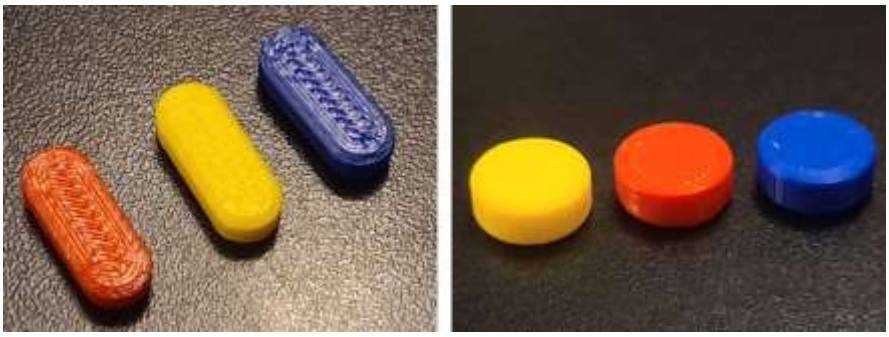
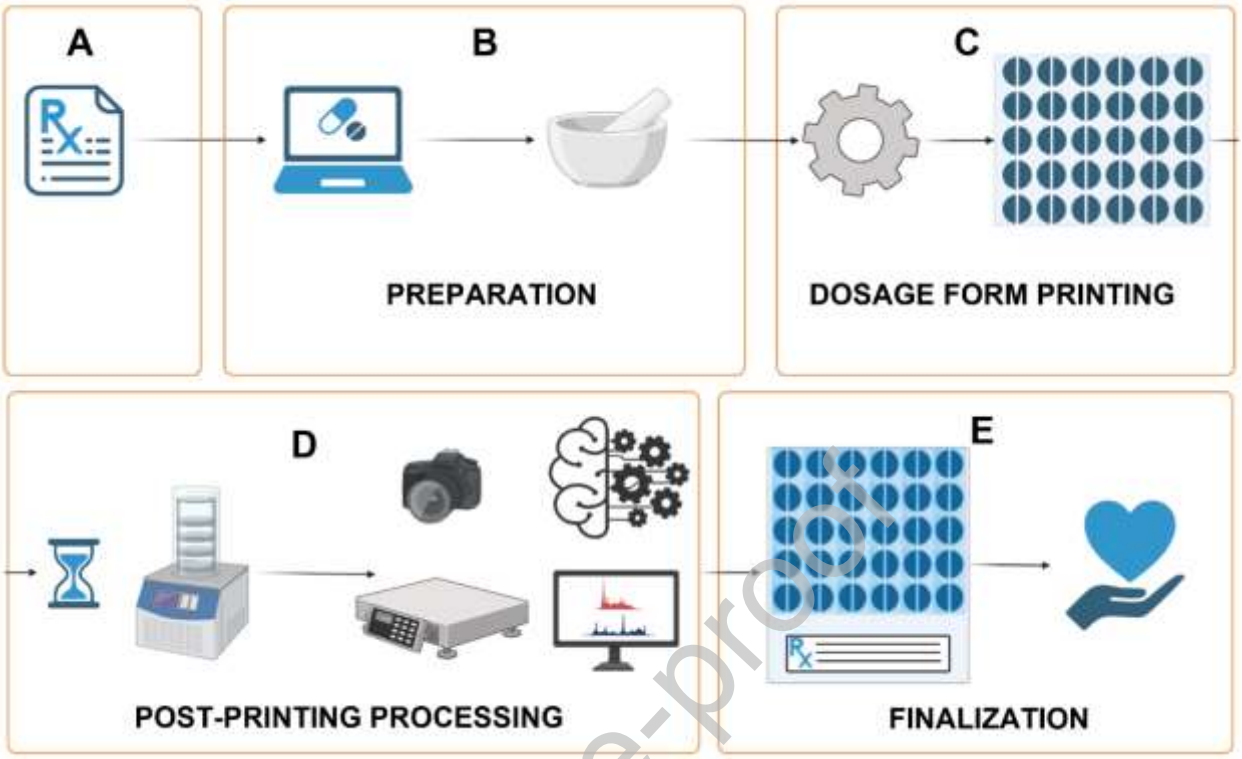


Figure 2



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